CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091294

Name: Abacavir Tablets 300mg

Sponsor: Mylan Pharmaceuticals

Approval Date: June 18, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA091294Orig1s000

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APPLICATION NUMBER:

ANDA 091294

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091294

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 28, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Abacavir Tablets USP, 300 mg.

Reference is also made to the tentative approval issued by this office on February 15, 2011, and to your amendments dated August 17, 2011; and April 5, April 24, May 14, May 25, and June 8, 2012.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Abacavir Tablets USP, 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ziagen Tablets, 300 mg, of VIIV Healthcare Company (VIIV). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, VIIV's Ziagen Tablets, is subject to an unexpired period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 6,294,540 (the '540 patent) is scheduled to expire (with pediatric exclusivity added) on November 14, 2018.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '540 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Abacavir Sulfate Tablets USP, 300 mg, under this ANDA. You have notified the agency that Mylan Pharmaceuticals, Inc (Mylan), complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(iii).

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '540 patent. Therefore, with this approval, Mylan is eligible for 180 days of generic drug exclusivity for Abacavir Tablets USP, 300 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

06/18/2012

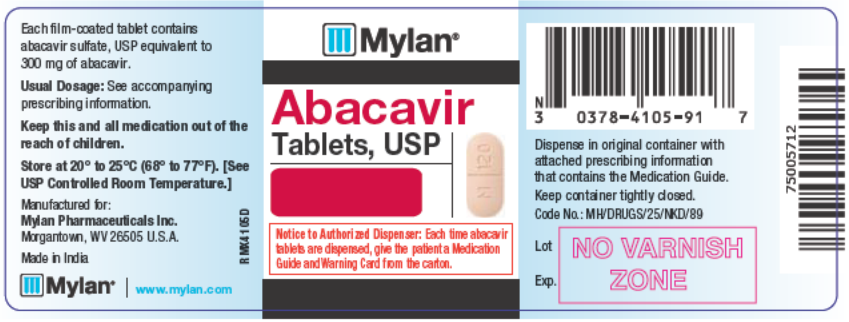
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

LABELING


Each film-coated tablet contains abacavir sulfate, USP equivalent to 300 mg of abacavir.
Usual Dosage: See accompanying prescribing information.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India
RMA4165D
Mylan | www.mylan.com
Mylan
Abacavir
Tablets, USP
N 120
Notice to Authorized Dispenser: Each time abacavir tablets are dispensed, give the patient a Medication Guide and Warning Card from the carton.
N 3 0378-4105-91 7
Dispense in original container with attached prescribing information that contains the Medication Guide.
Keep container tightly closed.
Code No.: MH/DRUGS/25/NKD/89
Lot
Exp.
NO VARNISH ZONE
75005712


75005713
VARNISH FREE AREA
For coding *Serial No.,
**GTIN No., and
***2D Barcode, along with
B.No./Lot. and Exp.
Lot
Exp.
Mylan®
Abacavir
Tablets, USP
M 120
Notice to Authorized Dispenser:
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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India
Code No.: MH/DRUGS/25/NKD/89
MX:4105:1C:R1
Mylan® | www.mylan.com
Mylan®
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Each time abacavir tablets are dispensed, give the patient a Medication Guide and Warning Card from the carton.
N 3 0378-4105-91 7
VARNISH FREE AREA
75005713

Abacavir Tablets, USP
300 mg
75006009
MX:ABCV:R2m

Abacavir Tablets, USP
300 mg
75006009
MX:ABCV:R2m

H GHLIGHTS OF PRESCRIBING NFORMATION

These highlights do not nclude a l the information needed to use abacavir tablets safely and effec ively See full prescribing information for abacavir tablets

Abacavir Tab ets USP for Oral Use

Init al U S App oval: 1998

WARNING: HYPERSENSITIV TY REACT ONS LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescr bing information for complete boxed warning

- **Serious and somet mes fatal hypersens tivity react ons have been associa ed wi h abacavir (abacavir sulfate) (5 1)**
- **Hypersensit v ty to abacavir is a mul i organ c inical syndrome (5 1)**
- **Patients who carry the HLA B*5701 allele are at high risk for experiencing a hypersensit v ty reaction to abacavir (5 1)**
- **Discont nue abacavir as soon as a hypersensitivi y react on is suspected Regardless of HLA B*5701 s atus permanent y discontinue abacavir if hypersensitivi y cannot be uled out even when o her diagnoses are possible (5 1)**
- **Fol ow ng a hype sensi ivity reaction to abacavir NEVER res art abacavir table s or any other abacavir contain ng product (5 1)**
- **Lactic ac dosis and severe hepatomegaly with steatosis inc uding fatal cases have been reported with the use of nucleos de analogues (5 2)**

RECENT MAJOR CHANGES

Dosage and Adm n s ra ion (2)	05/2012
Wa n ngs and Precau ions Hypersensi ivity React on (5 1)	05/2012
Wa n ngs and Precau ions Immune Reconstitut on Synd ome (5 3)	11/2011

NDICATIONS AND USAGE

Abacavir a nucleoside analogue is indicated in combina ion w th other anti e roviral agents for the treatment of HIV 1 infection (1)

DOSAGE AND ADMINISTRATION

A medication gu de and warning ca d should be dispensed w th each new prescription and refill (2)

Adults: 600 mg dai y adm n s ered as either 300 mg tw ce dai y or 600 mg once dai y (2 1)

Pediatr c Patients Aged 3 Months and Older: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice dai y (2 2)

Pa ien s with Hepa ic Impa rment: Mild hepatic mpairment 200 mg twice dai y; moderate/severe hepat c impa rment contra ndicated (2 3)

DOSAGE FORMS AND STRENGTHS

Tab e s: 300 mg scored (3)

CONTRAINDICATIONS

Prev ously demonstrated hypersensit vity to abacavir (4 5 1)

Moderate or severe hepat c impa rment (4)

WARNINGS AND PRECAUTIONS

Hypersensit v ty: Ser ous and somet mes fatal hypersens tivi y react ons have been assoc ated w th abacavir tablets and other abacavir conta n ng p oducts Read full prescribing nformation section 5 1 be ore prescr b ng abacavir ablets (5 1)

Lac ic acidosis and severe hepa omegaly with s eatosis have been reported w th the use of nuc eoside analogues (5 2)

Immune reconst tution syndrome (5 3) and redistr but on/accumu a ion of body fat have been repor ed n patients treated wi h comb nat on an iretroviral herapy (5 4)

ADVERSE REACTIONS

The most commonly reported adverse reactions of at east moderate intensi y (inc dence ≥ 10%) n adu t H V 1 cl n cal trials were nausea headache malaise and fat gue nausea and vomi ing and dreams/sleep d sorders (6 1)

The most commonly reported adverse react ons of at east moderate intensi y (ncidence ≥ 5%) n pediatr c HIV 1 cl n cal t ials were ever and/or chi ls nausea and vomi ing skin rashes and ear/nose/throat infec ions (6 1)

To report SUSPECTED ADVERSE REACTIONS contact Mylan Pharmaceuticals Inc at 1 877 446 3679 (1 877 4 INFO RX) or FDA at 1 800 FDA 1088 or www fda gov/medwatch

DRUG INTERACTIONS

Ethanol: Decreases e imination of abacav r (7 1)

Methadone: An increased methadone dose may be required n a small number of pat ents (7 2)

See 17 for PATIENT COUNSELING INFORMAT ON and Medicat on Guide

REVISED MAY 2012

MX:ABCV:R2m/MX:MG:ABCV:R1m

FULL PRESCRIBING INFORMAT ON: CONTENTS*

*Sections or subsections omi ted from the u l prescr b ng nformation are not isted

FULL PRESCRIBING INFORMAT ON

WARNING: RISK OF HYPERSENS TIVITY REACT ONS LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

Hypersensit v ty Reactions: Serious and sometimes fatal hypersens tivity react ons have been assoc ated wi h abacav r (abacavir sulfate)

Hypersensit v ty to abacavir is a mu ti organ c inical syndrome usually characterized by a sign or symp om in two or more of he following groups: (1) fever (2) rash (3) gas rointestinal (including nausea vomit ng diarrhea or abdominal pain) (4) consti u ional (including generalized malaise a igue or achiness) and (5) respiratory (including dyspnea cough or pharyngitis) Discontinue abacavir as soon as a hypersens tivity reac ion is suspected

Patients who carry the HLA B*5701 allele a e at high risk for exper encing a hypersensit v ty reaction o abacavir Prior to n tiating therapy with abacav r screen ng for he HLA B*5701 a lele s recommended; his approach has been found to decrease he risk of hypersensit v ty reaction Screening is also recommended pr or to re ni ia ion of abacavir in pa ients of unknown HLA B*5701 status who have previously tolera ed abacavir HLA B*5701 negat ve pa ients may deve op a suspected hypersensit vi y reac ion to abacav r; however his occurs significan ly less frequently han in HLA B*5701 positive pat ents

Regardless of HLA B*5701 status permanently discontinue abacavir f hypersens tivity cannot be ruled out even when o her diagnoses are possible

Fol owing a hypersensitivi y reac ion to abacavir NEVER restart abacavir ablets or any other abacavir containing product because more severe symptoms can occur within hours and may inc ude life hrea ening hypotens on and death

Reintroduc ion of abacavir tab ets or any other abacavir containing product even in patients who have no den ified history or unrecogn zed symptoms of hypersensit vi y to abacavir therapy can result in serious or atal hype sensi ivity reactions Such reactions can occur within hours *[see Warn ngs and Precautions (5 1)]*

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepa omegaly w th steatosis including fa al cases have been reported with he use of nuc eoside analogues a one or in comb nation including abacavir and other antiretrovirals *[see Warnings and Precautions (5 2)]*

1 INDICATIONS AND USAGE

Abacavir tablets in combina ion w th other antiretroviral agents are ndicated for the reatment of human immunodefic ency virus (HIV 1) infec ion

Addit onal mportant informat on on the use of abacavir ablets or trea ment of HIV 1 infect on:

Abacavir tab ets are one of mu tiple products containing abacav r Befo e s ar ing abacavir tablets review medical history or prior exposure to any abacavir containing product in order to avoid reintroduction in a patient wi h a history of hypersensit vity to abacavir *[see Warnings and Precau ions (5 1) Adverse Reactions (6)]*

2 DOSAGE AND ADMINISTRATION

A Medication Guide and Warn ng Card that provide informat on about recogni ion of hypersens tivi y reac ions should be d spensed wi h each new prescr p ion and refi l

Abacavir tab ets may be taken with or w thout food

2 1 Adult Patien s

The recommended oral dose of abacavir tablets for adu ts is 600 mg dai y administered as e ther 300 mg twice daily or 600 mg once daily in combination wi h other an iretroviral agents

2 2 Pediatric Pa ients

The recommended oral dose of abacav r oral so ut on in HIV 1 nfected pediat ic patients aged 3 months and older is 8 mg kg twice dai y (up o a maximum of 300 mg wice da ly) n comb nat on w th other anti e roviral agents

Abacavir is also avai able as a scored tab et for H V 1 infected ped a ric pa ien s we ghing greater than or equal to 14 kg for whom a so id dosage form s appropriate Be ore prescribing abacavir ablets ch ldren should be assessed for the abi ity to swallow tablets f a chi d s unable to rel ably swal ow abacav r tablets the oral so ut on formulation shou d be prescribed The recommended oral dosage of abacav r tablets for HIV 1 infected pediatric patients is presented in Tab e 1

Table 1 Dosing Recommendations or Abacav r Tablets in Pediatric Pa ients

We ght (kg)	Dosage Regimen Us ng Scored Tablet		To al Da ly Dose
	AM Dose	PM Dose	
14 o 21	½ tab et (150 mg)	½ tab et (150 mg)	300 mg
> 21 to < 30	½ tab et (150 mg)	1 tablet (300 mg)	450 mg
≥ 30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

2 3 Pa ients with Hepatic mpairment

The recommended dose of abacavir tab e s in pat ents with mi d hepat c impa rment (Child Pugh score 5 to 6) is 200 mg tw ce daily To enable dose reduct on abacavir oral solut on (10 mL wice dai y) should be used or the rea ment of these pat ents The safety efficacy and pharmacok net c proper ies of abacavir have not been estab ished n pat ents with moderate o severe hepatic impa rment; there ore abacavir tab ets are contraind cated n hese pat ents

3 DOSAGE FORMS AND STRENGTHS

Abacavir Tablets USP are ava lable containing abacav r su fate USP equivalent to 300 mg of abacav r

The 300 mg tablets are peach fi m coated capsu e shaped scored tablets debossed w th **M** on one side of the score and **120** on the o her side of the score on one side of the tab et and blank on he other side

4 CONTRA NDICATIONS

Abacavir tab ets are contraind cated in patients w th:

prev ously demonstrated hypersensit v ty o abacav r or any o her component of the products NEVER restart abacav r tab ets or any other abacav r containing product o lowing a hypersens tivi y reac ion to abacav r regardless of HLA B*5701 status *[see Warnings and Precau ions (5 1) Adverse Reactions (6)]*

moderate or severe hepatic mpai ment *[see Dosage and Administration (2 3)]*

5 WARNINGS AND PRECAUTIONS

5 1 Hypersens tivity Reaction

Ser ous and somet mes fatal hypersens tiv ty reactions have been associated w th abacavir tab ets and other abacavir con a n ng produc s Pat ents who carry the HLA B*5701 allele are at high isk for experienc ng a hypersensit vity reac ion o abacavir Pr or to init a ing therapy w th abacavir screening for the HLA B*5701 al ele is recommended; his approach has been found o decrease he risk of a hypersensit v ty react on Screening s also recommended p ior to re n tiation of abacavir n patients of unknown HLA B*5701 sta us who have previously tolerated abacav r For HLA B*5701 posi ive pa ien s treatment with an abacav r containing reg men s not recommended and should be cons dered on y w th c ose medical supervision and under exceptional c rcumstances when the potent al benefit outwe ghs the risk

HLA B*5701 negative patients may develop a hypersens tivi y react on to abacav r; however th s occurs s gnificant y less requent y han in HLA B*5701 posit ve patients Regardless of HLA B*5701 status permanen ly discont nue abacavir if hypersensi ivity cannot be ruled out even when other diagnoses are possible

Impor ant nformation on signs and symptoms of hypersens tivi y as we l as clinical management s presented below

S gns and Symptoms of Hypersensi ivity: Hypersensit v ty to abacavir is a mul i organ cl n cal syndrome usual y characterized by a sign or symptom in two or more of the fol ow ng groups

Group 1: Fever

Group 2: Rash

Group 3: Gastro n est nal (includ ng nausea vomi ing d arrhea or abdominal pain)

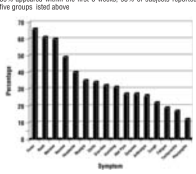
Group 4: Const tutional (includ ng generalized malaise fat gue or ach ness)

Group 5: Respi a ory (ncluding dyspnea cough or pharyngit s)

Hype sens tiv ty to abacavir fo lowing the presentat on of a sing e s gn or symptom has been reported infrequently

Hype sens tiv ty o abacavir was repor ed in approx mate y 8% of 2 670 subjects (n = 206) n nine cl n cal t ials (range: 2% to 9%) with enrol ment from November 1999 to February 2002 Da a on t me o onset and symptoms of suspec ed hypersensi ivity were co lected on a deta led data co lection module The requencies of symptoms are shown in F gure 1 Symptoms usual y appeared within the first 6 weeks of trea ment w th abacavir although he reaction may occur at any t me du ing therapy Med an t me to onset was 9 days; 89% appeared within the first 6 weeks; 95% of subjects reported symptoms from two or more of the five groups isted above

Figure 1 Hypersensit v ty re ated Symptoms Repo ted w th ≥ 10% Frequency in Cl nical Trials (n = 206 Subjects)



O her ess common signs and symp oms of hypersens tivi y include e hargy myolysis edema abnormal chest x ray find ngs (predominant y nfilt a es which can be ocal zed) and paresthesia Anaphylaxis iver failure renal a lure hypo ension adult resp ratory distress syndrome respiratory fa lure and death have occurred in associat on with hypersensi ivity react ons n one rial four subjects (11%) receiving abacavir 600 mg once da ly experienced hypo ension with a hypersensit v ty reaction compared wi h zero subjects receiving abacavir 300 mg twice daily

Physical find ngs associated with hypersens tivity to abacav r in some pat ents inc ude ymphadenopathy mucous membrane lesions (conjunctivi is and mouth ulcerations) and rash The rash usua ly appears macu opapular or urticarial but may be variable in appearance There have been reports of erythema mu tiforme Hypersensit v ty reac ions have occurred wi hout rash

Laboratory abnormali ies assoc ated with hypersensit v ty to abacavir n some pat ents nclude e evated iver funct on tests e evated creat ne phosphokinase e evated creat n ne and lymphopenia

Clinical Management of Hypersensi ivity: Discontinue abacavir as soon as a hypersensit v ty reaction s suspected To m n m ze the r sk of a ife threaten ng hypersensitiv ty react on permanen ly discontinue abacavir f hypersensit v ty cannot be ru ed out even when other diagnoses are possible (e g acute onset resp ratory d seases such as pneumonia bronchit s pharyng tis or influenza; gas roenterit s; or react ons to other medicat ons)

Following a hype sens tiv ty react on to abacav r NEVER restart abacav r tablets or any other abacavir conta n ng product because more severe symptoms can occur w th n hours and may nclude l fe threaten ng hypotension and death

When therapy wi h abacavir has been discont nued or reasons o her than symp oms of a hypersensit vity reaction and if reinit ation of abacavir tab e s or any other abacavir con a n ng product s under consideration careful y evaluate the reason for discont nuation of abacavir o ensure that the patient did not have symptoms of a hypersensit vity reaction If the patient s of unknown HLA B*5701 status screening for the allele is recommended prior o re n tiat on of abacavir

If hypersens tivi y cannot be ruled out DO NOT re ntroduce abacavir ablets or any other abacavir conta n ng product Even n the absence of the HLA B*5701 alle e t is important to permanen ly discontinue abacavir and not rechallenge w th abacavir f a hypersens tivity reaction cannot be ruled out on c inical grounds due to the potential for a severe or even atal react on

If symptoms consistent with hypersens tivi y are not dentified reintroduction can be unde taken w th con inued mon toring for symptoms of a hypersens tivi y reaction Make pat ents awa e that a hypersensit vity react on can occur with e nt oduct on of abacav r ablets or any o her abacavir conta ning product and that reintroduction of abacavir tab e s or any other abacavir con a n ng product needs to be under aken only f medical care can be readi y accessed by the pat ent or others

R sk Factor: HLA B*5701 Al e e: Tria s have shown that carr age of the HLA B*5701 al e e is associated w th a sign fican ly increased risk of a hypersensit vity reaction to abacav r

CNA106030 (PREDICT 1) a randomized doub e bl nd tr al evalua ed the clinical ut li y of prospective HLA B*5701 sc eening on the inc dence of abacav r hype sens tiv ty reaction n abacavir naive HIV 1 infected adul s (n = 1 650) In this trial use of pre therapy screening or the HLA B*5701 al ele and exclusion of subjects with h s al e e reduced the incidence of cl n ca ly suspected abacav r hypersensit vity react ons from 7 8% (66/847) to 3 4% (27/803) Based on this trial it s estimated that 61% of patients with the HLA B*5701 al e e will develop a c inically suspec ed hypersensit v ty reaction during he course of abacavir reatment compa ed wi h 4% of pat ents who do not have the HLA B*5701 a lele

Screening for carr age of he HLA B*5701 a lele is recommended pr or to init a ing treatment w th abacavir Sc eening is a so recommended pr or to re n tiat on of abacavir in patients of unknown HLA B*5701 status who have previous y to e a ed abacavir For HLA B*5701 pos tive pa ien s n tiat ng or re n tiat ng reatment w th an abacav r containing reg men s not recommended and should be cons dered only w th c ose med cal superv s on and under except onal circums ances where po ent al benefit outwe ghs the risk

Sk n patch tes ing s used as a research tool and should not be used to aid in the c inical diagnosis of abacavir hypersensi ivity

In any pat ent t eated with abacavir the cl n cal diagnosis of hypersens tivity reac ion must remain the basis of c inical dec s on mak ng Even in the absence of the HLA B*5701 al e e it s mportant to permanent y discontinue abacavir and not recha lenge with abacav r if a hypersens tiv ty reaction cannot be ru ed out on c inical grounds due to the po ent al for a severe or even fatal eaction

5 2 Lactic Ac dos s Severe Hepatomegaly with Steatosis

Lac ic ac dosis and severe hepatomegaly w th s eatosis nc uding fatal cases have been epo ted w th the use of nucleoside ana ogues alone or in combina ion inc uding abacav r and other ant retrov rals A majority of hese cases have been in women Obesity and pro onged nuc eoside exposure may be risk factors Par icu ar caution shou d be exerc sed when adm n stering abacavir o any pat ent with known r sk factors for liver disease; however cases have also been repor ed in pa ien s w th no known risk factors Treatment with abacavir should be suspended n any pa ient who deve ops cl n cal or laboratory findings suggestive of lactic acidosis or pronounced hepato oxic ty (which may include hepatomegaly and steatosis even n he absence of marked transaminase e evations)

5 3 Immune Reconst tu ion Syndrome

Immune reconsti ut on syndrome has been reported n pat ents treated with combination ant re rovi al therapy ncluding abacavir Dur ng the n tial phase of comb nat on ant retrov ral treatment patients whose immune systems respond may deve op an nflammatory response to ndolent or residual opportunist c nfect ons (such as *Mycobacterium avium* infection cytomegalov rus *Pneumocys is jirovecii* pneumonia [PCP] or tuberculos s) which may necessi a e further evaluation and treatment

Autoimmune disorders (such as Graves' disease polymyosit s and Gu lla n Ba ré syndrome) have also been reported to occur in the sett ng of immune recons itution however the ime to onset s more variable and can occur many mon hs after init a ion of trea ment

5 4 Fat Redistribution

Redistr bution/accumu a ion of body fat ncluding central obes ty dorsoce v cal fat enlargement (bu falo hump) peripheral was ing facial wast ng breast en argement and "cushingoid appearance" have been observed in pa ien s eceiving ant re roviral therapy The mechan sm and ong term consequences of these even s are currently unknown A causal relationship has not been estab ished

5 5 Myocardial Infarction

In a pub ished prospective observa ional epidem o ogical study designed to investigate the rate of myocardial nfarct on in pat ents on comb nat on ant retrov ral the apy the use of abacav r within the prev ous 6 months was corre ated w th an ncreased risk of myocard al infarction (MI) [1] In a sponsor conducted poo ed ana ys s of cl n cal rials no excess risk of myocardial infarc ion was observed in abacavir treated subjec s as compared with control subjects In o a ity he avai ab e data rom the observa ional cohort and from cl n cal tr a s a e inconc usive

As a precaut on the underlying risk of coronary heart d sease should be cons dered when prescribing antiretroviral therapies includ ng abacavir and action taken to m n m ze a l modifiable r sk fac ors (e g hypertens on hyper ipidem a diabetes mell tus smoking)

6 ADVERSE REACTIONS

The o lowing adverse reactions are discussed in greater detail in other sect ons of the labeling:

Ser ous and sometimes fatal hypersensit v ty react on In one trial once dai y dos ng of abacav r was assoc a ed wi h more severe hypersensit v ty eactions *[see Boxed Warning Warn ngs and Precautions (5 1)]*

Lac ic acidosis and severe hepa omega y *[see Boxed Warning Warn ngs and Precautions (5 2)]*

Immune reconst tu ion syndrome *[see Warnings and Precautions (5 3)]*

Fat redistribution *[see Warnings and Precautions (5 4)]*

Myocardial n arct on *[see Wa n ngs and Precau ions (5 5)]*

6 1 Clinical Trials Exper ence

Because cl n cal tria s are conducted under widely vary ng condit ons adverse react on rates obse ved n he cl n cal tr als of a drug cannot be d rec ly compared with rates in the cl n cal tr a s of another drug and may not reflect he rates observed n practice

Adults: *Therapy naive Adults:* Treatment emergent c in cal adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency dur ng the apy with abacav r 300 mg twice dai y am vudine 150 mg twice dai y and efav renz 600 mg daily compared w th zidovudine 300 mg twice dai y lamivudine 150 mg tw ce da ly and efav renz 600 mg daily from CNA30024 are listed in Tab e 2

Table 2 Treatment eme gent (All Causality) Adverse Reac ions of at Least Modera e In ensity (Grades 2 to 4 ≥ 5% Frequency) in Therapy naive Adults (CNA30024[a]) Through 48 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine p us Lamivudine plus Efavirenz (n = 325)
Dreams s eep disorders	10%	10%
Drug hypersensit v ty	9%	< 1%[b]
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
D a rhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastr tis/gastro n est nal signs and symptoms	6%	8%
Depressive disorders	6%	6%
D zziness	6%	6%
Musculoskeletal pain	6%	5%
B onchi is	4%	5%
Vomi ing	2%	9%

[a] Th s t ial used double blind ascertainment of suspected hype sens t vity reactions Dur ng the bl nded portion of he trial suspected hype sens t vity to abacavir was reported by nvest gato s n 9% of 324 subjects n the abacavir group and 3% of 325 subjects n the z dovud ne group

[b] Ten (3%) cases of suspected d ug hype sens t vity were reclass fied as not be ng due to abacav r following unbl nding

Treatment emergent clinical adverse react ons (rated by the nvestigator as moderate or severe) w th a greater han or equal to 5% frequency dur ng therapy w th abacavir 300 mg tw ce daily lamivudine 150 mg tw ce daily and zidovud ne 300 mg tw ce daily compared with indinav r 800 mg 3 t mes daily am vud ne 150 mg wice da ly and zidovud ne 300 mg twice dai y from CNA3005 are listed n Table 3

Tab e 3 Treatment emergent (All Causali y) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4 ≥ 5% Frequency) in Therapy na ve Adul s (CNA3005) Through 48 Weeks of Treatment

Adverse Reac ion	Abacavir plus Lamivudine Zidovudine (n = 262)	Indinav r plus Lam vudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and a igue	12%	12%
Nausea and vomi ing	10%	10%
Hypersensit v ty reac ion	8%	2%
Diarrhea	7%	5%
Fever and/or ch lls	6%	3%
Depress ve disorders	6%	4%
Musculoskeletal pa n	5%	7%
Sk n rashes	5%	4%
Ear/nose/throat infec ions	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs symptoms	< 1%	5%
Pa n (non s te specific)	< 1%	5%

F ve subjects receiving abacav r in CNA3005 experienced worsening of preexisting depress on compared with none in the indinavir a m The background rates of preexist ng depression were sim lar n the two treatment arms

Abacavir Once Dai y Versus Abacavir Twice Dai y (CNA30021): Treatment emergent cl n cal adverse eactions (ra ed by the investigator as at least modera e) with a grea er than or equal to 5% frequency during herapy w th abacavir 600 mg once dai y or abacav r 300 mg twice dai y both n comb nat on with lamivud ne 300 mg once dai y and efav renz 600 mg once da ly from CNA30021 were simi ar For hypersensi ivity reactions subjec s eceiving abacavir once daily showed a ra e of 9% in compar son with a rate of 7% for subjects rece v ng abacav r wice dai y However subjec s rece ving abacav r 600 mg once da ly experienced a significantly higher incidence of severe drug hypersensit v ty eactions and severe diarrhea compared wi h subjects who received abacavir 300 mg twice dai y F ve percent (5%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensit v ty eactions compared with 2% of subjects rece v ng abacav r 300 mg wice dai y Two percent (2%) of subjec s receiving abacav r 600 mg once dai y had severe diarrhea wh le none of the subjects receiv ng abacavir 300 mg wice da ly had h s event

Laboratory Abno ma ities: Labora ory abno mal ties (Grades 3 to 4) n therapy na ve adults dur ng herapy w th abacav r 300 mg tw ce dai y lamivud ne 150 mg wice da ly and efavirenz 600 mg da ly compared with zidovud ne 300 mg wice da ly am vud ne 150 mg twice da ly and efavirenz 600 mg dai y from CNA30024 are l sted n Table 4

Tab e 4 Labora ory Abnormali ies (Grades 3 o 4) in Therapy na ve Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3 4 Laboratory Abnormal ties	Abacavir plus Lamivudine p us Efavirenz (n = 324)	Zidovudine p us Lam vudine plus Efav renz (n = 325)
Elevated CPK (> 4 x ULN)	8%	8%
Elevated ALT (> 5 x ULN)	6%	6%
Elevated AST (> 5 x ULN)	6%	5%
Hypertriglyceridem a (> 750 mg/dL)	6%	5%
Hyperamylasemia (> 2 x ULN)	4%	5%
Neutropenia (ANC < 750 mm)	2%	4%
Anemia (Hgb ≤ 6 9 gm/dL)	< 1%	2%
Th ombocytopen a (P atelets < 50 000/mm³)	1%	< 1%
Leukopenia (WBC ≤ 1 500 mm³)	< 1%	2%

ULN Upper l mit of no mal

n Number of sub ects assessed

Laboratory abnormal ties n CNA3005 are isted in Table 5

Tab e 5 Treatment emergent Laboratory Abnormal ties (Grades 3 to 4) in CNA3005

Grade 3/4 Laboratory Abnormali ies	Number of Subjects by Treatment Group	
	Abacavir plus Lamivudine Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovud ne (n = 264)
Elevated CPK (> 4 x ULN)	18 (7%)	18 (7%)
ALT (> 5 x ULN)	16 (6%)	16 (6%)
Neutropenia (< 750/mm³)	13 (5%)	13 (5%)
Hypertriglyceridem a (> 750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (> 2 x ULN)	5 (2%)	1 (< 1%)
Hyperg ycemia (> 13 9 mmol L)	2 (< 1%)	2 (< 1%)
Anemia (Hgb ≤ 6 9 g dL)	0 (0%)	3 (1%)

ULN Upper l mit of no mal

n Number of sub ects assessed

The requencies of trea ment emergent laboratory abnormali ies were comparab e between reatment groups in CNA30021

Pediatric Trials: *Therapy experienced Pediatr c Subjects:* Treatment emergent cl n cal adverse react ons (a ed by the nvestigator as moderate or severe) wi h a greater than or equal to 5% frequency dur ng herapy w th abacav r 8 mg/kg twice da ly am vudine 4 mg/kg wice da ly and zidovud ne 180 mg/m² wice da ly compa ed w th lamivudine 4 mg/kg tw ce daily and z dovudine 180 mg/m² twice da ly from CNA3006 are isted in Table 6

Tab e 6 Treatment emergent (All Causal ty) Adverse React ons of at Least Moderate In ensity (Grades 2 to 4 ≥ 5% Frequency) in Therapy experienced Pediatr c Subjec s (CNA3006) Through 16 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine plus Z dovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or ch lls	9%	7%
Nausea and vomi ing	9%	2%
Sk n rashes	7%	1%
Ear/nose/throat infec ions	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

Laboratory Abnorma it es: n CNA3006 laboratory abnormal ties (anemia neut openia liver funct on est abnormal ties and CPK eleva ions) were observed w th simi ar frequencies as in a tr al of therapy naive adults (CNA30024) M ld e evat ons of blood glucose were more requent n pediatr c patients eceiving abacav r (CNA3006) as compared w th adult subjec s (CNA30024)

Other Adverse Events: In addit on to adverse react ons and abora ory abnorma it es reported in Tables 2 3 4 5 and 6 o her adverse react ons observed in the expanded access program were pancreat tis and inc eased GGT

6 2 Post marketing Exper ence

n addit on to adverse reac ions repor ed rom c in cal tr als he fol owing eactions have been iden ified during post marketing use of abacavir Because they are reported volun a ily from a popu a ion of unknown s ze estimates of frequency cannot be made These reac ions have been chosen for inclus on due o a combina ion of their se iousness frequency of report ng or potential causal connec ion to abacavir

Body as a Whole: Red s ribu ion/accumulation of body fat

Cardiovascular: Myocard al infarction

Hepat c: Lact c ac dosis and hepat c s eatosis

Skin: Suspected S evens Johnson syndrome (SJS) and tox c epidermal necrolysis (TEN) have been reported in pat ents rece v ng abacav r pr ma ily in combina ion w th medications known to be assoc ated with SJS and TEN respectively Because of the over ap of c inical s gns and symp oms between hypersens tivi y to abacavir and SJS and TEN and he possibi ity of mult p e drug sensit v ties n some pa ien s abacav r should be d scon inued and not res ar ed n such cases

The e have also been reports of erythema mult forme w th abacav r use

7 DRUG INTERACTIONS

7 1 E hanol

Abacavir has no effect on the pharmacok netic propert es of e hanol Ethanol decreases the el m nat on of abacavir causing an ncrease n overall exposure *[see Cl n cal Pharmacology (12 3)]*

7 2 Me hadone

The add tion of methadone has no c inically sign ficant ef ect on the pharmacok net c propert es of abacavir n a tr al of 11 HIV 1 infected subjects receiving me hadone ma ntenance therapy with 600 mg of abacavir tw ce daily (tw ce the currently recommended dose) oral methadone clearance ncreased *[see Cl n cal Pharmacology (12 3]* This a teration w ll not resu t in a me hadone dose modificat on in the major ty of pat ents; however an increased methadone dose may be requ red in a small number of pat ents

8 USE IN SPECIFIC POPULATIONS

8 1 Pregnancy

Teratogenic Effects: *Pregnancy Category C:* S udies in pregnant rats showed that abacavir s trans er ed to the e us through the placenta Fetal ma forma ions (increased incidences of fetal anasarca and skeletal mal ormations) and deve opmental tox c ty (depressed fetal body weight and educed c own rump length) were observed n rats at a dose wh ch produced 35 imes the human exposure based on AUC Embryon c and fetal tox c ties (ncreased resorptions decreased fetal body weights) and tox c ties to the of spring (increased inc dence of sti lbirth and ower body we ghts) occurred at ha f of the above mentioned dose in separate ferti ity studies conducted n rats In the rabb t no developmen al tox city and no ncreases n fetal malformations occurred at doses that produced 8 5 t mes he human exposure at the recommended dose based on AUC

The e are no adequate and we l cont ol ed studies in pregnant women Abacavir shou d be used dur ng pregnancy only if the potential benefits ou weigh he r sk

Antiretroviral Pregnancy Registry: To monitor ma ernal fetal outcomes of pregnant women exposed to abacavir an Ant retrov ral Pregnancy Registry has been estab ished Physicians are encouraged to register patients by ca ling 1 800 258 4263

8 3 Nursing Mothers

The Cen ers for D sease Control and Prevention recommend that HIV 1 infected mothers not breast feed their infants o avoid risking postna al transm ssion of H V 1 infection

Al hough t is not known if abacav r is excreted in human mi k abacavir s secreted into the m lk of actat ng rats Because of both he potential or H V 1 transmission and the potential for serious adverse react ons n nursing nfants mothers should be ins ructed not o breast feed if hey are receiving abacav r

8 4 Pedia ric Use

The safety and effectiveness of abacavir have been established n pediatr c pat ents 3 mon hs to 13 years of age Use of abacavir in these age groups is suppor ed by pharmacok net c trials and evidence from adequa e and we l control ed tr als of abacavir n adu ts and pediatr c patients *[see Dosage and Adm n stration (2 2) C inical Pharmacology (12 3) C in cal Studies (14 2)]*

8 5 Geriatric Use

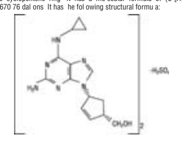
Cl n cal stud es of abacavir d d not nc ude sufficient numbe s of pat ents aged 65 and over to de erm ne whether they respond d fferently from younger patients n general dose selec ion for an elderly patient should be cautious reflec ing the greater frequency of decreased hepa ic renal or cardiac function and of concomi ant d sease or other drug herapy

10 OVERDOSAGE

The e is no known ant dote for abacavir It is not known whe her abacavir can be emoved by per toneal d a ys s or hemodia ysis

11 DESCRIPTION

Abacavir su fate is a synthe ic carbocycl c nuc eoside analogue with inhibitory act v ty against HIV 1 The chemical name of abacav r sul a e s (1*S cis*) 4 [2 amino 6 (cyclopropy am no) 9*H* pur n 9 yl] 2 cyclopentene 1 me hanol sul a e (sal) (2 1) Abacavir sulfate is the enantiomer with 1*S* 4*R* absolute configurat on on the cyclopentene ring It has a mo ecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecu ar weight of 670 76 dal ons It has he fol owing structural formu a:



MEDICATION GUIDE
ABACAVIR TABLETS, USP
(a bak′ a vir sul′ fate)
300 mg

Read this Medication Guide before you start taking abacavir tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to carry your Abacavir Tablets Warning Card with you at all times.

What is the most important information I should know about abacavir tablets?

1. Serious allergic reaction (hypersensitivity reaction). Abacavir tablets contain abacavir (also contained in EPZICOM®** and TRIZIVIR®**). Patients taking abacavir tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

If you get a symptom from two or more of the following groups while taking abacavir tablets, call your healthcare provider right away to find out if you should stop taking abacavir tablets.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry this Warning Card with you at all times.**

If you stop abacavir tablets because of an allergic reaction, never take abacavir tablets (abacavir sulfate) or any other abacavir-containing medicine (EPZICOM® and TRIZIVIR®**) again.** If you take abacavir tablets or any other abacavir-containing medicine again after you have had an allergic reaction, **within hours** you may get **life threatening symptoms** that may include **very low blood pressure** or **death**. If you stop abacavir tablets for any other reason, even for a few days, and you are not allergic to abacavir, talk with your healthcare provider before taking it again. Taking abacavir tablets again can cause a serious allergic or life threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take abacavir again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

2. Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir tablets, can cause a rare but serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.

Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:

- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you have stomach pain with nausea and vomiting
- you feel cold, especially in your arms and legs
- you feel dizzy or light-headed
- you have a fast or irregular heartbeat

3. Serious liver problems. Some people who have taken medicines like abacavir tablets have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.

Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- your urine turns dark
- your bowel movements (stools) turn light in color
- you don't feel like eating food for several days or longer
- you feel sick to your stomach (nausea)
- you have lower stomach area (abdominal) pain

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

What is abacavir?

Abacavir is a prescription medicine used to treat HIV infection. Abacavir is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Abacavir is always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir helps lower the amount of HIV in your blood.

- **Abacavir does not cure HIV infection or AIDS.**
- It is not known if abacavir will help you live longer or have fewer of the medical problems that people get with HIV or AIDS.
- It is very important that you see your doctor regularly while you are taking abacavir tablets.

Who should not take abacavir tablets?

Do not take abacavir tablets if you:

- **are allergic to abacavir or any of the ingredients in abacavir tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir tablets.**
- **have certain liver problems.**

What should I tell my healthcare provider before taking abacavir tablets?

Before you take abacavir tablets, tell your healthcare provider if you:

- **have been tested and know whether or not you have a particular gene variation called HLA-B*5701**
- **have hepatitis B virus infection or have other liver problems**
- **have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**
- **are pregnant or plan to become pregnant.** It is not known if abacavir will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **Pregnancy Registry.** If you take abacavir tablets while you are pregnant, talk to your healthcare provider about how you can take part in the Pregnancy Registry for abacavir tablets. The purpose of the pregnancy registry is to collect information about the health of you and your baby.
- **are breast-feeding or plan to breast-feed. Do not breast-feed.** We do not know if abacavir can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast-feed because HIV-1 can be passed to the baby in the breast milk.

- **Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.**

Especially tell your healthcare provider if you take:

- alcohol
- methadone
- TRIZIVIR®** (abacavir sulfate, lamivudine, and zidovudine)
- EPZICOM®** (abacavir sulfate and lamivudine)

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

Abacavir tablets may affect the way other medicines work, and other medicines may affect how abacavir tablets work.

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take abacavir tablets?

- **Take abacavir exactly as your healthcare provider tells you to take it.**
- **Abacavir is taken by mouth as a tablet or a liquid.**
- Abacavir tablets may be taken with or without food.
- Do not skip doses.
- Children aged 3 months and older can also take abacavir. The child's healthcare provider will decide the right dose and whether the child should take the tablet or liquid, based on the child's weight. The dose should not be more than the recommended adult dose.
- **Do not let your abacavir tablets run out.** If you stop your anti-HIV medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat. If you take too much abacavir, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of abacavir tablets?

- **Abacavir tablets can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See "What is the most important information I should know about abacavir tablets?"**
- **Changes in immune system (Immune Reconstitution Syndrome).** Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new or worse symptoms of infection after you start taking abacavir tablets.
- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including abacavir tablets.

  These changes may include:
  - more fat in or around your trunk, upper back and neck (buffalo hump), breast, or chest
  - loss of fat in your legs, arms, or face
- **Heart attack (myocardial infarction).** Some HIV medicines including abacavir tablets may increase your risk of heart attack.

The most common side effects of abacavir in adults include:

- bad dreams or sleep problems
- nausea
- headache
- tiredness
- vomiting

The most common side effects of abacavir in children include:

- fever and chills
- nausea
- vomiting
- rash
- ear, nose, or throat infections

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of abacavir tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store abacavir tablets?

- Store abacavir tablets at room temperature, at 20° to 25°C (68° to 77°F).
- Do not freeze abacavir tablets.
- **Keep abacavir tablets and all medicines out of the reach of children.**

General information for safe and effective use of abacavir tablets

Avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use abacavir for a condition for which it was not prescribed. Do not give abacavir tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about abacavir tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information that is written for healthcare professionals.

For more information call Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679).

What are the ingredients in abacavir tablets?

Active ingredient: abacavir sulfate, USP

Inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, titanium dioxide and yellow iron oxide.

This Medication Guide has been approved by the US Food and Drug Administration.

** The brand names mentioned are registered trademarks of their respective manufacturers.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad — 500 034, India
Code No.: MH/DRUGS/25/NKD/89

Manufactured for:
Mylan®
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

75006009

MARCH 2012
MX:MG:ABCV:R1m

Abacavir sulfate, USP is an off-white to cream colored crystalline powder with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient (log P) of approximately 1.20 at 25°C.

Abacavir tablets, USP are for oral administration. Each tablet contains abacavir sulfate, USP equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, titanium dioxide and yellow iron oxide.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir tablets are expressed in terms of abacavir.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir is an antiviral agent *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-1-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir concentration (C_{max}) was 3 ± 0.89 mcg/mL (mean ± SD) and $AUC_{(0-12 h)}$ was 6.02 ± 1.73 mcg•h/mL. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•h/mL.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In three subjects, the CSF $AUC_{(0-6 h)}$ to plasma abacavir $AUC_{(0-6 h)}$ ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5′-carboxylic acid) and glucuronyl transferase (to form the 5′-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination: Elimination of abacavir was quantified in a mass balance trial following administration of a 600 mg dose of ¹⁴C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose trials, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.8 ± 0.24 L/hr/kg (mean ± SD).

Effects of Food on Oral Absorption: Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasting states; therefore, abacavir tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of abacavir oral solution and abacavir tablets. Therefore, these products may be used interchangeably.

Special Populations: *Renal Impairment:* The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Hepatic Impairment: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of abacavir oral solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore abacavir is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 68 pediatric subjects. Following multiple-dose administration of abacavir 8 mg/kg twice daily, steady-state $AUC_{(0-12 h)}$ and C_{max} were 9.8 ± 4.56 mcg•h/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively *[see Use in Specific Populations (8.4)]*. In addition, to support dosing of abacavir scored tablet (300 mg) for pediatric patients 14 kg to greater than 30 kg, analysis of actual and simulated pharmacokinetic data indicated comparable exposures are expected following administration of 300 mg scored tablet and the 8 mg/kg dosing regimen using oral solution.

Geriatric Patients: The pharmacokinetics of abacavir have not been studied in patients over 65 years of age.

Gender: A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight.

Race: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Lamivudine and/or Zidovudine: Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-1-infected subjects were enrolled in a crossover trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Ethanol: Due to the common metabolic pathways of abacavir and ethanol via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-1-infected male subjects. Each subject received the following treatments on separate occasions: a single 600 mg dose of abacavir, 0.7 g/kg ethanol (equivalent to five alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone: In a study of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients. The addition of methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.

12.4 Microbiology

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1$_{IIIB}$ in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1$_{BaL}$ in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1 μM against HIV-1$_{IIIB}$ and HIV-1$_{BaL}$, respectively, and was 0.26 ± 0.18 μM against eight clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture and were also obtained from subjects treated with abacavir. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a trial of therapy-naive adults receiving abacavir 600 mg once daily (n = 384) or 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was similar between the two groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this trial showed that the RT substitutions that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily arm had a greater than 2.5-fold decrease in abacavir susceptibility with a median fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median fold decrease of 0.92 (range: 0.7 to 13).

Cross-resistance: Cross-resistance has been observed among NRTIs. Isolates containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Abacavir was administered orally at three dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Impairment of Fertility: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

14 CLINICAL STUDIES

14.1 Adults

Therapy-naive Adults: CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells/mm³ and median plasma HIV-1 RNA was 4.79 log_{10} copies/mL. The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (CNA30024)

Outcome	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder[a]	69% (73%)	69% (71%)
Virologic failures[b]	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons[c]	10%	11%

[a] Subjects achieved and maintained confirmed HIV-1 RNA ≤ 50 copies/mL (< 400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test 1.0 PCR).

[b] Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed ≤ 50 copies/mL by Week 48.

[c] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm³ in the group receiving abacavir and 155 cells/mm³ in the zidovudine group. Through Week 48, eight subjects (2%) in the group receiving abacavir (five CDC classification C events and three deaths) and five subjects (2%) on the zidovudine arm (three CDC classification C events and two deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naive adults were randomized to receive either abacavir (300 mg twice daily) plus COMBIVIR®** (lamivudine 150 mg/zidovudine 300 mg twice daily) or indinavir (800 mg 3 times a day) plus COMBIVIR®** twice daily. The trial was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA greater than 100,000 copies/mL. Trial participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count was 360 cells/mm³ and median baseline plasma HIV-1 RNA was 4.8 log_{10} copies/mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies/mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

Table 8. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	Abacavir plus Lamivudine/ Zidovudine (n = 262)	Indinavir plus Lamivudine/ Zidovudine (n = 265)
Responder[a]	49%	50%
Virologic failures[b]	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons[c]	11%	10%

[a] Subjects achieved and maintained confirmed HIV-1 RNA < 400 copies/mL.

[b] Includes viral rebound and failure to achieve confirmed < 400 copies/mL by Week 48.

[c] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 9.

Table 9. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	Abacavir plus Lamivudine/ Zidovudine (n = 262)		Indinavir plus Lamivudine/ Zidovudine (n = 265)	
	< 400 copies/mL	n	< 400 copies/mL	n
≥ 10,000 to ≤ 100,000	50%	166	48%	165
> 100,000	48%	96	52%	100

In subjects with baseline viral load greater than 100,000 copies/mL, percentages of subjects with HIV-1 RNA levels less than 50 copies/mL were 31% in the group receiving abacavir versus 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³ was observed in both treatment arms. Through Week 48, nine subjects (3.4%) in the group receiving abacavir (six CDC classification C events and three deaths) and three subjects (1.5%) in the group receiving indinavir (two CDC classification C events and one death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm³ (range: 21 to 918 cells/mm³) and the median baseline plasma HIV-1 RNA was 4.89 log_{10} copies/mL (range: 2.6 to 6.99 log_{10} copies/mL).

The outcomes of randomized treatment are provided in Table 10.

Table 10. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	Abacavir 600 mg q.d. plus EPIVIR®** plus Efavirenz (n = 384)	Abacavir 300 mg b.i.d. plus EPIVIR®** plus Efavirenz (n = 386)
Responder[a]	64% (71%)	65% (72%)
Virologic failures[b]	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons[c]	11%	13%

[a] Subjects achieved and maintained confirmed HIV-1 RNA < 50 copies/mL (< 400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1.0).

[b] Includes viral rebound, failure to achieve confirmed < 50 copies/mL (< 400 copies/mL) by Week 48, and insufficient viral load response.

[c] Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm³ in the group receiving abacavir 600 mg once daily and 200 cells/mm³ in the group receiving abacavir 300 mg twice daily. Through Week 48, six subjects (2%) in the group receiving abacavir 600 mg once daily (four CDC classification C events and two deaths) and ten subjects (3%) in the group receiving abacavir 300 mg twice daily (seven CDC classification C events and three deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Trials

Therapy-experienced Pediatric Subjects: CNA3006 was a randomized, double-blind trial comparing abacavir 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log_{10} copies/mL. Eighty percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was significantly higher in subjects receiving abacavir plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log_{10} copies/mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 log_{10} copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm³ in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells/mm³ in the group receiving lamivudine plus zidovudine.

15 REFERENCES

1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. Lancet. 2008;371 (9622):1417-1426.

16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir Tablets, USP are available containing abacavir sulfate, USP equivalent to 300 mg of abacavir.

The 300 mg tablets are peach film-coated, capsule-shaped, scored tablets debossed with M on one side of the score and 120 on the other side of the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-4105-91
carton of one bottle containing 60 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in original container with attached prescribing information that contains the Medication Guide and a Warning Card.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Information About Therapy with Abacavir Tablets

Hypersensitivity Reaction: Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir tablets, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir tablets. (The complete text of the Medication Guide is reprinted at the end of this document.)
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their doctor right away to determine if they should stop taking abacavir tablets.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir tablets are not immediately discontinued.
- that in one trial, more severe hypersensitivity reactions were seen when abacavir was dosed 600 mg once daily.
- to not restart abacavir tablets or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir tablets are stopped right away.
- that if they have interrupted abacavir for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart abacavir tablets or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- abacavir tablets should not be coadministered with EPZICOM®** (abacavir sulfate and lamivudine) Tablets or TRIZIVIR®** (abacavir sulfate, lamivudine, and zidovudine) Tablets.

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including abacavir tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Redistribution/Accumulation of Body Fat: Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.4)]*.

Information About HIV-1 Infection: Abacavir is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using abacavir tablets.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breast feed.** We do not know if abacavir can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast feed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

MEDICATION GUIDE
ABACAVIR TABLETS, USP
(a bak' a vir sul' fate)
300 mg

Read this Medication Guide before you start taking abacavir tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to carry your Abacavir Tablets Warning Card with you at all times.

What is the most important information I should know about abacavir tablets?

1. **Serious allergic reaction (hypersensitivity reaction).** Abacavir tablets contain abacavir (also contained in EPZICOM®** and TRIZIVIR®**). Patients taking abacavir tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

   If you get a symptom from two or more of the following groups while taking abacavir tablets, call your healthcare provider right away to find out if you should stop taking abacavir tablets.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, sore throat

   A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry the Warning Card with you at all times.**

   If you stop abacavir tablets because of an allergic reaction, never take abacavir tablets (abacavir sulfate) or any other abacavir-containing medicine (EPZICOM® and TRIZIVIR®**) again.** If you take abacavir tablets or any other abacavir-containing medicine again after you have had an allergic reaction, **within hours you may get life-threatening symptoms that may include very low blood pressure or death.** If you stop abacavir tablets for any other reason, even for a few days, and you are not allergic to abacavir, talk with your healthcare provider before taking it again. Taking abacavir tablets again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

   If your healthcare provider tells you that you can take abacavir again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

2. **Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir tablets, can cause a rare but serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.**

   Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:
   - you feel very weak or tired
   - you have unusual (not normal) muscle pain
   - you have trouble breathing
   - you have stomach pain with nausea and vomiting
   - you feel cold, especially in your arms and legs
   - you feel dizzy or light-headed
   - you have a fast or irregular heartbeat

3. **Serious liver problems. Some people who have taken medicines like abacavir tablets have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.**

   Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:
   - your skin or the white part of your eyes turns yellow (jaundice)
   - your urine turns dark
   - your bowel movements (stools) turn light in color
   - you don't feel like eating food for several days or longer
   - you feel sick to your stomach (nausea)
   - you have lower stomach area (abdominal) pain

   You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

What is abacavir?

Abacavir is a prescription medicine used to treat HIV infection. Abacavir is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Abacavir is always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir helps lower the amount of HIV in your blood.

- **Abacavir does not cure HIV infection or AIDS.**
- It is not known if abacavir will help you live longer or have fewer of the medical problems that people get with HIV or AIDS.
- It is very important that you see your doctor regularly while you are taking abacavir tablets.

Who should not take abacavir tablets?

Do not take abacavir tablets if you:

- **are allergic to abacavir or any of the ingredients in abacavir tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir tablets.**
- **have certain liver problems.**

What should I tell my healthcare provider before taking abacavir tablets?

Before you take abacavir tablets, tell your healthcare provider if you:

- **have been tested and know whether or not you have a particular gene variation called HLA-B*5701.**
- **have hepatitis B virus infection or have other liver problems.**
- **have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**
- **are pregnant or plan to become pregnant.** It is not known if abacavir will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

  Pregnancy Registry. If you take abacavir tablets while you are pregnant, talk to your healthcare provider about how you can take part in the Pregnancy Registry for abacavir tablets. The purpose of the pregnancy registry is to collect information about the health of you and your baby.
- **are breast-feeding or plan to breast-feed. Do not breast feed.** We do not know if abacavir can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast feed because HIV-1 can be passed to the baby in the breast milk.
- **Tell your healthcare provider about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- alcohol
- methadone
- TRIZIVIR®** (abacavir sulfate, lamivudine, and zidovudine)
- EPZICOM®** (abacavir sulfate and lamivudine)

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

Abacavir tablets may affect the way other medicines work, and other medicines may affect how abacavir tablets work.

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take abacavir tablets?

- **Take abacavir exactly as your healthcare provider tells you to take it.**
- **Abacavir is taken by mouth as a tablet or a liquid.**
- Abacavir tablets may be taken with or without food.
- Do not skip doses.
- Children aged 3 months and older can also take abacavir. The child's healthcare provider will decide the right dose and whether the child should take the tablet or liquid, based on the child's weight. The dose should not be more than the recommended adult dose.
- **Do not let your abacavir tablets run out.** If you stop your anti-HIV medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat. If you take too much abacavir, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of abacavir tablets?

- **Abacavir tablets can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See "What is the most important information I should know about abacavir tablets?"**
- **Changes in immune system (Immune Reconstitution Syndrome).** Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new or worse symptoms of infection after you start taking abacavir tablets.
- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including abacavir tablets.

  These changes may include:
  - more fat in or around your trunk, upper back and neck (buffalo hump), breast, or chest
  - loss of fat in your legs, arms, or face
- **Heart attack (myocardial infarction).** Some HIV medicines including abacavir tablets may increase your risk of heart attack.

The most common side effects of abacavir in adults include:

- bad dreams or sleep problems
- nausea
- headache
- tiredness
- vomiting

The most common side effects of abacavir in children include:

- fever and chills
- nausea
- vomiting
- rash
- ear, nose, or throat infections

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of abacavir tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store abacavir tablets?

- Store abacavir tablets at room temperature, at 20° to 25°C (68° to 77°F).
- Do not freeze abacavir tablets.
- **Keep abacavir tablets and all medicines out of the reach of children.**

General information for safe and effective use of abacavir tablets

Avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use abacavir for a condition for which it was not prescribed. Do not give abacavir tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about abacavir tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information that is written for healthcare professionals.

For more information call Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679).

What are the ingredients in abacavir tablets?

Active ingredient: abacavir sulfate, USP

Inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, titanium dioxide and yellow iron oxide.

This Medication Guide has been approved by the US Food and Drug Administration.

** The brand names mentioned are registered trademarks of their respective manufacturers.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad — 500 034, India
Code No.: MH/DRUGS/25/NKD/89

Manufactured for:
Mylan®
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

75006009

REVISED MAY 2012
MX:ABCV:R2m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

LABELING REVIEWS

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091294

Date of Submission: April 24, 2012, May 25, 2012 and June 8, 2012 (Amendments)

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Abacavir Tablets USP, 300 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

REMS Check Boxes
RISK EVALUATION AND MITIGATIONSTRATEGY

REMS required? No

MedGuides and/or PPIs (505-1(e))	☐ Yes ☒ No
Communication plan (505-1(e))	☐ Yes ☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes ☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes ☒ No
Timetable for assessment (505-1(d))	☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	FPL	Submission Date	Recommendation
Container – 60s	yes	4/24/2012	AC FOR AP
Carton – 1 x 60s	yes	4/24/2012	AC FOR AP
Insert (6 pts)	yes	5/25/2012	AC FOR AP
Medication Guide (9.5 pts)	yes	5/25/2012	AC FOR AP
Warning Card (6 pts)	yes	4/24/2012	AC FOR AP
SPL - DLDE	N/A	5/25/2012	AC FOR AP

REVISONS NEED POST-APPROVAL:

From: Park, Chan H
Sent: Friday, June 08, 2012 12:18 PM
To: 'Wayne.Talton@mylanlabs.com'
Cc: Lee, Koung U
Subject: ANDA 091284 (Abacavir Tablets)

Hi Wayne,

We note that the font size of the final printed medication guide submitted 5/25/2012 is 9.5 pts.
Please be advised that the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text.
Since your proposal is so close to the requirement, I may accept your proposal for approval, provided the Team Leader concurs. Please increase the font size of the medication guide to be 10 pts, at a minimum, post-approval. In addition, we note that the font size of the Warning Card is 6 pts. As this card contains very important safety information, we ask that you increase the font size significantly for sufficient readability. Please submit the revised medication guide and warning card in an annual report post-approval of this application. Thanks,

Chan,

*****MYLAN submitted the following commitment on 6/8/2012 in response to the above email:**

MYLAN'S RESPONSE: Mylan acknowledges the Agency's comments and commits to revise the Medication Guide to conform to the minimum 10 point font requirement as indicated in 21 CFR 208.20. Mylan also commits to increase the font size of the Warning Card for patient readability. Mylan will put these changes into effect post-ANDA approval and will report the revised final printed Medication Guide and Warning Card in the first Annual Report post-approval.

FOR THER ECORD:

---

1. MODEL LABELING - 020977/S-025 (Ziagen Tablets), approved 5/18/2012. The AP letter on this supplement indicates that the Ziagen® labeling was revised to remove the information associated with the Abacavir Hypersensitivity Reaction Registry. It was confirmed with the ONDQA that it is not necessary to maintain this registry anymore.

2. This drug product is now the subject of a USP monograph. (6/8/2012) There is no specific labeling requirement.

3. PF – No new information (6/8/2012)

4. This application was **NOT** filed under the provision of PEPFAR.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 3.2.p.1.

   Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, titanium dioxide and yellow iron oxide.

6. The iron element calculation;
   Maximum daily dose of the product is 600 mg once daily (two tablets a day).
   (b) (4)

7. PATENTS/EXCLUSIVITIES (6/8/2012)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	Patent Certification	Labeling Impact

020977	001	5034394	Dec 18, 2011		III	None
020977	001	5034394*PED	Jun 18, 2012			
020977	001	6294540	May 14, 2018	U-65	IV	None
020977	001	6294540*PED	Nov 14, 2018	U-65		

Exclusivity Data

There is no unexpired exclusivity for this product.

There is no unexpired exclusivity.
The sponsor's patent certifications and exclusivity statement is accurate.

U-65 METHOD OF TREATMENT OF A PATIENT INFECTED WITH HIV

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: "Store at 20 to 25oC (68 to 77oF). [see USP Controlled Room Temperature]"

9. DISPENSING STATEMENT

RLD - **Notice to Authorized Dispensers**: Each time Abacavir is dispensed, give the patient a Medication Guide and Warning Card from the carton.

ANDA - Same as the RLD

10. PACKAGING CONFIGURATIONS

RLD: Bottle of 60s and Unit-dose blister packs of 60 tablets
ANDA - Bottle of 60s (b) (4)

(b) (4)
(b) (4) the labeling submitted 5/25/2012 reflects only bottle of 60s. Refer to the email below:

From: "Park, Chan H" <Chan.Park@fda.hhs.gov>
To: "'Wayne.Talton@mylanlabs.com'" <Wayne.Talton@mylanlabs.com>
Cc: "Park, Chan H" <Chan.Park@fda.hhs.gov>
Date: 06/08/2012 12:56 PM
Subject: FW: ANDA 091284 (Abacavir Tablets)

Hi Wayne,

I have one more question. It appears that you are not seeking approval of the bottle (b) (4) Thanks,

Chan

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Friday, June 08, 2012 1:44 PM
To: Park, Chan H
Subject: Re: FW: ANDA 091284 (Abacavir Tablets)

Hi Chan

(b) (4)

(b) (4)

(b) (4).

Wayne

11. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

The 300 mg tablet is a peach film-coated, capsule shaped, scored tablet debossed with **M** on one side of the score and **120** on the other side of the score on one side of the tablet and blank on the other side

12. SCORING - RLD - Scored
ANDA - Scored

The sponsor submitted the CMC information regarding scored tablet in the amendment of December 1, 2009.

13. CONTAINER/CLOSURE

Configuration	Container	Closure
60's Bottle#	HDPE 100 cc White (b) (4) (b) (4)	Closure (b) (4) CR cap with safe gard (b) (4) (b) (4) Liner (b) (4)

 # The pack is part of original submission and therefore packaging details and supporting stability is part of original submission and hence not reproduced.

(b) (4)

14. This drug product is solely being manufactured by (b) (4)

15. REMS – No (6/8/2012)

16. MedWatch – No new information (6/8/2012)

17. The sponsor joined the Antiretroviral Pregnancy Registry.

Date of Review: 6/8/2012 **Date of Submission: 4/24/2012 & 5/25/2012**

Primary Reviewer: Chan Park **Date:**

Team Leader: Koung Lee **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHAN H PARK
06/11/2012

KOUNG U LEE
06/11/2012
For Wm. Peter Rickman

(TENTATIVE APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091294 Date of Submission: November 9, 2010

Applicant's Name: Matrix Laboratories, Inc.

Established Name: Abacavir Sulfate Tablets, 300 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

REMS Check Boxes
RISK EVALUATION AND MITIGATION STRATEGY

REMS required?
☒ Yes ☐ No

REMS acceptable?
☒ Yes ☐ No ☐ n/a

CONTAINER LABELS - 60s (b) (4)

Satisfactory in DRAFT as of the 11/9/10 submission

CARTON - 1 X 60s (b) (4)

Satisfactory in DRAFT as of the 11/9/10 submission

WARNING CARD

Satisfactory in DRAFT as of the 11/9/10 submission

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in DRAFT as of the 11/9/10 submission

MEDICATION GUIDE

Satisfactory in DRAFT as of the 11/9/10 submission

STRUCTURED PRODUCT LABELING

Satisfactory as of the 11/9/10 submission

FOR THE RECORD:

1. MODEL LABELING - 020977/S-019 (Ziagen Tablets), approved 12/19/08. It was approved for pediatric use with scored tablet. No W/H exclusivity was granted to the innovator for this new pediatric indication. The WARNING Card was last approved on 7/18/08 in 020977/S-017. The approval letter of 7/31/09 is for the fulfillment of the Post-marketing Commitments (PMC) only without associated revised labeling. 020977/S-020, approved 8/4/10, involves REMS change, in which the Medication Guide was not revised, but only in the schedule for submission of assessment. It will not affect the generic labeling.

2. This drug product is not the subject of a USP monograph.

3. This application was **NOT** filed under the provision of PEPFAR.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 3.2.p.1.

Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, titanium dioxide and yellow iron oxide.

5. The iron element calculation;

Maximum daily dose of the product is 600 mg once daily (two tablets a day)

(b) (4)

6. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	Patent Certification	Labeling Impact
020977	001	5034394	Dec 18, 2011		III	None
020977	001	5034394*PED	Jun 18, 2012			
020977	001	6294540	May 14, 2018	U-65	IV	None
020977	001	6294540*PED	Nov 14, 2018	U-65		

Exclusivity Data

There is no unexpired exclusivity for this product.

There is no unexpired exclusivity.
The sponsor's patent certifications and exclusivity statement is accurate.

U-65 METHOD OF TREATMENT OF A PATIENT INFECTED WITH HIV

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: "Store at 20 to 25oC (68 to 77oF). [see USP Controlled Room Temperature]"

8. DISPENSING STATEMENT

RLD - **Notice to Authorized Dispensers**: Each time Abacavir is dispensed, give the patient a Medication Guide and Warning Card from the carton.

ANDA - Same as the RLD

9. PACKAGING CONFIGURATIONS

RLD: Bottle of 60s and Unit-dose blister packs of 60 tablets
ANDA - Bottle of 60s (b) (4)

(b) (4)

10. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

The 300 mg tablet is a peach film-coated, capsule shaped, scored tablet debossed with **M** on one side of the score and **120** on the other side of the score on one side of the tablet and blank on the other side

11. SCORING - RLD - Scored

ANDA - Scored

The sponsor submitted the CMC information regarding scored tablet in the amendment of December 1, 2009.

12. CONTAINER/CLOSURE

Configuration	Container	Closure
60's Bottle#	HDPE 100 cc White Round (b) (4) (b) (4)	Closure (b) (4) CR cap with (b) (4) (b) (4) Liner (b) (4) (b) (4)

 # The pack is part of original submission and therefore packaging details and supporting stability is part of original submission and hence not reproduced.

(b) (4)

13. This drug product is solely being manufactured by (b) (4)

14. The sponsor committed that they will submit verification for the Hypersensitivity Reaction Registry at the time of expecting full approval. We will allow the sponsor include this information in the draft labeling for TA as has been the case in the past for another application.

15. **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

I. GOAL(S)

The goal of the REMS is to inform patients of the serious risks associated with Abacavir Sulfate Tablets, including for patients who carry the HLA-B*5701 allele the increased risk of developing abacavir hypersensitivity, which in some cases may be severe or fatal.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Abacavir Sulfate Tablets prescription. A complete copy of the Medication Guide appears at the end of the prescribing information (i.e., package outsert) which is attached to each 60 count (b) (4) bottle, which are contained in unit-of-use cartons. Each container label and package outsert includes a note to instruct the authorized dispenser to dispense a Medication Guide with each prescription. Pursuant to 21 CFR 208.24(d), this instruction appears prominently in red text on the principle display panel of each container label and indicates how the Medication Guide is provided. For the unit-of-use cartons which contain one 60 count (b) (4)t bottle, the statement reads "**Notice to Authorized Dispenser:** Each time abacavir sulfate tablets are dispensed, give the patient a Medication Guide and Warning Card from the carton."

Pursuant to 21 CFR 208.24(b)(1), the Medication Guide will be made available in sufficient numbers to US distributors of Abacavir Sulfate Tablets. US distributors will provide the Medication Guide with every pharmacy shelf container of Abacavir Sulfate Tablets to ensure its availability for dispensing to patients who are dispensed Abacavir Sulfate Tablets.

Please see the appended Medication Guide.

B. Communication Plan

Not applicable.

C. Elements to Assure Safe Use

Not applicable.

D. Implementation System

Not applicable.

E. Timetable for Submission of Assessments

Not applicable.

Date of Review:11/10/10	**Date of Submission: 11/9/10**
Primary Reviewer: Chan Park	**Date:**
Team Leader: Lillie Golson	**Date:**

C:\Documents and Settings\parkc\My Documents\91294.TA.LABELING.doc

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHAN H PARK
12/07/2010

LILLIE D GOLSON
12/08/2010

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-294 Date of Submission: January 28, 2009 and April 27, 2009

Applicant's Name: Matrix Laboratories, Inc.

Established Name: Abacavir Sulfate Tablets, 300 mg

Labeling Deficiencies:

1. CONTAINER - 60s

   a. Please print the pharmacy directive in color, preferably in red to enhance the prominence. In addition, relocate this to the principal display panel for better attention.

   b. It is preferable to revise to read "Each film-coated tablet…".

   c. The text on your label looks too cluttered. Please allow one space line between sections.

   d. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe that this package should comply with the Act. Please comment.

2. CARTON - 1 x 60s

   See comments under CONTAINER above.

3. (b) (4)

4.

5. WARNING CARD

   a. Revise the first paragraph of the front side to read as follows:

   (b) (4)

   b. Delete the sentence (b) (4) on the back side.

6. PACKAGE INSERT LABELING

a. GENERAL

i. Please note that the labeling for the reference listed drug, Ziagen® Tablets, was updated December 19, 2008. Please revise your labeling accordingly.

ii. Please be advised that the half page requirement for the highlight section **is only applicable if it** was printed in 2 columns on a standard size piece of typing paper (8 1/2 x 11), single spaced, in 8 point type with 1/2 inch margins on all sides and between columns. Please ensure that the highlight sections and the entire insert can easily be read and that the point type not be smaller than 6

iii Please include the margin markers designating the recent changes appearing in your proposal. We refer you to the innovator's labeling.

iv. Abacavir Hypersensitivity Reaction Registry

We note that you included information regarding the Abacavir Hypersensitivity Reaction Registry. Please submit your commitment that you will put this registry in place prior to full approval of your application. You are required to join this registry for full approval.

b. HIGHLIGHTS of PRESCRIBING INFORMATION

i. BOXED WARNING

Add a bullet to the text "Discontinue abacavir sulfate…possible (5.1)" and relocate to be the 4th bulleted text.

ii. RECENT MAJOR CHANGES

Please include the dates appearing in the innovator's labeling, not your own.

iii. DOSAGE FORMS AND STRENGTHS

You indicated that your tablet is scored. However, the CMC information regarding your finished drug product does not support this. Please be advised that the innovator's 300 mg tablet is scored for pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage from is appropriate. It has been the Agency's policy that the generic firms' drug product should follow the same scoring configuration of the innovator's product. Please revise the scoring configuration of your drug product and revise the labeling accordingly, wherever necessary. In addition, please submit all CMC information associated with the scoring change.

c. FULL PRESCRIBING INFORMATION

i. 2.2 Pediatric Patients

A) See comment 6(b)(iii) above.

B) Revise the 1st sentence to read "Abacavir sulfate is available as…" [delete "also"]

ii. DOSAGE FORMS AND STRENGTHS

See comment 6(b)(iii) above.

iii. 6 ADVERSE REACTIONS

(b) (4)

iv. DESCRIPTION

We note that your drug product contains iron complexes. In accordance with the 21 CFR 73.1200(c), the amount of elemental iron contained in the formulation cannot exceed 5 mg per day at the maximum recommended dosage. Please provide calculations of the amount of elemental iron of this product if consumed at the maximum daily recommended dosage.

v. 16 HOW SUPPLIED/STORAGE AND HANDLING
See comment 6(b)(iii) above.

7. MEDICATION GUIDE

a. We note that you did not submit your proposal for a separate medication guide to be dispensed to patients. Please submit one.

b. Please note that the point type for the final printed medication guide may not be smaller than 10. We refer you to 21 CFR 208.20 for guidance.

c. You are responsible for ensuring that this medication guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24]. Please explain how you will comply with this requirement.

d. Include the disclaimer statement for the proprietary names appearing in the medication guide.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Dr. Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Note to Chemist:

From: Park, Chan H
Sent: Wednesday, September 23, 2009 10:26 AM
To: Bain, Sam
Cc: Park, Chan H
Subject: 91-294

Hi Sam,

I am asking the sponsor to change the unscored tablet to be scored to be the same as the RLD and submit all associated CMC information. Thanks,

Chan

FOR THE RECORD:

1. MODEL LABELING - 20-977/S-019 (Ziagen Tablets), approved 12/19/08. It was approved for the pediatric use with scored tablet. No W/H exclusivity was granted to the innovator for this new pediatric indication. The WARNING Card was last approved on 7/18/08 in 20-977/S-017. the approval letter of 7/31/09 is for the fulfillment of the Post-marketing Commitments (PMC) only without associated revised labeling.

2. This drug product is not the subject of a USP monograph.

3. This application was **NOT** filed under the provision of PEPFAR.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 3.2.p.1.

5. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	Patent Certification	Labeling Impact
020977	001	5034394	Dec 18, 2011		III	None
020977	001	5034394*PED	Jun 18, 2012			
020977	001	5089500	Jun 26, 2009	U-248	III	None
020977	001	5089500*PED	Dec 26, 2009			
020977	001	6294540	May 14, 2018	U-65	IV	None
020977	001	6294540*PED	Nov 14, 2018	U-65		

Exclusivity Data

There is no unexpired exclusivity for this product.

There is no unexpired exclusivity.
The sponsor's patent certifications and exclusivity statement is accurate.

U-248 TREATMENT OF HIV
U-65 METHOD OF TREATMENT OF A PATIENT INFECTED WITH HIV

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: "Store at 20 to 25oC (68 to 77oF). [see USP Controlled Room Temperature]"

8. DISPENSING STATEMENT

RLD - Notice to Authorized Dispensers: Each time Abacavir is dispensed, give the patient a Medication Guide and Warning Card from the carton.

ANDA - See comment 1(a) above.

9. PACKAGING CONFIGURATIONS

RLD: Bottle of 60s and Unit-dose blister packs of 60 tablets
ANDA - Bottle of 60s, (b) (4). See comment 1(b) above.

10. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

Peach colored capsule shaped, (b) (4) film coated tablet, (b) (4)

11. SCORING - RLD - Scored

ANDA - Unscored. See comment 6(c)(ii) above.

12. CONTAINER/CLOSURE

Summary of the container closure system

Type	Description	Supplier	DMF
Container	(b) (4) HDPE Bottles	(b) (4)	(b) (4)
Closure	(b) (4) CR plastic caps (b) (4)		
Lidding Foil	(b) (4)		
Forming Film			
Forming Film			

13. This drug product is solely being manufactured by (b) (4)

14. Regarding the Hypersensitivity Reaction Registry, refer to the e-mail from Cecelia Parise below:
It should be reviewed for the TA but they won't need to have it in place (activated) until the application is fully approved. They should include a commitment prior to TA to have the registry in place prior to full approval and this should be noted in the TA letter.
The same type of procedure should be followed for the pregnancy registry for the PEPFAR since the TA may be issued several years prior to the full approval.
Cec

15. The submission of 4/27/09 was assigned as MC, but it contains labeling. It should have been assigned as a labeling amendment. It was notified to the D.R.

Date of Review: 9/23/09	**Date of Submission: 1/28/09 & 4/27/09**
Primary Reviewer: Chan Park	**Date:**
Team Leader: Lillie Golson	**Date:**

V:\FIRMSAM\MATRIX LABORATORIES\LTRS&REV\91294NA1.LABELING.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHAN H PARK
09/28/2009

LILLIE D GOLSON
09/28/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

CHEMISTRY REVIEWS

APPROVABLE

REVIEW #: 5

ANDA 091294

Abacavir Sulfate Tablets USP, 300 mg

Mylan Pharmaceuticals Inc.

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 091294

2. REVIEW #: 5

3. REVIEW DATE: 10-MAY-2012, 11-JUN-2012

4. REVIEWER: Sukhamaya (Sam) Bain, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Location
Original Submission	28-JAN-2009	Vol 1.1-1.6
Amendment	27-APR-2009	Vol 2.1
Amendment	27-AUG-2009	EDR
Chemistry Review #1	28-SEP-2009	DARRTS
Amendment	01-DEC-2009	EDR
Amendment	25-MAR-2010	EDR
Chemistry Review #2	14-SEP-2011	DARRTS
Gratuitous Amendment	09-NOV-2010	EDR
Chemistry Review #2a	30-NOV-2010	DARRTS
Amendment	09-FEB-2011	EDR
Chemistry Review #3*	14-FEB-2011	DARRTS
Post-TA Amendment	17-AUG-2011	EDR
Chemistry Review #4	21-DEC-2011	DARRTS

* Tentative approval of the ANDA.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Amendment*	05-APR-2012	EDR
Gratuitous Amendment	14-MAY-2012	EDR
Telephone Amendment	08-JUN-2012	EDR

* Request for the final approval of the ANDA.

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.*
	781 Chestnut Ridge Road
Address	P.O. Box 4310
	Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

* Transfer of ownership of the ANDA from Matrix to Mylan has been acknowledged by the Agency; T. W. Ames, 30-DEC-2009.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Abacavir Sulfate Tablets USP

9. LEGAL BASIS FOR SUBMISSION:

RLD: Ziagen
Applicant: GlaxoSmithKline
NDA Number: 020977
Approval Date: 17-DEC-1998

Patent Certification: Module 1.3.5.2

Following are the unexpired patents that claim the RLD:

US Patent #	Expiration Date	Expiration Date with Pediatric Exclusivity
5034394	18-DEC-2011	18-JUN-2012
6294540	14-MAY-2018	14-NOV-2018

The firm provides Paragraph III certification for patents 5034394, and Paragraph IV certification for patent 6294540.

Exclusivity Statement: Module 1.3.5.2

There is no unexpired exclusivity that covers the RLD.

10. PHARMACOL. CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

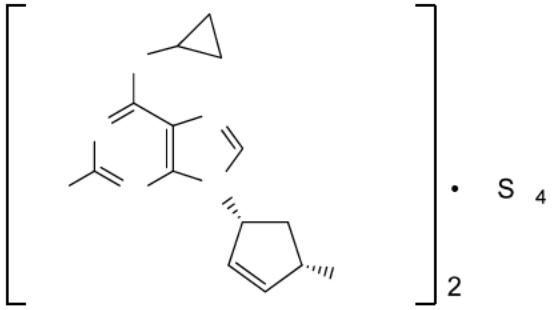
_____NANO product – Form Completed (See Appendix A.4)

__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (*1S,4R*)-4-[2-Amino-6-(cyclopropylamino)-*9H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate

Structural Formula:



Molecular Formula: $(C_{14}H_{18}N_6O)_2, H_2SO_4$

Molecular Weight: 670.76

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Module 1.4.1

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER/ DATE
18229	II	Matrix Laboratories Ltd	Abacavir Sulfate	3	Adequate	S. Bain 10-MAY-2012
[redacted]			(b) (4)	4		
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[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		
EES	Pending	09-APR-2012	EES PROD
Methods Validation	Satisfactory	11-JUN-2012	S. Bain
Labeling	Satisfactory	11-JUN-2012	C. H. Park
Bioequivalence	Satisfactory	19-FEB-2010	C. H. lee
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 091294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

Note: This Chemistry Review #5 (CR5) is for the applicant's request for the final approval of the ANDA.

The ANDA was tentatively approved by the Office on 15-FEB-2011. Since then the firm has submitted one more CMC amendment, other than this current one. That amendment, dated 17-AUG-2011, provided for the firm to fulfill their commitment of scoring the tablets as per the RLD, and was approved by the Office on 21-DEC-2011.

This current CR5 cumulatively includes reviews (CR1, CR2 and CR3) of all pre-tentative approval information, along with the review of the current submissions, dated 05-APR-2012, 14-MAY-2012 and 08-JUN-2012. For the review (CR4) of the post-tentative approval submission dated 17-AUG-2011, please see the DARRTS document dated 21-DEC-2011.

A. Description of the Drug Product(s) and Drug Substance(s)

Abacavir Sulfate Tablet, 300 mg, are peach, film-coated, capsule shaped, biconvex, beveled edge tablets, debossed with M on one side of the score and 120 on the other side of the score on one side of the tablet and blank on the other side.

The drug product contains the active ingredient, Abacavir Sulfate, which is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25 ºC. [redacted] (b) (4) partition coefficient (log P) of approximately 1.20 at 25 ºC.

The tablets contain the following inactive ingredients: Colloidal Silicon Dioxide NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Sodium Starch

Glycolate NF, Hypromellose USP, Iron Oxide Red, Polyethylene Glycol NF, Synthetic Yellow Iron Oxide, and Titanium Dioxide NF.

B. Description of How the Drug Product is Intended to Be Used

A Medication Guide and Warning Card that provides information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

The drug product may be taken orally with or without food. The recommended oral dose for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

C. Basis for Approvability or Not-Approval Recommendation

No Chemistry deficiency.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer: SBain	Date: 10-MAY-2012, 11-JUN-2012
Team Leader: PCapella	Date: 04-JUN-2012, 11-JUN-2012
Project Manager: TNhu	Date:

C. CC Block

Chemistry Assessment

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

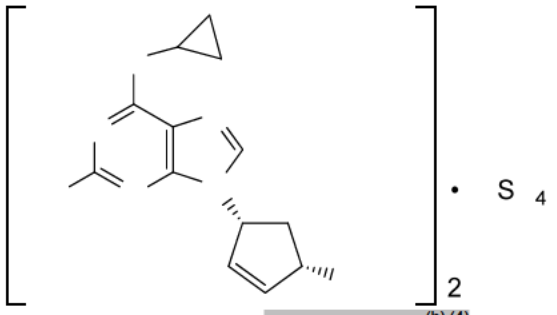
S DRUG SUBSTANCE

S.1 General Information: Satisfactory

What are the nomenclature, molecular structure, molecular formula, and molecular weight and CAS Registry No.?

Firm's Response Edited by the Reviewer:

Generic Name: Abacavir Sulfate
Chemical Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]- 2-cyclopentene-1-methanol Sulfate
Molecular Structure:



Molecular Formula: (b) (4)
Molecular Weight: (b) (4)
CAS #: [188062-50-2]

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

What are the physicochemical properties including physical description, solubility, pH, pKa potential isomerism polymorphism and partition coefficient?

Firm's Response Summarized by the Reviewer:

Description: Off-white to cream color crystalline powder.
Solubility: Soluble in water across (b) (4)

(b) (4)

Potential Isomerism: The drug substance molecule has two chiral centers, which provide for four possible sterioisomers.

(b) (4)

Reviewer's Assessments: Satisfactory; the firm's response is adequate.

S.2 Manufacture: Satisfactory

Who manufactures the drug substance?

Firm's Response Summarized by the Reviewer:

Matrix Laboratories Limited (Unit-8)
G.Chodavaram Village, Pusapatirega (M),
Vizianagaram District,
Andhra Pradesh, India

Establishment Registration #3002785310
Satisfactory FDA Inspection Date: May, 2006

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; M. Manzoni, 21-JAN-2010.

S.3 Characterization: Satisfactory

How was the drug substance structure elucidated and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency.

How were potential impurities identified and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229, and identifies the following impurities in the drug substance:

(b) (4)

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency. The firm's response is adequate. We note that the applicant monitors all of these impurities for the release and stability of the drug product.

S.4 Controls of Drug Substance: Satisfactory

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Firm's Response Summarized by the Reviewer:

Applicant's Specification for Abacavir Sulfate (Please see the updated specification at the end of this module):

Test	Specification
Description	Off-white to cream colored crystalline powder
Solubility	(b) (4) soluble in water, (b) (4)

Identification: IR HPLC Chemical Test	Spectrum matches that of the standard. Retention time matches that of the standard. (b) (4)

(b) (4)

Reviewer's Assessments: Satisfactory.

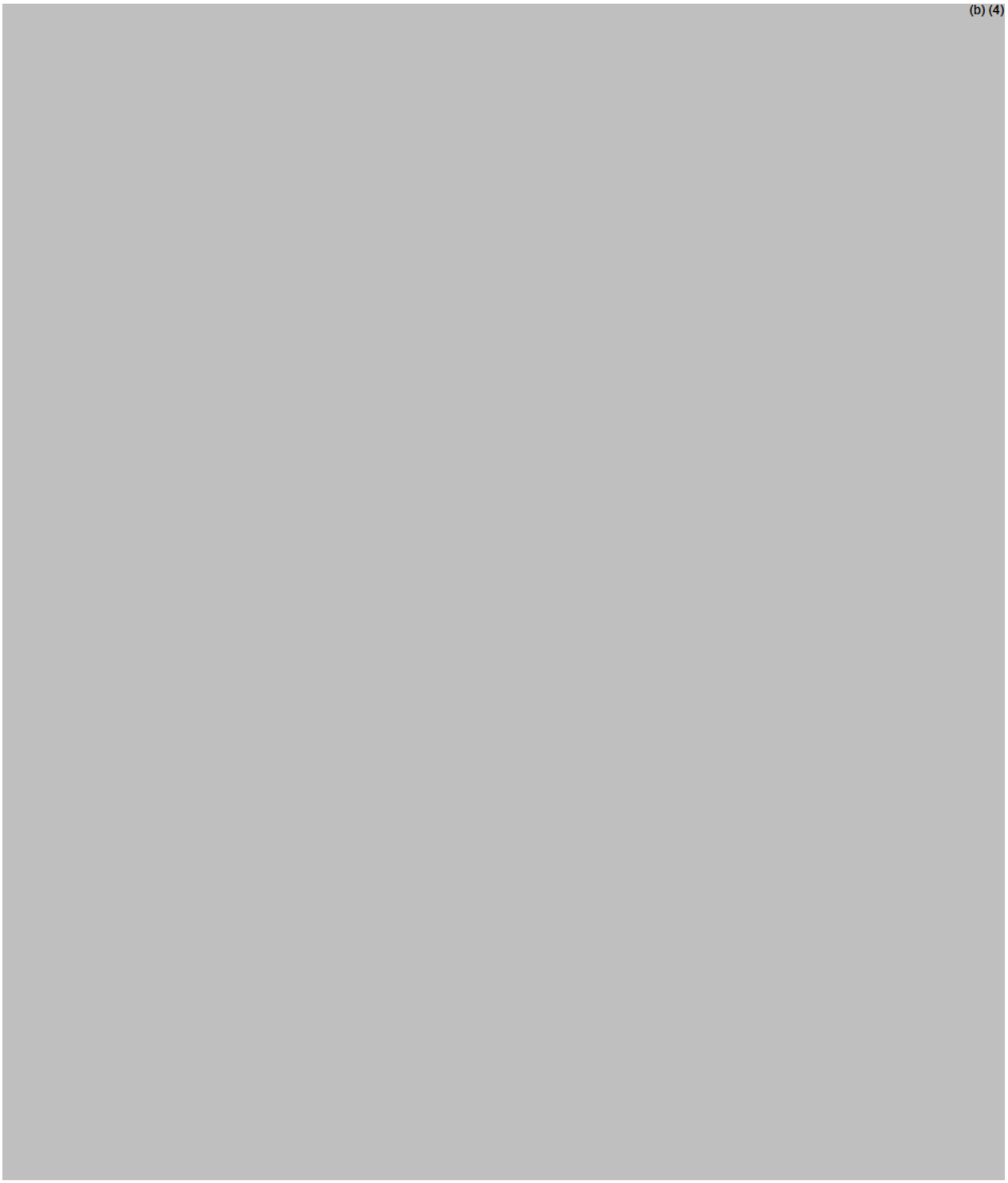
The drug substance specification is similar/same as what have been acceptable to the Agency (ANDAs 78-119, 78-742).

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Firm's Response Summarized by the Reviewer:

The firm refers to ICH and Agency guidelines and test results using validated methods to justify the specification for the drug substance.

(b) (4)



III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 091294 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets USP, 300 mg.

No Chemistry deficiency.

Sincerely yours,

Glen J. Smith, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 091294
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/S.Bain/10-MAY-2012, 11-JUN-2012

HFD-640/PCapella/04-JUN-2012, 11-JUN-2012
HFD-617/TNhu/13-JUN-2012

F/T by/

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
06/13/2012

PETER CAPELLA
06/14/2012

TINA T NHU
06/14/2012

ENDORSEMENTS:

Primary Reviewer	S. Bain, 03-NOV-2011
Team Leader	P. Capella, 19-DEC-2011
Project Manager	S. Eng 12-20-11

ANDA: 091294

DRUG PRODUCT NAME: Abacavir Sulfate Tablets, 300 mg

APPLICANT:

ANDA Holder Name	Mylan Pharmaceuticals Inc.
Address	1-1-151/1 4th Floor, Sairam Towers Alexander Road, Secunderabad, 500 003 Andhra Pradesh, India
US Agent	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Contact Name	S. Wayne Talton
Contact Phone	(304) 599-2595
Contact Fax	(304) 285-6407

ANDA TENTATIVE APPROVAL DATE: 15-FEB-2011

AMENDMENT DATE:

Submission Type	Submission Date	DARRTS Doc #	Location
Original Amendment	17-AUG-2011	15	EDR

PURPOSES OF THE AMENDMENT:

Fulfillment of commitment made on February 9, 2011, related to tablet scoring.

CHEMISTRY EXECUTIVE SUMMARY:

The applicant has provided adequate documentation, including an executed batch record for the scored tablets, executed batch COA, and a comparison of the dissolution profiles of the new executed batch and the bioequivalence batch, to fulfill the aforementioned commitment. The amendment is acceptable.

DETAILED CHEMISTRY ASSESSMENT:

In support of the changes, the applicant has provided the following:

- An executed batch record for the scored tablets. Batch #1068110; (b) (4) tablets, the same as the bio batch. The applicant notes that the EBR includes up to the manufacturing stage, as the packaging activity was underway on the date of the amendment submission. The new EBR is similar to the original exhibit batch record, with

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Mylan Pharmaceuticals Inc.
Agent Matrix Laboratories Limited
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your amendment dated August 17, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application (ANDA) for the drug product, Abacavir Sulfate Tablets, 300 mg.

This ANDA was tentatively approved on February 15, 2011.

The amendment provides for Fulfillment of commitment made on February 9, 2011, related to tablet scoring.

We have completed the review of this amendment and have determined that the amendment is acceptable.

There is no change in the status of your application, and ANDA 091294 remains tentatively approved.

The material submitted is being retained in our files.

Sincerely yours,

Glen J. Smith, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
12/21/2011

PETER CAPELLA
12/21/2011

SIMON S ENG
12/21/2011

ANDA 091294

Abacavir Sulfate Tablets, 300 mg

Mylan Pharmaceuticals Inc.

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 091294

2. REVIEW #: 3

3. REVIEW DATE: 10-FEB-2011

4. REVIEWER: Sukhamaya (Sam) Bain, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Location
Original Submission	28-JAN-2009	Vol 1.1-1.6
Amendment	27-APR-2009	Vol 2.1
Amendment	27-AUG-2009	EDR
Amendment	01-DEC-2009	EDR
Amendment	25-MAR-2010	EDR
Gratuitous Amendment	09-NOV-2010	EDR

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Amendment	09-FEB-2011	EDR

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.*
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

* Transfer of ownership of the ANDA from Matrix to Mylan has been acknowledged by the Agency; T. W. Ames, 30-DEC-2009.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Abacavir Sulfate Tablets

9. LEGAL BASIS FOR SUBMISSION:

RLD: Ziagen
Applicant: GlaxoSmithKline
NDA Number: 020977
Approval Date: 17-DEC-1998

Patent Certification: Module 1.3.5.2

Following are the unexpired patents that claim the RLD:

US Patent #	Expiration Date	Expiration Date with Pediatric Exclusivity
5034394	18-DEC-2011	18-JUN-2012
6294540	14-MAY-2018	14-NOV-2018

The firm provides Paragraph III certification for patents 5034394, and Paragraph IV certification for patent 6294540.

Exclusivity Statement: Module 1.3.5.2

There is no unexpired exclusivity that covers the RLD.

10. PHARMACOL. CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

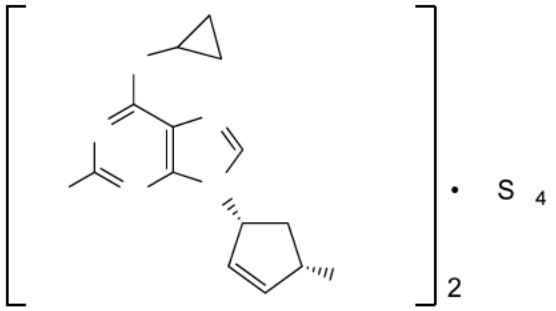
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (*1S,4R*)-4-[2-Amino-6-(cyclopropylamino)-*9H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate

Structural Formula:



Molecular Formula: $(C_{14}H_{18}N_6O)_2, H_2SO_4$

Molecular Weight: 670.76

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs: Module 1.4.1

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER/ DATE
18229	II	Matrix Laboratories Ltd	Abacavir Sulfate	3	Adequate	M. Pineiro-Sanchez 10-NOV-2010
(b) (4)	IV	(b) (4)		4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		
EES	Acceptable	04-OCT-2010	A. Inyard
Methods Validation	Satisfactory	17-FEB-2010	S. Bain
Labeling	Satisfactory	07-DEC-2010	C. Park
Bioequivalence	Satisfactory	19-FEB-2010	C. H. lee
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 091294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abacavir Sulfate Tablet, 300 mg, are peach, film-coated, capsule shaped, biconvex, beveled edge tablets, debossed with M on one side of the score and 120 on the other side of the score on one side of the tablet and blank on the other side.

The drug product contains the active ingredient, Abacavir Sulfate, which is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25 ºC. It has an (b) (4) partition coefficient (log P) of approximately 1.20 at 25 ºC.

The tablets contain the following inactive ingredients: Colloidal Silicon Dioxide NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Sodium Starch Glycolate NF, Hypromellose USP, Iron Oxide Red, Polyethylene Glycol NF, Synthetic Yellow Iron Oxide, and Titanium Dioxide NF.

B. Description of How the Drug Product is Intended to Be Used

A Medication Guide and Warning Card that provides information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

The drug product may be taken orally with or without food. The recommended oral dose for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

C. Basis for Approvability or Not-Approval Recommendation

No Chemistry deficiency.

Chemistry Assessment

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

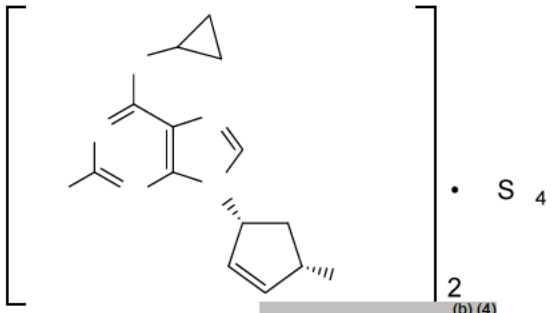
S DRUG SUBSTANCE

S.1 General Information: Satisfactory

What are the nomenclature, molecular structure, molecular formula, and molecular weight and CAS Registry No.?

Firm's Response Edited by the Reviewer:

Generic Name: Abacavir Sulfate
Chemical Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]- 2-cyclopentene-1-methanol Sulfate
Molecular Structure:



Molecular Formula: (b) (4)
Molecular Weight: (b) (4)
CAS #: [188062-50-2]

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

What are the physicochemical properties including physical description, solubility, pH, pKa potential isomerism polymorphism and partition coefficient?

Firm's Response Summarized by the Reviewer:

Description: Off-white to cream color crystalline powder.
Solubility: Soluble in water (b) (4)
(b) (4)

Potential Isomerism: The drug substance molecule has two chiral centers, which provide for four possible sterioisomers.

(b) (4)

Reviewer's Assessments: Satisfactory; the firm's response is adequate.

S.2 Manufacture: Satisfactory

Who manufactures the drug substance?

Firm's Response Summarized by the Reviewer:

Matrix Laboratories Limited (Unit-8)
G.Chodavaram Village, Pusapatirega (M),
Vizianagaram District,
Andhra Pradesh, India

Establishment Registration #3002785310
Satisfactory FDA Inspection Date: May, 2006

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; M. Manzoni, 21-JAN-2010.

S.3 Characterization: Satisfactory

How was the drug substance structure elucidated and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency.

How were potential impurities identified and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229, and identifies the following impurities in the drug substance:

(b) (4)

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency. The firm's response is adequate. We note that the applicant monitors all of these impurities for the release and stability of the drug product.

S.4 Controls of Drug Substances: Satisfactory

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Firm's Response Summarized by the Reviewer:

Applicant's Specification for Abacavir Sulphate:

Test	Specification
Description	Off-white to cream colored crystalline powder
Solubility	(b) (4) soluble in (b) (4) water,
Identification:	

IR HPLC Chemical Test	Spectrum matches that of the standard. Retention time matches that of the standard. (b) (4)

(b) (4)

Reviewer's Assessments: Satisfactory.

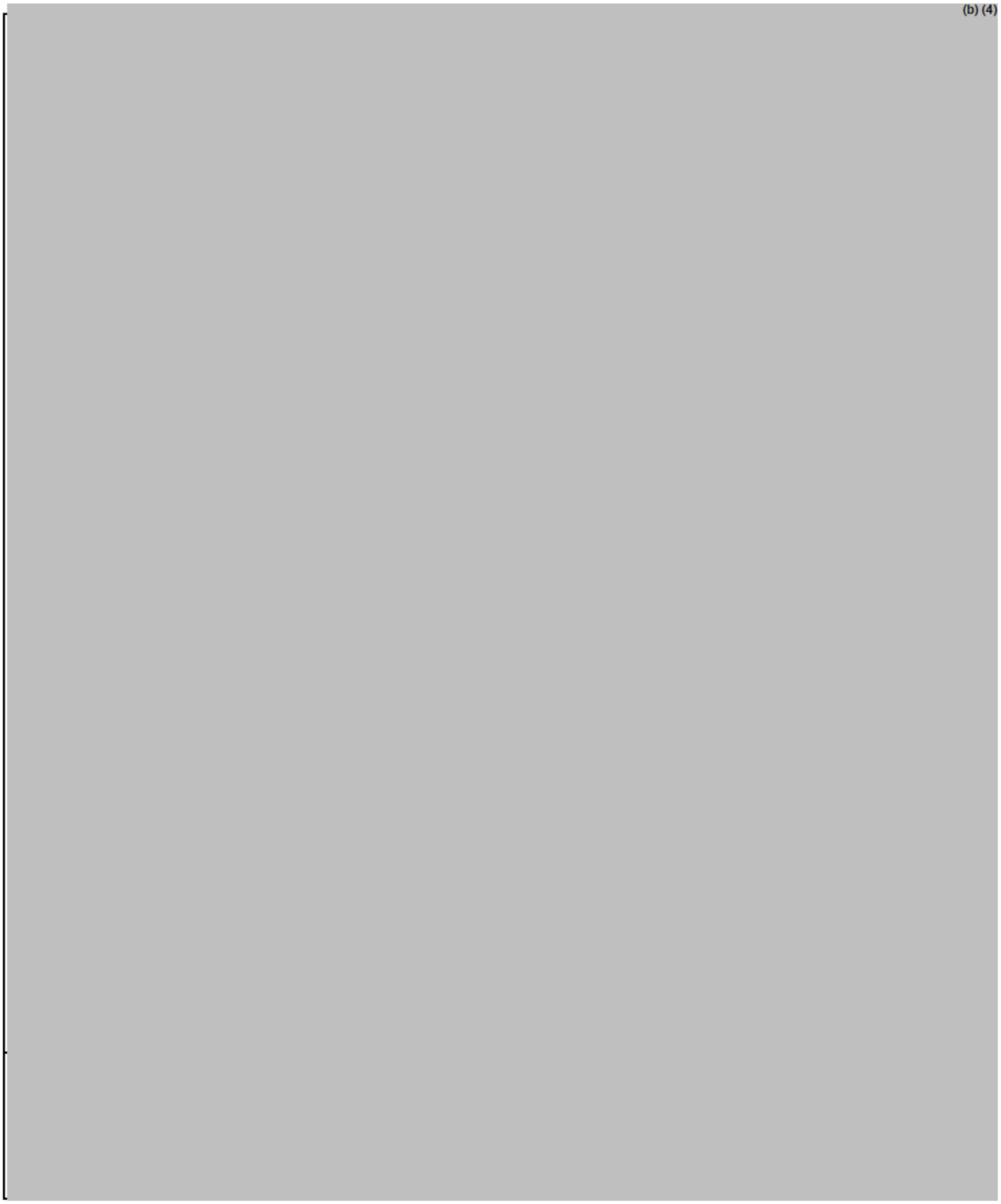
The drug substance specification is similar/same as what have been acceptable to the Agency (ANDAs 78-119. (b) (4)

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Firm's Response Summarized by the Reviewer:

The firm refers to ICH and Agency guidelines and test results using validated methods to justify the specification for the drug substance.

(b) (4)



24 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer: SBain	Date: 10-FEB-2011
Team Leader: PCapella	Date:
Project Manager: SEng	Date:

C. CC Block

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 091294 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg.

No Chemistry deficiency.

Sincerely yours,

Florence S. Fang, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 091294
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/S.Bain/10-FEB-2011

HFD-640/PCapella/14-Feb-2011

HFD-640/SEng/2-14-2011

F/T by/se

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
02/14/2011

PETER CAPELLA
02/14/2011

SIMON S ENG
02/14/2011

ANDA 091294

Abacavir Sulfate Tablets, 300 mg

Mylan Pharmaceuticals Inc.

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 091294

2. REVIEW #: 2a

3. REVIEW DATE: 10-NOV-2010

4. REVIEWER: Sukhamaya (Sam) Bain, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Location
Original Submission	28-JAN-2009	Vol 1.1-1.6
Amendment	27-APR-2009	Vol 2.1
Amendment	27-AUG-2009	EDR
Amendment	01-DEC-2009	EDR
Amendment	25-MAR-2010	EDR

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Gratuitous Amendment	09-NOV-2010	EDR

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.*
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

* Transfer of ownership of the ANDA from Matrix to Mylan has been acknowledged by the Agency; T. W. Ames, 30-DEC-2009.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Abacavir Sulfate Tablets

9. LEGAL BASIS FOR SUBMISSION:

RLD: Ziagen
Applicant: GlaxoSmithKline
NDA Number: 020977
Approval Date: 17-DEC-1998

Patent Certification: Module 1.3.5.2

Following are the unexpired patents that claim the RLD:

US Patent #	Expiration Date	Expiration Date with Pediatric Exclusivity
5034394	18-DEC-2011	18-JUN-2012
6294540	14-MAY-2018	14-NOV-2018

The firm provides Paragraph III certification for patents 5034394, and Paragraph IV certification for patent 6294540.

Exclusivity Statement: Module 1.3.5.2

There is no unexpired exclusivity that covers the RLD.

10. PHARMACOL. CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

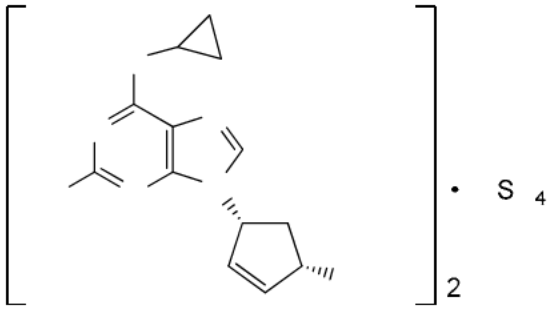
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (*1S,4R*)-4-[2-Amino-6-(cyclopropylamino)-*9H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate

Structural Formula:



Molecular Formula: $(C_{14}H_{18}N_6O)_2, H_2SO_4$

Molecular Weight: 670.76

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs: Module 1.4.1

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER/ DATE
18229	II	Matrix Laboratories Ltd.	Abacavir Sulfate	3	Adequate	M. Pineiro-Sanchez 10-NOV-2010
(b) (4)	IV		(b) (4)	4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		
EES	Acceptable	04-OCT-2010	A. Inyard
Methods Validation	Satisfactory	17-FEB-2010	S. Bain
Labeling	pending		C. Park
Bioequivalence	Satisfactory	19-FEB-2010	C. H. lee
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 091294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

(b) (4)

A. Description of the Drug Product(s) and Drug Substance(s)

Abacavir Sulfate Tablet, 300 mg, are peach, film-coated, capsule shaped, biconvex, beveled edge tablets, debossed with M on one side of the score and 120 on the other side of the score on one side of the tablet and blank on the other side.

The drug product contains the active ingredient, Abacavir Sulfate, which is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25 °C. It has an (b) (4) partition coefficient (log P) of approximately 1.20 at 25 °C.

The tablets contain the following inactive ingredients: Colloidal Silicon Dioxide NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Sodium Starch Glycolate NF, Hypromellose USP, Iron Oxide Red, Polyethylene Glycol NF, Synthetic Yellow Iron Oxide, and Titanium Dioxide NF.

B. Description of How the Drug Product is Intended to Be Used

A Medication Guide and Warning Card that provides information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

The drug product may be taken orally with or without food. The recommended oral dose for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

C. Basis for Approvability or Not-Approval Recommendation

No Chemistry deficiency.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer: SBain	Date: 10-NOV-2010
Team Leader: PCapella	Date: 23-NOV-2010
Project Manager: LLongstaff	Date:

C. CC Block

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 091294 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg.

No Chemistry deficiency.

Sincerely yours,

Florence S. Fang, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 091294
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/S.Bain/10-NOV-2010

HFD-640/PCapella/

HFD-640/LLongstaff/Simon 11-24-10

F/T by/se

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
11/30/2010

PETER CAPELLA
11/30/2010

SIMON S ENG
11/30/2010

ANDA 091294

Abacavir Sulfate Tablets, 300 mg

Mylan Pharmaceuticals Inc.

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 091294

2. REVIEW #: 2

3. REVIEW DATE: 17-FEB-2010, 22-MAR-2010, 26-MAR-2010, 02-APR-2010

4. REVIEWER: Sukhamaya (Sam) Bain, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Location
Original Submission	28-JAN-2009	Vol 1.1-1.6
Amendment	27-APR-2009	Vol 2.1

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Amendment	27-AUG-2009	EDR
Amendment	01-DEC-2009	EDR
Amendment	25-MAR-2010	EDR

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.*
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

* Transfer of ownership of the ANDA from Matrix to Mylan has been acknowledged by the Agency; T. W. Ames, 30-DEC-2009.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Abacavir Sulfate Tablets

9. LEGAL BASIS FOR SUBMISSION:

RLD: Ziagen
Applicant: GlaxoSmithKline
NDA Number: 020977
Approval Date: 17-DEC-1998

Patent Certification: Module 1.3.5.2

Following are the unexpired patents that claim the RLD:

US Patent #	Expiration Date	Expiration Date with Pediatric Exclusivity
5034394	18-DEC-2011	18-JUN-2012
6294540	14-MAY-2018	14-NOV-2018

The firm provides Paragraph III certification for patents 5034394, and Paragraph IV certification for patent 6294540.

Exclusivity Statement: Module 1.3.5.2

There is no unexpired exclusivity that covers the RLD.

10. PHARMACOL. CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

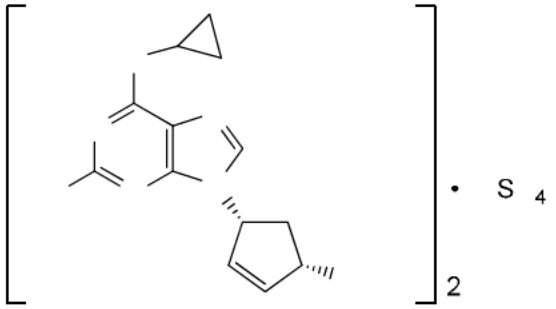
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (*1S,4R*)-4-[2-Amino-6-(cyclopropylamino)-*9H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate

Structural Formula:



Molecular Formula: $(C_{14}H_{18}N_6O)_2, H_2SO_4$

Molecular Weight: 670.76

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs: Module 1.4.1

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER/ DATE
18229	II	Matrix Laboratories Ltd.	Abacavir Sulfate	3	Adequate	21-JAN-2010 M. Manzoni
(b) (4)	IV	(b) (4)		4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		
EES	Pending		
Methods Validation	Satisfactory	17-FEB-2010	S. Bain
Labeling	Deficient	28-SEP-2009	C. Park
Bioequivalence	Satisfactory	19-FEB-2010	C. H. lee
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 091294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abacavir Sulfate Tablet, 300 mg, are peach, film-coated, capsule shaped, biconvex, beveled edge tablets, debossed with M on one side of the score and 120 on the other side of the score on one side of the tablet and blank on the other side.

The drug product contains the active ingredient, Abacavir Sulfate, which is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25 °C. It has an (b) (4) partition coefficient (log P) of approximately 1.20 at 25 °C.

The tablets contain the following inactive ingredients: Colloidal Silicon Dioxide NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Sodium Starch Glycolate NF, Hypromellose USP, Iron Oxide Red, Polyethylene Glycol NF, Synthetic Yellow Iron Oxide, and Titanium Dioxide NF.

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A Medication Guide and Warning Card that provides information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

The drug product may be taken orally with or without food. The recommended oral dose for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

C. Basis for Approvability or Not-Approval Recommendation

No Chemistry deficiency.

Chemistry Assessment

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

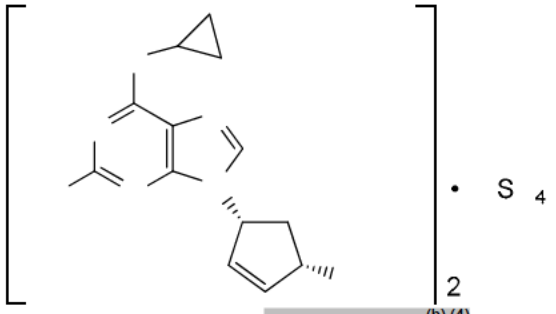
S DRUG SUBSTANCE

S.1 General Information: Satisfactory

What are the nomenclature, molecular structure, molecular formula, and molecular weight and CAS Registry No.?

Firm's Response Edited by the Reviewer:

Generic Name: Abacavir Sulfate
Chemical Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]- 2-cyclopentene-1-methanol Sulfate
Molecular Structure:



Molecular Formula: (b) (4)
Molecular Weight: (b) (4)
CAS #: [188062-50-2]

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

What are the physicochemical properties including physical description, solubility, pH, pKa potential isomerism polymorphism and partition coefficient?

Firm's Response Summarized by the Reviewer:

Description: Off-white to cream color crystalline powder.
Solubility: Soluble in water (b) (4)
(b) (4)

Potential Isomerism: The drug substance molecule has two chiral centers, which provide for four possible sterioisomers.

(b) (4)

Reviewer's Assessments: Satisfactory; the firm's response is adequate.

S.2 Manufacture: Satisfactory

Who manufactures the drug substance?

Firm's Response Summarized by the Reviewer:

Matrix Laboratories Limited (Unit-8)
G.Chodavaram Village, Pusapatirega (M),
Vizianagaram District,
Andhra Pradesh, India

Establishment Registration #3002785310
Satisfactory FDA Inspection Date: May, 2006

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; M. Manzoni, 21-JAN-2010.

S.3 Characterization: Satisfactory

How was the drug substance structure elucidated and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency.

How were potential impurities identified and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229, and identifies the following impurities in the drug substance:

(b) (4)

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency. The firm's response is adequate. We note that the applicant monitors all of these impurities for the release and stability of the drug product.

S.4 Controls of Drug Substances: Satisfactory

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Firm's Response Summarized by the Reviewer:

Applicant's Specification for Abacavir Sulphate:

Test	Specification
Description	Off-white to cream colored crystalline powder
Solubility	(b) (4), soluble in water, (b) (4)
Identification:	

IR HPLC Chemical Test	Spectrum matches that of the standard. Retention time matches that of the standard. (b) (4)

(b) (4)

Reviewer's Assessments: Satisfactory.

The drug substance specification is similar/same as what have been acceptable to the Agency (ANDAs 78-119, 78-742).

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Firm's Response Summarized by the Reviewer:

The firm refers to ICH and Agency guidelines and test results using validated methods to justify the specification for the drug substance.

(b) (4)

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer: SBain	Date: 02-APR-2010
Team Leader: GSmith	Date:
Project Manager: LLongstaff	Date:

C. CC Block

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 091294 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg.

No Chemistry deficiency.

Sincerely yours,

Florence S. Fang, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 091294
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/S.Bain/02-APR-2010

HFD-640/PCapella/13-Jul-2010

HFD-640/LLongstaff/

F/T by/

TYPE OF LETTER: APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MYLAN PHARMACEUTICALS INC	ABACAVIR SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
09/13/2010

PETER CAPELLA
09/13/2010

LAURA A LONGSTAFF
09/14/2010

ANDA 91-294

Abacavir Sulfate Tablets, 300 mg

Matrix Laboratories Inc.

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 91-294

2. REVIEW #: 1

3. REVIEW DATE: 05-AUG-2009

4. REVIEWER: Sukhamaya (Sam) Bain, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Location
Original Submission	28-JAN-2009	Vol 1.1-1.6
Amendment	27-APR-2009	Vol 2.1

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Laboratories Inc.
Address	76 South Orange Avenue, Suite 301 South Orange, NJ 07079
Representative:	Keith Giunta
Telephone:	(973) 761-1600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Abacavir Sulfate Tablets

9. LEGAL BASIS FOR SUBMISSION:

RLD: Ziagen
Applicant: GlaxoSmithKline
NDA Number: 020977
Approval Date: 17-DEC-1998

Patent Certification: Module 1.3.5.2

Following are the unexpired patents that claim the RLD:

US Patent #	Expiration Date	Expiration Date with Pediatric Exclusivity
5034394	18-DEC-2011	18-JUN-2012
5089500		26-DEC-2009
6294540	14-MAY-2018	14-NOV-2018

The firm provides Paragraph III certification for patents 5034394 and 5089500, and Paragraph IV certification for patent 6294540.

Exclusivity Statement: Module 1.3.5.2

There is no unexpired exclusivity that covers the RLD.

10. PHARMACOL. CATEGORY: Antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

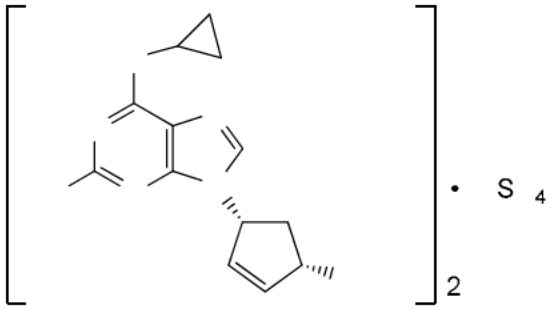
_____SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (*1S,4R*)-4-[2-Amino-6-(cyclopropylamino)-*9H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate

Structural Formula:



Molecular Formula: $(C_{14}H_{18}N_6O)_2, H_2SO_4$

Molecular Weight: 670.76

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Module 1.4.1

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER/ DATE
18229	II	Matrix Laboratories Ltd.	Abacavir Sulfate	3	Adequate	13-MAY-2009 S. Rosencrance
(b) (4)	IV	(b) (4)		4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		
EES	Pending		
Methods Validation	Not satisfactory	05-AUG-2009	S. Bain
Labeling	Pending		
Bioequivalence	Incomplete	14-JUL-2009	G. S. Johnson
EA	N/A		

Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 91-294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Major Amendment.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abacavir Sulfate Tablet, 300 mg, is a peach colored, capsule shaped, biconvex, film-coated tablet, [redacted] (b) (4).

The drug product contains the active ingredient, Abacavir Sulfate, which is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25 ºC. It has an [redacted] (b) (4) partition coefficient (log P) of approximately 1.20 at 25 ºC.

The tablets contain the following inactive ingredients: Colloidal Silicon Dioxide NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Sodium Starch Glycolate NF, Hypromellose USP, Iron Oxide Red, Polyethylene Glycol NF, Synthetic Yellow Iron Oxide, and Titanium Dioxide NF.

B. Description of How the Drug Product is Intended to Be Used

A Medication Guide and Warning Card that provides information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

The drug product may be taken orally with or without food. The recommended oral dose for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

C. Basis for Approvability or Not-Approval Recommendation

The exhibit batch has already been used for a different ANDA, 78-742.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer: SBain	Date: 05-AUG-2009
Team Leader: GSmith	Date:
Project Manager: LLongstaff	Date:

C. CC Block

Chemistry Assessment

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

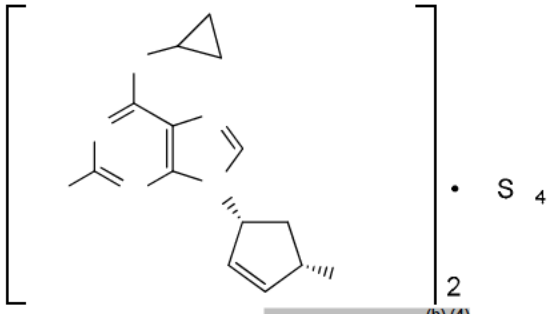
S DRUG SUBSTANCE

S.1 General Information: Satisfactory

What are the nomenclature, molecular structure, molecular formula, and molecular weight and CAS Registry No.?

Firm's Response Edited by the Reviewer:

Generic Name: Abacavir Sulfate
Chemical Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]- 2-cyclopentene-1-methanol Sulfate
Molecular Structure:



Molecular Formula: (b) (4)
Molecular Weight (b) (4)
CAS #: [188062-50-2]

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

What are the physicochemical properties including physical description, solubility, pH, pKa potential isomerism polymorphism and partition coefficient?

Firm's Response Summarized by the Reviewer:

Description: Off-white to cream color crystalline powder.
Solubility: Soluble in water across the pH range of 1.2 to 8.0. (b) (4)
pKa: 4.85; *pH:* 3.51 (1% aqueous solution)

Potential Isomerism: The drug substance molecule has two chiral centers, which provide for four possible sterioisomers.

(b) (4)

Reviewer's Assessments: Satisfactory; the firm's response is adequate.

S.2 Manufacture: Satisfactory

Who manufactures the drug substance?

Firm's Response Summarized by the Reviewer:

Matrix Laboratories Limited (Unit-8)
G.Chodavaram Village, Pusapatirega (M),
Vizianagaram District,
Andhra Pradesh, India

Establishment Registration #3002785310
Satisfactory FDA Inspection Date: May, 2006

Reviewer's Assessments: Satisfactory; the firm's response is complete and adequate.

How do the manufacturing processes and controls ensure consistent production of drug substance?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; S. Rosencrance, 13-MAY-2009.

S.3 Characterization: Satisfactory

How was the drug substance structure elucidated and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229.

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; S. Rosencrance, 13-MAY-2009.

How were potential impurities identified and characterized?

Firm's Response Summarized by the Reviewer:

The firm refers to DMF 18229, and identifies the following impurities in the drug substance:

(b) (4)

Reviewer's Assessments: Satisfactory.

DMF 18229 has been found adequate by the Agency; S. Rosencrance, 13-MAY-2009. The firm's response is adequate. We note that the applicant monitors all of these impurities for the release and stability of the drug product.

S.4 Controls of Drug Substances: Not satisfactory

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Firm's Response Summarized by the Reviewer:

Applicant's Specification for Abacavir Sulphate:

Test	Specification
Description	Off-white to cream colored crystalline powder
Solubility	(b) (4) soluble in (b) (4) water,
Identification:	

IR HPLC Chemical Test	Spectrum matches that of the standard. Retention time matches that of the standard. (b) (4)

(b) (4)

Reviewer's Assessments: Satisfactory.

The drug substance specification is similar/same as what have been acceptable to the Agency (ANDAs 78-119, (b) (4)

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Firm's Response Summarized by the Reviewer:

The firm refers to ICH and Agency guidelines and test results using validated methods to justify the specification for the drug substance.

(b) (4)

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cc: ANDA 91-294
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/S.Bain/05-AUG-2009

HFD-640/GSmith/

HFD-640/LLongstaff/

F/T by/

TYPE OF LETTER: NOT APPROVABLE - MAJOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUKHAMAYA BAIN
09/24/2009

GLEN J SMITH
09/25/2009

LAURA A LONGSTAFF
09/28/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091294		
Drug Product Name	Abacavir Sulfate Tablets		
Strength(s)	300mg		
Applicant Name	Mylan Pharmaceuticals Inc.*		
Address	781 Chestnut ridge Road P.O. Box 4310 Morgantown, WV 26504-4310		
Applicant's Point of Contact	Wayne Talton, VP, Regulatory Affairs		
Contact's Telephone Number	304-599-2595		
Contact's Fax Number	304-285-6407		
Original Submission Date(s)	January 28, 2009		
Submission Date(s) of Amendment(s) Under Review	None.		
Reviewer	Christina Lee, Pharm.D.		
Study Number (s)	06-VIN-132	06-VIN-133	
Study Type (s)	Fasting	Fed	
Strength (s)	300 mg	300 mg	
Clinical Site	veeda clinical research Pvt. Ltd.		
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi Ahmedabad – 380 015, India		
Analytical Site	(b) (4)		
Analytical Site Address			

OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**300 MG**	**ADEQUATE**
1	**FASTING STUDY**	**300 MG**	**ADEQUATE**
1	**FED STUDY**	**300 MG**	**ADEQUATE**

*The 356 form submitted with the original application was under the applicant Matrix Laboratories Limited; however, the 356 form submitted with the dissolution amendment, dated August 27, 2009, was under the applicant Mylan Pharmaceuticals Inc. (**Mylan acquired Matrix Laboratories, Ltd in March 2009**).

EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing Matrix Laboratories Ltd. (Mylan)'s Abacavir Sulfate Tablets, 300 mg, to the reference-listed drug (RLD), Ziagen® 300 mg Tablets (VIIV Healthcare[1]). Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. In this ANDA, the firm referenced ANDA 078742, Abacavir Sulfate Tablets, 300 mg by Matrix Laboratories, India, for which the ANDA applicant was a separate group company, Matrix Laboratories, Ltd. ANDA 078742 contained a paragraph III certification and was reviewed by the Agency under the provisions of PEPFAR and received tentative approval on April 5, 2007. The firm also claimed that the content of ANDA 091294 complies with all the recommendations by the Agency during review of ANDA 078742[2]. In addition, the firm also provided a letter authorizing the Agency to reference ANDA 078742, during review of ANDA 091294.

The firm's fasting and fed BE studies submitted in ANDA 078742 were acceptable. The results are summarized in the tables below.

Abacavir, 300 mg Fasting Bioequivalence Study No. 06-VIN-132, **N=28 (Male=28) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	6060.15	6211.25	0.98	94.25	101.00
AUC∞ (ng·hr/mL)	6161.04	6300.90	0.98	94.41	101.27
Cmax (ng/mL)	2798.99	2943.52	0.95	86.54	104.49

Abacavir, 300 mg Fed Bioequivalence Study No. 06-VIN-133, **N=24 (Male=24) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	5749.58	5836.59	0.99	93.64	103.63
AUC∞ (ng·hr/mL)	5834.68	5928.00	0.98	93.62	103.48
Cmax (ng/mL)	2149.11	2248.57	0.96	87.44	104.47

Mylan has conducted acceptable comparative dissolution testing using the FDA-recommended dissolution method (DARRTS: REV-BIOEQ-02 Dissolution Review by Dr. Glendolynn Johnson). In DBE Dissolution amendment review, dated 10/30/2009, the DBE acknowledged that the firm's dissolution testing method and specification was acceptable.

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: *NLT 80% (Q) of abacavir is dissolved in 15 minutes.*

[1] Transfer ownership acknowledge by the Agency on Nov 6, 2009 from GlaxoSmithKline to ViiV Healthcare Company

[2] DARRTS: COR-ANDAACTION-03(Tentative Approval), 4/5/2007.

This reviewer has reviewed the submitted information in the current ANDA 091294 and compare them to the submission of ANDA 078742 and concurs the conclusion drawn by the reviewer of ANDA 078742 (See attachment I for detail of the reviewer of ANDA 078742).

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is acceptable with no deficiencies.

TABLE OF CONTENTS

ATTACHMENT I

(REVIEW OF ANDA 78742: DARRTS: REV-BIOEQ-01(GENERAL REVIEW))

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-742
Drug Product Name	Abacavir Sulfate Tablets
Strengths	300 mg
Applicant Name	Matrix Laboratories Ltd.
Address	1-1-151/1, 4th floor, Sairam Towers, Alexander Road, Secunderabad – 500 003, Andhra Pradesh (AP), India
U.S. Contact	Keith Giunta (Phone 973-761-1600, Fax 973-761-1680)
Submission Date(s)	December 27, 2006
Amendment Date(s)	January 23, 2007
Reviewer	Sarah Robertson, Pharm.D.
Clinical Site	Veeda Clinical Research Pvt. Ltd., Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India
Analytical Site	(b) (4)
First Generic	No

I. EXECUTIVE SUMMARY

This submission contains two bioequivalence (BE) studies comparing Matrix Laboratories' Abacavir Sulfate Tablets, 300 mg, to the reference-listed drug (RLD), Ziagen® 300 mg Tablets (GlaxoSmithKline) under fasting and fed conditions. Both studies were single-dose, two-way crossover studies conducted in healthy adult male volunteers (n=28 fasting, n=24 fed).

Results of the statistical analyses for the fasting study are (point estimate, 90% CI): LAUCT of 0.98, 94.3 – 101.0%; LAUCI of 0.98, 94.4 – 101.3%; and LCmax of 0.95, 86.5 – 104.5%. Results of the fed study are (point estimate, 90% CI): LAUCT of 0.99, 93.6 – 103.6%; LAUCI of 0.98, 93.6 – 103.5%; and LCmax of 0.96, 87.4 – 104.5%. The results of the fasting and fed BE studies are acceptable.

The dissolution data submitted by the firm for their Abacavir Sulfate Tablets, 300 mg, is acceptable. The application is complete with no deficiencies.

II. TABLE OF CONTENTS

III. SUBMISSION SUMMARY

A. Drug Product Information

Test Product	Abacavir Sulfate Tablets, 300 mg
Reference Product	Ziagen® Tablets, 300 mg
RLD Manufacturer	GlaxoSmithKline
NDA No.	20-977
RLD Approval Date	December 17, 1998
Indication	Ziagen® Tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

B. PK/PD Information

Bioavailability	83%
Food Effect	There is no significant difference in systemic exposure ($AUC_{0-\infty}$) in the fed and fasting states; therefore, Ziagen® Tablets may be administered with or without food.
Tmax	(b) (4)
Metabolism and Excretion	Abacavir first-pass metabolism was calculated to be limited to a maximum of approximately 17%. The primary routes of elimination are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). Metabolism by cytochrome P450 enzymes is insignificant. Approximately (b) (4) of an abacavir dose is found in the urine. Fecal elimination accounted for 16% of the dose.
Half-life	Plasma half-life of 1.54 ± 0.63 hours. (b) (4) .
Relevant OGD or DBE History	There are two approved generic products for Abacavir Tablets, 300 mg: 77-844 (Aurobindo, approved 5/17/06) and 78-119 (Cipla, approved 11/6/06)

ANDAs

(b) (4)

Protocols

05-012 (Roxane), 06-001 (Cipla)

Control Documents

(b) (4) 05-012 (Roxane); (b) (4)

The DBE makes the following recommendations to establish bioequivalence:

1. The following studies are recommended to establish bioequivalence of abacavir tablets, 300 mg:
   a. A single-dose, two-way, crossover fasting *in vivo* bioequivalence study comparing Abacavir Sulfate Tablets, 300 mg, to the reference listed drug (RLD), Ziagen® (Abacavir Sulfate) Tablets, 300 mg.
   b. A single-dose, two-way, crossover fed *in vivo* bioequivalence study comparing Abacavir Sulfate Tablets, 300 mg, to the RLD.
2. Measure only the parent compound, abacavir, in plasma.
3. Conduct dissolution testing on 12 dosage units each of

all strengths of the test and reference product using the following FDA method:

Apparatus:	USP Apparatus 2 (Paddle)
Speed:	75 rpm
Media:	0.1 N HCl
Volume:	900 ml
Sampling times:	5, 10, 15, and 30 minutes

Agency Guidance	None
Drug Specific Issues	None
Application Specific Issue	PEPFAR Application A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Information Requested	Data
Analyte	Abacavir
Internal standard (IS)	(b) (4)
Method description	(b) (4)
Limit of quantitation (ng/mL)	29.817
Average recovery of drug (%)	69.45%
Average recovery of IS (%)	78.99%
Standard curve concentrations (ng/mL)	29.817 to 9317.804
QC concentrations (ng/mL)	HQC - 7494.755; MQC - 4197.063; LQC - 82.262ng/mL; LLOQ QC - 30.437
QC Intrabatch precision range (%)	1.31 to 14.38%
QC Intrabatch accuracy range (%)	87.73 to 110.58%
QC Interbatch precision range (%)	3.81 to 10.81%
QC Interbatch accuracy range (%)	95.80 to 103.48%
Bench-top stability (hrs)	For about 06 hours at ambient temperature.
Stock stability (days)	For about 07 days at below 8°C and for about 06 hours at ambient temperature.
Processed stability (hrs)	For about 27.5 hours at 5°C.
Freeze-thaw stability (cycles)	3 Cycles at below -20°C.
Long-term storage stability (days)	65 days at a set temp. of -60°C (range -48 to -70°C)
Dilution integrity	1/5 (%CV 1.4) and 1/10 (%CV 3.32)
Selectivity	No interfering peaks noted in blank plasma samples
Bioanalytical method is acceptable?	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	06-VIN-132
Study Design	Randomized two-way crossover study under fasting conditions
No. of subjects enrolled	28
No. of subjects completing	28
No. of subjects analyzed	28
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	All males
Test product	Abacavir Sulfate Tablets
Reference product	Ziagen® (Abacavir Sulfate) Tablets
Strength tested	300 mg
Dose	1 x 300 mg

Summary of Statistical Analysis – Abacavir		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC$_{0\text{-}t}$	0.98	94.25 – 101.00
LAUCinf	0.98	94.41 – 101.27
LC$_{max}$	0.95	86.54 – 104.49

Reanalysis of Study Samples

Study No.: 06-VIN-132 (Fasting Bioequivalence study)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason A Inconsistent Internal Standard Area (IIS)	01	0.0	0.18	0.0	01	0.0	0.18	0.0
Reason B	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason C	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Etc.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	01	0.0	0.18	0.0	01	0.0	0.18	0.0

Did use of recalculated plasma concentration data change study outcome? No

2. Single-dose Fed Bioequivalence Study

Study Summary	
Study No.	06-VIN-133
Study Design	Randomized two-way crossover study under fed conditions
No. of subjects enrolled	24
No. of subjects completing	24
No. of subjects analyzed	24
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	All males
Test product	Abacavir Sulfate Tablets
Reference product	Ziagen® (Abacavir Sulfate) Tablets
Strength tested	300 mg
Dose	1 x 300 mg

Summary of Statistical Analysis - Abacavir		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC$_{0\text{-}t}$	0.99	93.64 – 103.63
LAUCinf	0.98	93.62 – 103.48
LC$_{max}$	0.96	87.44 – 104.47

Reanalysis of Study Samples

Study No.: 06-VIN-133 (Fed Bioequivalence study)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	R	T	R	T	R	T	R
Pharmacokinetic	04	01	0.9	0.2	04	01	0.9	0.2
Reason A (Analytical Batch Failure)	36	36	8.3	8.3	36	36	8.3	8.3
Reason B	0	0	0.0	0.0	0	0	0.0	0.0
Reason C	0	0	0.0	0.0	0	0	0.0	0.0
Etc.	0	0	0.0	0.0	0	0	0.0	0.0
Total	40	37	9.2	8.5	40	37	9.2	8.5

Did use of recalculated plasma concentration data change study outcome? No

F. Formulation

Location in appendix	Section B
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	Type II (Paddle)
Rotation (rpm)	75 rpm
FDA-recommended specifications	NLT 80% (Q) in 15 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving drug
Is method acceptable?	Yes
If not then why?	N/A

H. Waiver Request(s)

None

I. Deficiency Comments

None

J. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Matrix Laboratories on the drug product, Abacavir Sulfate Tablets, 300 mg, Lot ABSA536001, comparing it to GlaxoSmithKline's Ziagen® Tablets, 300 mg, Lot 6ZP7570, is acceptable.

2. The *in vivo* bioequivalence study conducted under fed conditions by Matrix Laboratories on the drug product, Abacavir Sulfate Tablets, 300 mg, Lot ABSA536001, comparing it to GlaxoSmithKline's Ziagen® Tablets, 300 mg, Lot 6ZP7570, is acceptable.

3. The *in vitro* dissolution testing conducted by the firm on its Abacavir Sulfate Tablets, 300 mg is acceptable. The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37ºC using USP Apparatus 2 (Paddle) at 75 rpm. The test product should meet the following specification:

Not less than 80% (Q) of the labeled amount of drug is dissolved in 15 minutes.

The firm should be informed of the above recommendations.

Sarah Robertson, Pharm.D.
Division of Bioequivalence
Review Branch III

Chandra Charasia, Ph.D.
Team Leader, Division of Bioequivalence
Review Branch III

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

APPENDIX

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	06-VIN-132
Study Title	A randomized, open label, two treatment, two period, two sequence single dose crossover bioequivalence study of Abacavir Sulfate 300 mg tablets of Matrix Laboratories Ltd (India) and Ziagen (Abacavir Sulfate) 300 mg tablets GlaxoSmithKline Research Triangle Park, NC, USA in healthy human adult male subjects, under fasting conditions.
Clinical Site	Veeda Clinical Research Pvt. Ltd., Ahmedabad, India
Principal Investigator	Dharmesh Domadia, MD
Study/Dosing Dates	10/11/06 (Period I) and 10/19/06 (Period II)
Analytical Site	(b) (4)
Analytical Director	
Analysis Dates	
Storage Period	26 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Abacavir Sulfate Tablets	Ziagen® Tablets
Manufacturer	Matrix Laboratories	GlaxoSmithKline
Batch/Lot No.	ABSA536001	6ZP7570
Manufacture Date	06/2006	N/A
Expiration Date	06/2008	11/2008
Strength	300 mg	300 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	99.90%	97.7%
Content Uniformity	Acceptance Value: 1.4%	Not provided
Formulation	See Appendix Section B	Not provided
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization Scheme	AB: (b) (6) BA:
Blood Sampling Times	Pre-dose, 0.167, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, frozen at -28°C until completion of the period, and then at -60°C until analyzed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight (≥ 10 hours pre-dose) and until 4 hours post-dose
Length of Confinement	10 hours pre-dose and until 12 hours post-dose
Safety Monitoring	Vital signs were measured prior to each dose and at specified blood draw times.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Study No. 06-VIN-132 (Fasting Bioequivalence study)		
	Treatment Groups	
	Test Product N =28	Reference Product N =28
Age (years)		
Mean ± SD	27.32 ± 5.71	27.32 ± 5.71
Range	18 - 37	18 - 37
Groups		
< 18	0 (0%)	0 (0%)
18 – 40	28(100%)	28(100%)
40 – 64	0 (0%)	0 (0%)
65 – 75	0 (0%)	0 (0%)
> 75	0 (0%)	0 (0%)
Sex		
Female	0 (0%)	0 (0%)
Male	28(100%)	28(100%)
Race		
Asian	28(100%)	28(100%)
Black	0 (0%)	0 (0%)
Caucasian	0 (0%)	0 (0%)
Hispanic	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
Other Factors		
Height (cm)		
Mean ± SD	167.93 ± 5.48	167.93 ± 5.48
Range	157.0 - 182.0	157.0 - 182.0
Weight (kg)		
Mean ± SD	59.75 ± 5.85	59.75 ± 5.85
Range	51.0 - 72.0	51.0 - 72.0

Table 2 Dropout Information

There were no study dropouts.

Table 3 Study Adverse Events

Body System/Adverse Event	**Fasted Bioequivalence Study**

	Study No. 06-VIN-132	
	Test	**Reference**
Skin		
Skin rash	1(50%)	-
Itching	1(50%)	-
Body as whole		
Running nose	-	1(50%)
Feverish feeling	-	1(50%)
Gastrointestinal		
Nausea	-	-
Pain abdomen	-	-
Vomiting	-	-
Indigestion	-	-
Total	2(100%)	2(100%)

Table 4 Protocol Deviation

Blood draw deviations are reported in Appendix 16.2.5 (vol. 1.3). The following concomitant medications were administered during the study: 1 subject took cetirizine 10 mg orally b.i.d. for 2 days for an adverse event which occurred on 10/15/06.

Comments on Dropouts/Adverse Events/Protocol Deviations: The reported adverse events and protocol deviations are not likely to compromise the integrity of study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

Analysis	Abacavir
QC Conc. (ng/mL)	81.329, 4149.417, 7409.673
Inter day Precision (%CV)	4.34 – 5.36
Inter day Accuracy (%)	93.86 – 103.11
Cal. Standards Conc. (ng/mL)	30.215 – 9212.026
Inter day Precision (%CV)	1.76 – 4.00
Inter day Accuracy (%)	91.81 – 105.32
Linearity Range	$R^2 \geq 0.9958$

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4)		Repeat Analysis

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	-

Summary/Conclusions, Study Assays: Assay results are acceptable.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=28)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	6206.03	22.09	6400.74	24.88	0.97
AUCI	6304.40	21.74	6487.31	24.55	0.97
CMAX	2912.28	28.92	3054.36	29.01	0.95
TMAX	0.65	61.74	0.65	66.71	1.00
KE	0.57	15.25	0.58	18.12	0.99
THALF	1.24	15.94	1.24	18.45	1.00

Units: AUC=ng*hr/mL, Cmax=ng/mL, Tmax=hr

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N=28)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	6060.15	6211.25	0.98	94.25	101.00
LAUCI	6161.04	6300.90	0.98	94.41	101.27
LCMAX	2798.99	2943.52	0.95	86.54	104.49

Table 10 Additional Study Information

Root mean square error, LAUCT	0.075794
Root mean square error, LAUCI	0.076893
Root mean square error, LCmax	0.206799
Ke and AUCi determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	2
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis: Acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The study had a sufficient number of early sampling time points, in accordance with the BA/BE Guidance. As such, the sampling is considered adequate, despite the 2 first measurable drug concentrations as Cmax.

The 90% confidence intervals for LAUCt, LAUCi, and LCmax are within the acceptable range limits of 80-125%.

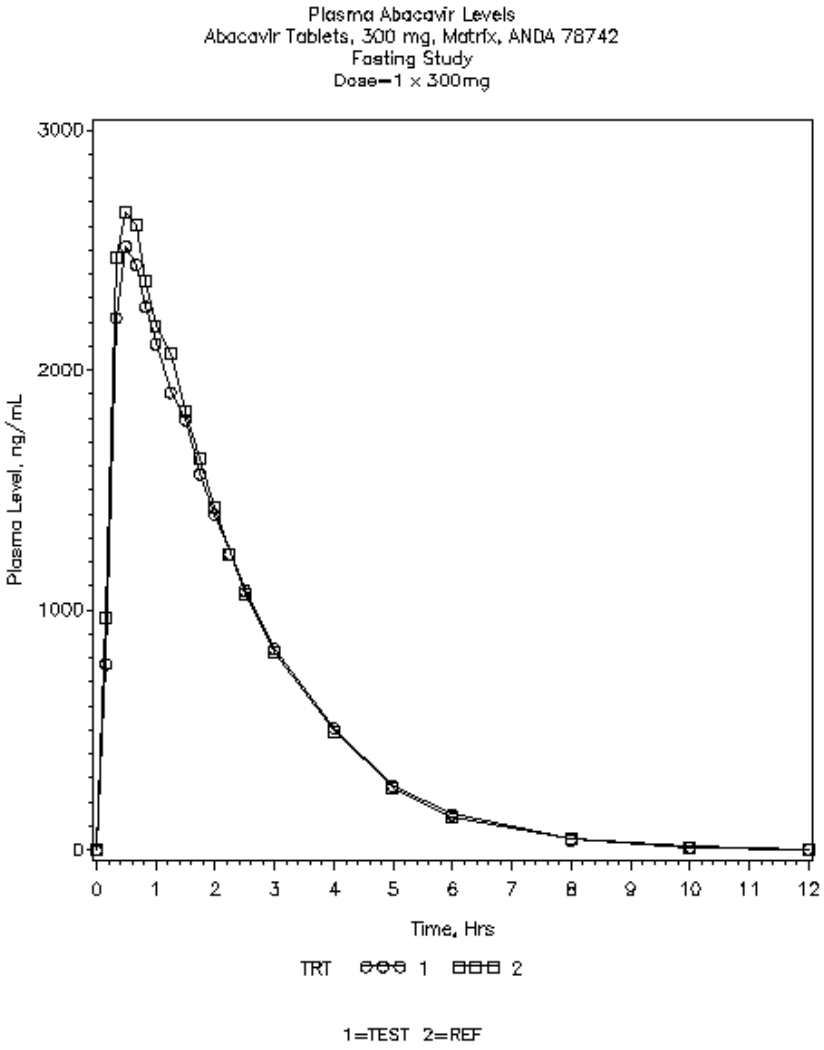
Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (N=28)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
0.167	775.46	144.67	970.80	107.01	0.80
0.33	2217.77	54.44	2471.85	53.92	0.90
0.5	2516.27	38.04	2657.86	36.44	0.95
0.67	2440.55	29.35	2605.67	30.50	0.94
0.83	2264.00	23.04	2373.67	28.32	0.95

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
1	2110.08	22.62	2184.82	23.68	0.97
1.25	1906.94	20.87	2068.99	22.86	0.92
1.5	1793.74	22.34	1826.64	22.94	0.98
1.75	1567.65	24.35	1629.50	27.93	0.96
2	1397.89	23.84	1428.86	28.72	0.98
2.25	1234.75	24.17	1235.55	28.90	1.00
2.5	1083.75	25.63	1064.36	28.76	1.02
3	839.02	28.42	825.87	32.49	1.02
4	509.22	29.63	495.67	35.99	1.03
5	267.39	36.40	255.70	42.12	1.05
6	148.92	33.82	138.99	43.93	1.07
8	42.24	68.46	45.69	69.12	0.92
10	11.09	179.54	12.04	166.69	0.92
12	3.39	294.42	2.61	367.17	1.30

Units = ng/mL

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	06-VIN-133
Study Title	A randomized, open label, two treatment, two period, two sequence single dose crossover bioequivalence study of Abacavir Sulfate 300 mg tablets of Matrix Laboratories Ltd (India) and Ziagen (Abacavir Sulfate) 300 mg tablets GlaxoSmithKline Research Triangle Park, NC, USA in healthy human adult male subjects, under fed conditions.
Clinical Site	Veeda Clinical Research Pvt. Ltd., Ahmedabad, India
Principal Investigator	Dharmesh Domadia, MD
Study/Dosing Dates	10/09/06 (Period I) and 10/17/06 (Period II)
Analytical Site	(b) (4)
Analytical Director	
Analysis Dates	
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	21 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Abacavir Sulfate Tablets	Ziagen® Tablets
Manufacturer	Matrix Laboratories	GlaxoSmithKline
Batch/Lot No.	ABSA536001	6ZP7570
Manufacture Date	06/2006	N/A
Expiration Date	06/2008	11/2008
Strength	300 mg	300 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	99.90%	97.7%
Content Uniformity	Acceptance Value: 1.4%	Not provided
Formulation	See Appendix Section B	Not provided
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Orally with 240 mL of water within 30 min. of high-fat breakfast.	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization Scheme	AB: (b) (6) BA:
Blood Sampling Times	Pre-dose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.25, 2.50, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, then frozen at -28°C until completion of the period, then stored at -60°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 12
Length of Fasting	Overnight (≥ 10 hours) and 4 hours post-dose
Contents of Meal	High-fat, high-calorie (1000 calories) breakfast (approx. 27% of calories from carbohydrates, 15% of calories from protein, and 58% of calories from fat)
Length of Confinement	10 hours pre-dose and until 12 hours post-dose
Safety Monitoring	Vital signs were measured prior to each dose and at specified blood draw times.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects

Study No. 06-VIN-133 (Fed Bioequivalence study)		
	Treatment Groups	
	Test Product N =24	Reference Product N =24
Age (years)		
Mean ± SD	28.96 ± 8.18	28.96 ± 8.18
Range	18-47	18-47
Groups		
< 18	0 (0%)	0 (0%)
18 – 40	22 (92%)	22 (92%)
40 – 64	2(8%)	2(8%)
65 – 75	0 (0%)	0 (0%)
> 75	0 (0%)	0 (0%)

Sex		
Female	0 (0%)	0 (0%)
Male	24(100%)	24(100%)
Race		
Asian	24(100%)	24(100%)
Black	0 (0%)	0 (0%)
Caucasian	0 (0%)	0 (0%)
Hispanic	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
Other Factors		
Height (cm)		
Mean ± SD	167.40 ± 4.50	167.40 ± 4.50
Range	159.0 – 177.0	159.0 – 177.0
Weight (kg)		
Mean ± SD	57.42 ± 5.61	57.42 ± 5.61
Range	50.10 – 71.0	50.10 – 71.0

Table 13 Dropout and Exclusion Information

There were no study dropouts.

Table 14 Study Adverse Events

Body System/Adverse Event	**Fed Bioequivalence Study Study No. 06-VIN-133**	
	Test	**Reference**
Skin		
Skin rash	-	-
Itching	-	-
Body as whole		
Running nose	-	-
Feverish feeling	-	-
Gastrointestinal		
Nausea	1 (25%)	-
Pain abdomen	1 (25%)	-
Vomiting	1 (25%)	-
Indigestion	1 (25%)	-
Total	4(100%)	-

Table 15 Protocol Deviations

In addition to blood draw deviations (Vol. 1.9), the following protocol deviations occurred:

Subject	Deviation	Period	Excluded from analysis?
(b) (6)	Serum triglycerides were not measured at the time of screening	N/A	No
	Temperature of the deep freezer were out of range briefly during Period I	I	No
	Subject received one dose of ondansetron 4 mg i.v. on 10/9/06 for treatment of an adverse event	I	No

Comments on Dropouts/Adverse Events/Protocol Deviations:
The single episode of emesis by Subject (b) (6) occurred approximately 6 hours after drug ingestion during Period I. As this is > 2 times the reported median Tmax value, inclusion of the subject in the statistical analysis was appropriate.

The reported adverse events and protocol deviations are not likely to compromise the integrity of study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

Analysis	Abacavir
QC Conc. (ng/mL)	81.796, 4173.24, 7452.214
Inter day Precision (%CV)	5.44 – 6.93
Inter day Accuracy (%)	95.01 – 97.82
Cal. Standards Conc. (ng/mL)	29.906 – 9345.479
Inter day Precision (%CV)	2.09 – 5.35
Inter day Accuracy (%)	97.47 – 101.56
Linearity Range	$R^2 \geq 0.9975$

Comments on Study Assay Quality Control: The assay results are acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4)		Repeat Analysis

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	-

Summary/Conclusions, Study Assays:
There were a total of 5 PK repeats – 4 for Test treatment and 1 for Reference. The PK repeats appear appropriate, and repeated values were used in the statistical analysis in accordance with SOP (b) (4)

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=24)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	5902.80	21.54	5968.95	20.57	0.99
AUCI	5986.40	21.31	6056.21	20.18	0.99
CMAX	2273.24	31.23	2325.49	26.03	0.98
TMAX	1.55	33.24	1.29	35.95	1.20
KE	0.53	17.34	0.53	18.27	1.01
THALF	1.34	20.85	1.35	18.73	0.99

Units: AUC=ng*hr/mL, Cmax=ng/mL, Tmax=hr

Table 20 Least Squares Geometric Means and 90% Confidence Intervals (N=24)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	5749.58	5836.59	0.99	93.64	103.63
LAUCI	5834.68	5928.00	0.98	93.62	103.48
LCMAX	2149.11	2248.57	0.96	87.44	104.47

Table 21 Additional Study Information

Root mean square error, LAUCT	0.102185
Root mean square error, LAUCI	0.101071
Root mean square error, LCmax	0.179399
Ke and AUCi determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	1
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis: Acceptable

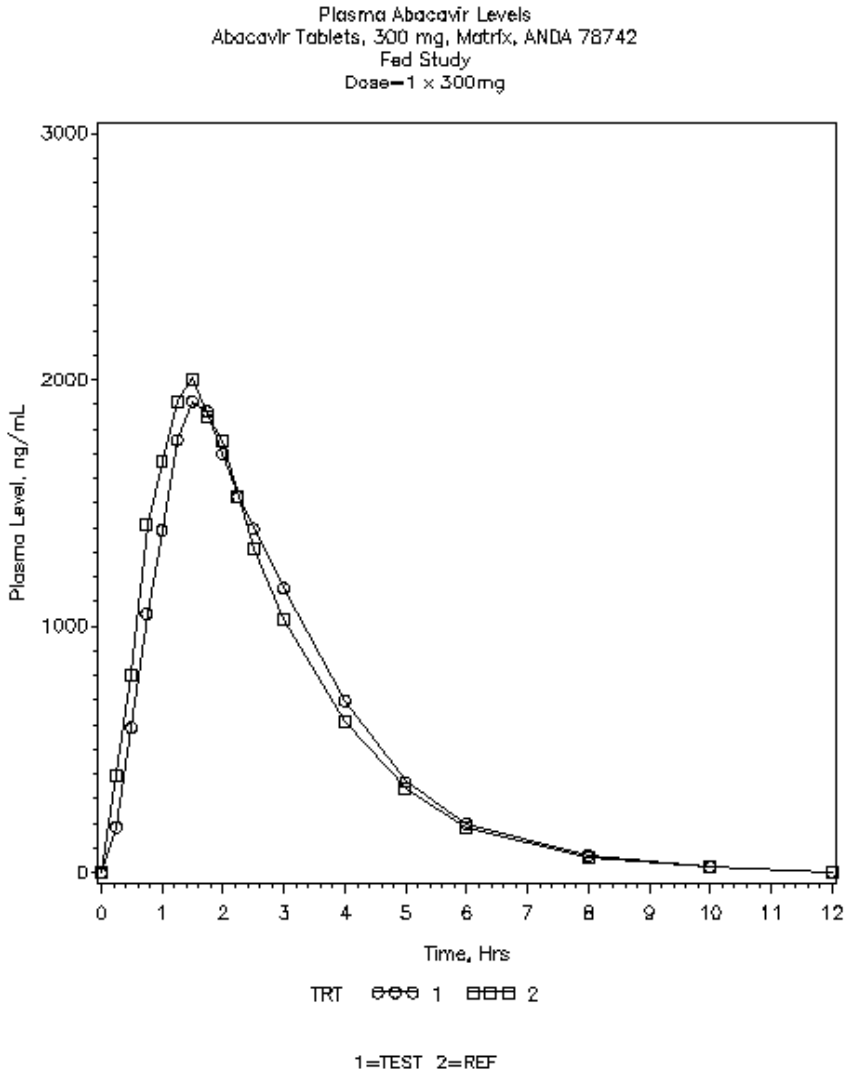
Summary and Conclusions, Single-Dose Non-Fasting Bioequivalence Study: The 90% confidence intervals for LAUCt, LAUCi, and LCmax are within the acceptable range limits of 80-125%.

Table 22 Mean Plasma Concentrations, Single-Dose Non-Fasting Bioequivalence Study (N=24)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
0.25	185.27	248.86	398.51	146.27	0.46
0.5	589.14	124.97	805.06	82.14	0.73
0.75	1052.25	87.54	1411.47	53.29	0.75
1	1390.18	66.08	1669.94	38.67	0.83
1.25	1756.40	47.04	1914.73	34.63	0.92
1.5	1913.15	40.08	2004.68	32.75	0.95
1.75	1871.62	35.63	1854.02	28.24	1.01
2	1701.30	28.95	1752.69	28.41	0.97
2.25	1526.08	24.93	1527.14	29.63	1.00
2.5	1396.07	24.69	1316.04	25.41	1.06
3	1154.25	25.21	1028.90	30.21	1.12
4	698.23	39.40	611.44	34.29	1.14
5	368.22	36.80	340.39	43.18	1.08
6	198.20	36.72	184.01	45.05	1.08
8	71.28	46.46	64.32	55.46	1.11
10	23.08	107.97	26.54	94.47	0.87
12	4.45	271.12	3.12	339.90	1.43

Unit: ng/mL

Figure 2 Mean Plasma Concentrations, Single-Dose Non-Fasting Bioequivalence Study



B. Formulation Data

Quantitative Composition :

INGREDIENT	MG/TABLET	% W/W
Abacavir Sulfate (Eqv. to 300 mg of abacavir)	(b) (4)	(b) (4)
Microcrystalline Cellulose*		
Colloidal Silicone Dioxide		
Magnesium Stearate		
(b) (4)		
Sodium Starch Glycolate		
(b) (4)		
(b) (4)		
Titanium Dioxide		
PEG (b) (4)		
Iron oxide yellow		
Iron oxide red		
Coated Tablet Weight	**820.00**	**100.00**

C. Dissolution Data

Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl (at 37°C)
Volume (mL)	900 mL
USP Apparatus type	Type II (Paddle)
Rotation (rpm)	75 rpm
Firm's proposed specifications	NLT (Q) 80% at 15 min.

Table 1 Comparative Dissolution Profiles

PRODUCT (BATCH)	MEAN (%RSD), RANGE				
	5 min.	**10 min.**	**15 min.**	**20 min.**	**30 min.**
Ziagen Tablets, 300 mg (6ZP7570)	101 (b) (4)	102 (b) (4)	102 (b) (4)	10 (b) (4)	102 (b) (4)
Abacavir Sulfate Tablets, 300 mg (ABSA536001)	102 (b) (4)	103 (b) (4)	103 (b) (4)	104 (b) (4)	104 (b) (4)

D. Consult Reviews N/A

E. SAS Output

1. Fasting

```
        ODS RTF file='FAST.rtf' style=styles.jlo;
*FILENAME=C:\SAS\BE02dvp04.SAS;
%INCLUDE "C:\SAS\MACROLIB.SAS";

        *ASSIGN WHETHER HAVE GROUP EFFECT:
        TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
        TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
        TRTGROUP =        NO GROUP EFFECT IN STUDY
        NOTE:  group variable has to be named GRP in the dataset;

%let trtgroup=;
%let drug=Abacavir;
%let strength=300 mg;
%let doseform=Tablet;
%let anda=78742;
%let studytype=FAST;
%let studydir=C:\Documents and Settings\robertsons\My Documents\OGD Work\ANDAs\Current\Abacavir
(pepfar)\SAS\Fast;
* %let plasmadata=apone250.dat;
* %let pkdata=apone250.pkv;

options mlogic mprint symbolgen;

        *NAME OF OUTPUT TABLE FILE;
%LET ODSFILE=&studydir\&studytype..doc;

        *NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC FILE;
%LET PLOTFILE=&studydir\&studytype..gif;

        *VARIABLE LIST FOR SORTING AND MERGING;
%LET VARSORT=SUB PER;
%GLOBAL SUB SEQ PER TRT TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME THALF CLAST KE_FIRST KE_LAST OLDNAME
NEWNAME;

        *STEP 1: SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
                 SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE WILL BE USED
FOR
                 CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS.
                 SELECT CONTINU2.SAS FOR STATISTICS ON CALCULATED PARAMETERS;

%LET FNAME=%QUOTE(C:\SAS\CONTINU.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CONTINU2.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CALCKE.SAS);

        *STEP 2: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
                 IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
                 IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3
                 IF MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4;

*FILENAME ORGPLASM DDE 'EXCEL|Fast-IB!R2C1:R65C23';
*FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1;                                /* FIRST OBSERVATION */
*%LET VARPLASM=SUB PER SEQ TREAT $ c_5 c_25 C1-C15; /* VARIABLE LIST FOR THE PLASMA DATA FILE */
*%LET PLASMLS=256;                                    /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
*RUN;

        *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME CONCDATA "P:\Data\Firms\Roxane\77262\Fast";

        *SPECIFY NAME OF THE CONCENTRATION SAS DATASET*;
*%let cdata=plconc;
*DATA PLASMA;
*       SET CONCDATA.&CDATA(rename=(seq=_seq trt=treat));
*       rename subj = sub;
*                if _seq = "AB" then seq = 1;
*                else if _seq = "BA" then seq = 2;
*                if treat = "A" then trt = 1;
*                else if treat = "B" then trt = 2;
*RUN;
*%SORTDS(PLASMA, &VARSORT)
```

```
*RUN;

        *STEP 3: PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
                 IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
                 IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4*;

*FILENAME ORGPARAM DDE 'EXCEL|Fast-IB!R2C25:R65C29';
*FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1;                                   /* FIST OBSERVATION */
*%LET VARPARAM=SUB PER SEQ TREAT $ COHORT AUCT AUCI CMAX TMAX THALF KE; /* VARIABLE LIST */
*%LET PARAMLS=256;                                          /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;

        *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME PKDATA "P:\Data\Firms\(b) (4)\Fast";

        *SPECIFY NAME OF THE PK SAS DATASET*;
*%let pdata=params;
*DATA PARAME;
*       SET CONCDATA.&PDATA(rename=(seq=_seq trt=treat));
*       sub = subj;
*       if _seq = "AB" then seq = 1;
*       else if _seq = "BA" then seq = 2;
*       if treat = "A" then trt = 1;
*       else if treat = "B" then trt = 2;
*       rename lambda_z = KE;
*RUN;
*%SORTDS(PARAME, &VARSORT)
*RUN;

        *STEP 4: WRITE THE FILENAME OF THE MERGED DATA
                 IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 2 OR 3
                 IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE*;

FILENAME ORGMERGE DDE 'EXCEL|Data!R2C1:R57C30';
*FILENAME ORGMERGE 'C:\Data\Firms\(b) (4)Fasting\FDA.1';
%LET FIRSTOBS=1;                                    /* WRITE LINE NUMBER FOR THE FIRST OBSERVATION */
%LET VARMERGE=SUB SEQ PER TREAT$ C1-C20 AUCT AUCI CMAX KE THALF TMAX;
%LET MERGELS=500;                                   /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
RUN;
%SORTDS(MERGED, &VARSORT)
RUN;

        *STEP 5: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY;

%LET    CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18,
C19, C20);

        *STEP 6: ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME;

%LET    TIME=%STR(T1=0; T2=0.167; T3=0.33; T4=0.5; T5=0.67; T6=0.83; T7=1; T8=1.25; T9=1.5; T10=1.75;
T11=2; T12=2.25;
        T13=2.5; T14=3; T15=4; T16=5; T17=6; T18=8; T19=10; T20=12);

        *STEP 7: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS;

%LET NO_ASSAY=20;

        *STEP 8: INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT IN THE DATA
SUBMITTED;

%LET KE_FIRST=&NO_ASSAY-5;
%LET KE_LAST=&NO_ASSAY-1;

        *STEP 9: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION
                 VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL
                 LEAVE AS IT IS IF NO CHANGE IS DESIRED;

*%LET REMOVSUB=%STR(IF SUB^=26);
*       IF SUB^=15;
*%LET REMOVSUB=%STR(IF TMAX^=0.25);

        *STEP 10:        IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
                 CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC
                 IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED;

%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST; IF TREAT='A' THEN TRT=1; ELSE TRT=2);

        *PK REPEATS - USE ORIGINAL CONCENTRATIONS;
```

```
*DATA plasma;
*        set plasma;
*        if sub="S06" and peri="P2" then t8=123.256;
*        if sub="S17" and peri="P1" then t6=340.101;
*RUN;

         *STEP 11:        DATA STEP FOR ORIGIN (MASTER DATA SET) OPEN OR CLOSE LINES IF NEEDED;

DATA ORIGIN;
         ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
         ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
*        SET PLASMA;
*        SET PARAME;
         SET MERGED;
&TIME;
KE_FIRST=0;
KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
RUN;

         *STEP 12:        DESCRIBE TITLES FOR TABLES;

%LET TITLE1=Mean Plasma Abacavir Levels;
%LET TITLE2=Mean Plasma Abacavir Levels for Test & Reference Products;

         *DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH;
%LET TITLE3=     Plasma Abacavir Levels;
%LET TITLE4=     Abacavir Tablets, 300 mg, Matrix, ANDA 78742;
%LET TITLE5=     Fasting Study;
%LET TITLE6=     Dose=1 x 300mg;
%LET FOOTNOT1=   1=TEST  2=REF;
%LET FOOTNOT2=   UNIT: Plasma Level=ng/mL  Time=hrs;
%LET FOOTNOT3=   UNIT: AUC=ng hr/mL  CMAX=ng/mL  TMAX=hr;
%LET FOOTNOT4=   Log-transformed Data Were Converted To Anti-log In The Table;
%LET LABEL1=     Plasma Level, ng/mL;
%LET LABEL2=     Time, Hrs;
%LET LABEL3=     Test;
%LET LABEL4=     Reference;

         *PRINT THE ORIGINAL DATASET SUBMITTED;
%PRINT(ORIGIN, ORIGINAL DATA SUBMITTED)
RUN;

         *TO CHECK >0 CONC FOR C1;
*PROC PRINT data=origin;
*        where c1 > 0;
*        var sub per seq c1 cmax;
*RUN;

%COPYDS(ORIGIN, NEW)
RUN;

         *STEP 13:        OPEN IF YOU WANT TO REMOVE, ADD OR EDIT;

*%REMUVSUB(NEW, NEW)
RUN;

%ADDVARIA(NEW, NEW)
RUN;

%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST)              /* TO EDIT KE-FIRST AND KE-LAST */
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
         *TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE NAMES;
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;
```

ORIGINAL DATA SUBMITTED

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	28	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of observations	56

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	113658689.1	3919265.1	16.73	<.0001
Error	26	6090956.9	234267.6		
Corrected Total	55	119749645.9			

R-Square	Coeff Var	Root MSE	AUCT Mean
0.949136	7.678602	484.0120	6303.386

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	347290.9	347290.9	1.48	0.2343
SUB(SEQ)	26	112645481.0	4332518.5	18.49	<.0001
PER	1	135157.4	135157.4	0.58	0.4543
TRT	1	530759.8	530759.8	2.27	0.1443

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	347290.9	347290.9	1.48	0.2343
SUB(SEQ)	26	112645481.0	4332518.5	18.49	<.0001
PER	1	135157.4	135157.4	0.58	0.4543
TRT	1	530759.8	530759.8	2.27	0.1443

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	347290.8570	347290.8570	0.08	0.7793

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-194.708542	129.357636	-1.51	0.1443

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	113304861.7	3907064.2	16.06	<.0001
Error	26	6326073.9	243310.5		
Corrected Total	55	119630935.7			

R-Square	Coeff Var	Root MSE	AUCI Mean
0.947120	7.712261	493.2652	6395.857

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	295822.7	295822.7	1.22	0.2803
SUB(SEQ)	26	112400106.1	4323081.0	17.77	<.0001
PER	1	140556.1	140556.1	0.58	0.4541
TRT	1	468376.8	468376.8	1.93	0.1771

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	295822.7	295822.7	1.22	0.2803
SUB(SEQ)	26	112400106.1	4323081.0	17.77	<.0001
PER	1	140556.1	140556.1	0.58	0.4541
TRT	1	468376.8	468376.8	1.93	0.1771

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	295822.6501	295822.6501	0.07	0.7957

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-182.908415	131.830664	-1.39	0.1771

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: CMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	30925655.53	1066401.91	2.86	0.0042
Error	26	9703298.77	373203.80		
Corrected Total	55	40628954.30			

R-Square	Coeff Var	Root MSE	CMAX Mean
0.761173	20.47733	610.9041	2983.319

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	4866.53	4866.53	0.01	0.9100
SUB(SEQ)	26	28312368.29	1088937.24	2.92	0.0041
PER	1	2325808.81	2325808.81	6.23	0.0192
TRT	1	282611.90	282611.90	0.76	0.3922

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	4866.53	4866.53	0.01	0.9100
SUB(SEQ)	26	28312368.29	1088937.24	2.92	0.0041
PER	1	2325808.81	2325808.81	6.23	0.0192
TRT	1	282611.90	282611.90	0.76	0.3922

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	4866.531457	4866.531457	0.00	0.9472

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-142.079429	163.270984	-0.87	0.3922

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	2.91401812	0.10048338	17.49	<.0001
Error	26	0.14936485	0.00574480		
Corrected Total	55	3.06338297			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.951242	0.869023	0.075794	8.721804

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00137885	0.00137885	0.24	0.6283
SUB(SEQ)	26	2.90301822	0.11165455	19.44	<.0001
PER	1	0.00112942	0.00112942	0.20	0.6611
TRT	1	0.00849164	0.00849164	1.48	0.2350

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00137885	0.00137885	0.24	0.6283
SUB(SEQ)	26	2.90301822	0.11165455	19.44	<.0001
PER	1	0.00112942	0.00112942	0.20	0.6611
TRT	1	0.00849164	0.00849164	1.48	0.2350

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00137885	0.00137885	0.01	0.9124

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02462814	0.02025692	-1.22	0.2350

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	2.80853209	0.09684593	16.38	<.0001
Error	26	0.15372510	0.00591250		
Corrected Total	55	2.96225719			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.948105	0.880060	0.076893	8.737224

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00104956	0.00104956	0.18	0.6770
SUB(SEQ)	26	2.79921598	0.10766215	18.21	<.0001
PER	1	0.00121255	0.00121255	0.21	0.6544
TRT	1	0.00705400	0.00705400	1.19	0.2847

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00104956	0.00104956	0.18	0.6770
SUB(SEQ)	26	2.79921598	0.10766215	18.21	<.0001
PER	1	0.00121255	0.00121255	0.21	0.6544
TRT	1	0.00705400	0.00705400	1.19	0.2847

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00104956	0.00104956	0.01	0.9221

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02244676	0.02055047	-1.09	0.2847

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	3.14135100	0.10832245	2.53	0.0095
Error	26	1.11190660	0.04276564		
Corrected Total	55	4.25325760			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.738575	2.597258	0.206799	7.962188

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00254152	0.00254152	0.06	0.8093
SUB(SEQ)	26	2.86702170	0.11027007	2.58	0.0094
PER	1	0.23629782	0.23629782	5.53	0.0266
TRT	1	0.03548996	0.03548996	0.83	0.3707

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00254152	0.00254152	0.06	0.8093
SUB(SEQ)	26	2.86702170	0.11027007	2.58	0.0094
PER	1	0.23629782	0.23629782	5.53	0.0266
TRT	1	0.03548996	0.03548996	0.83	0.3707

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00254152	0.00254152	0.02	0.8805

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.05034875	0.05526924	-0.91	0.3707

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6206.03173	91.46966	<.0001	-1.51	0.1443
2	6400.74027	91.46966	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6304.40301	93.21836	<.0001	-1.39	0.1771
2	6487.31142	93.21836	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2912.27954	115.45002	<.0001	-0.87	0.3922
2	3054.35896	115.45002	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.70949004	0.01432381	<.0001	-1.22	0.2350
2	8.73411819	0.01432381	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.72600099	0.01453137	<.0001	-1.09	0.2847
2	8.74844775	0.01453137	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.93701412	0.03908125	<.0001	-0.91	0.3707
2	7.98736287	0.03908125	<.0001		

SEQ	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6382.13638	91.46966	<.0001	1.22	0.2343
2	6224.63562	91.46966	<.0001		

SEQ	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6468.53835	93.21836	<.0001	1.10	0.2803
2	6323.17608	93.21836	<.0001		

SEQ	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2992.64139	115.45002	<.0001	0.11	0.9100
2	2973.99711	115.45002	<.0001		

SEQ	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.72676620	0.01432381	<.0001	0.49	0.6283
2	8.71684203	0.01432381	<.0001		

SEQ	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.74155359	0.01453137	<.0001	0.42	0.6770
2	8.73289515	0.01453137	<.0001		

SEQ	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.96892528	0.03908125	<.0001	0.24	0.8093
2	7.95545171	0.03908125	<.0001		

PER	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6254.25836	91.46966	<.0001	-0.76	0.4543
2	6352.51364	91.46966	<.0001		

PER	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6345.75801	93.21836	<.0001	-0.76	0.4541
2	6445.95642	93.21836	<.0001		

PER	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2779.52450	115.45002	<.0001	-2.50	0.0192
2	3187.11400	115.45002	<.0001		

PER	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.71731322	0.01432381	<.0001	-0.44	0.6611
2	8.72629502	0.01432381	<.0001		

PER	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.73257112	0.01453137	<.0001	-0.45	0.6544
2	8.74187762	0.01453137	<.0001		

PER	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.89723002	0.03908125	<.0001	-2.35	0.0266
2	8.02714697	0.03908125	<.0001		

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6206.03173	91.46966	<.0001	-1.51	0.1443
2	6400.74027	91.46966	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6304.40301	93.21836	<.0001	-1.39	0.1771
2	6487.31142	93.21836	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2912.27954	115.45002	<.0001	-0.87	0.3922
2	3054.35896	115.45002	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.70949004	0.01432381	<.0001	-1.22	0.2350
2	8.73411819	0.01432381	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.72600099	0.01453137	<.0001	-1.09	0.2847
2	8.74844775	0.01453137	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.93701412	0.03908125	<.0001	-0.91	0.3707
2	7.98736287	0.03908125	<.0001		

2. Fed

```
ODS RTF file='FED.rtf' style=styles.jlo;
*FILENAME=C:\SAS\BE02dvp04.SAS;
%INCLUDE "C:\SAS\MACROLIB.SAS";

        *ASSIGN WHETHER HAVE GROUP EFFECT:
        TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
        TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
        TRTGROUP =        NO GROUP EFFECT IN STUDY
        NOTE:  group variable has to be named GRP in the dataset;

%let trtgroup=;
%let drug=Abacavir;
%let strength=300 mg;
%let doseform=Tablet;
%let anda=78742;
%let studytype=FED;
%let studydir=C:\Documents and Settings\robertsons\My Documents\OGD Work\ANDAs\Current\Abacavir
(pepfar)\SAS\Fed;
* %let plasmadata=apone250.dat;
* %let pkdata=apone250.pkv;

options mlogic mprint symbolgen;

        *NAME OF OUTPUT TABLE FILE;
%LET ODSFILE=&studydir\&studytype..doc;

        *NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC FILE;
%LET PLOTFILE=&studydir\&studytype..gif;

        *VARIABLE LIST FOR SORTING AND MERGING;
%LET VARSORT=SUB PER;
%GLOBAL SUB SEQ PER TRT TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME THALF CLAST KE_FIRST KE_LAST OLDNAME
NEWNAME;

        *STEP 1: SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
                 SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE WILL BE USED
FOR
                 CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS.
                 SELECT CONTINU2.SAS FOR STATISTICS ON CALCULATED PARAMETERS;

%LET FNAME=%QUOTE(C:\SAS\CONTINU.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CONTINU2.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CALCKE.SAS);

        *STEP 2: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
                 IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
                 IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3
                 IF MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4;

*FILENAME ORGPLASM DDE 'EXCEL|Fast-IB!R2C1:R65C23';
*FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1;                                  /* FIRST OBSERVATION */
*%LET VARPLASM=SUB PER SEQ TREAT $ c_5 c_25 C1-C15; /* VARIABLE LIST FOR THE PLASMA DATA FILE */
*%LET PLASMLS=256;                                        /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
*RUN;

        *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME CONCDATA "P:\Data\Firms\Roxane\77262\Fast";

        *SPECIFY NAME OF THE CONCENTRATION SAS DATASET*;
*%let cdata=plconc;
*DATA PLASMA;
*       SET CONCDATA.&CDATA(rename=(seq=_seq trt=treat));
*       rename subj = sub;
*                if _seq = "AB" then seq = 1;
*                else if _seq = "BA" then seq = 2;
*                if treat = "A" then trt = 1;
*                else if treat = "B" then trt = 2;
*RUN;
*%SORTDS(PLASMA, &VARSORT)
*RUN;

        *STEP 3: PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
                 IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
```

```
                IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4*;

*FILENAME ORGPARAM DDE 'EXCEL|Fast-IB!R2C25:R65C29';
*FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1;                                   /* FIST OBSERVATION */
*%LET VARPARAM=SUB PER SEQ TREAT $ COHORT AUCT AUCI CMAX TMAX THALF KE; /* VARIABLE LIST */
*%LET PARAMLS=256;                                          /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;

        *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME PKDATA "P:\Data\Firms\          (b) (4)Fast";

        *SPECIFY NAME OF THE PK SAS DATASET*;
*%let pdata=params;
*DATA PARAME;
*       SET CONCDATA.&PDATA(rename=(seq=_seq trt=treat));
*       sub = subj;
*       if _seq = "AB" then seq = 1;
*       else if _seq = "BA" then seq = 2;
*       if treat = "A" then trt = 1;
*       else if treat = "B" then trt = 2;
*       rename lambda_z = KE;
*RUN;
*%SORTDS(PARAME, &VARSORT)
*RUN;

        *STEP 4: WRITE THE FILENAME OF THE MERGED DATA
                IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 2 OR 3
                IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE*;

FILENAME ORGMERGE DDE 'EXCEL|Data!R2C1:R49C28';
*FILENAME ORGMERGE 'C:\Data\Firms          (b) (4)\Fasting\FDA.1';
%LET FIRSTOBS=1;                                    /* WRITE LINE NUMBER FOR THE FIRST OBSERVATION */
%LET VARMERGE=SUB SEQ PER TREAT$ C1-C18 AUCT AUCI CMAX KE THALF TMAX;
%LET MERGELS=500;                                   /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
RUN;
%SORTDS(MERGED, &VARSORT)
RUN;

        *STEP 5: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY;

%LET    CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18);

        *STEP 6: ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME;

%LET    TIME=%STR(T1=0; T2=0.25; T3=0.5; T4=0.75; T5=1.0; T6=1.25; T7=1.5; T8=1.75; T9=2; T10=2.25;
T11=2.5; T12=3;
        T13=4; T14=5; T15=6; T16=8; T17=10; T18=12);

        *STEP 7: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS;

%LET NO_ASSAY=18;

        *STEP 8: INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT IN THE DATA
SUBMITTED;

%LET KE_FIRST=&NO_ASSAY-5;
%LET KE_LAST=&NO_ASSAY-1;

        *STEP 9: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION
                VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL
                LEAVE AS IT IS IF NO CHANGE IS DESIRED;

*%LET REMOVSUB=%STR(IF SUB^=26);
*       IF SUB^=15;
*%LET REMOVSUB=%STR(IF TMAX^=0.25);

        *STEP 10:       IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
                CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC
                IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED;

%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST; IF TREAT='A' THEN TRT=1; ELSE TRT=2);

        *PK REPEATS - USE ORIGINAL CONCENTRATIONS;
*DATA plasma;
*       set plasma;
*       if sub="S06" and peri="P2" then t8=123.256;
*       if sub="S17" and peri="P1" then t6=340.101;
*RUN;
```

```
        *STEP 11:        DATA STEP FOR ORIGIN (MASTER DATA SET) OPEN OR CLOSE LINES IF NEEDED;

DATA ORIGIN;
        ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
        ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
*       SET PLASMA;
*       SET PARAME;
        SET MERGED;
&TIME;
KE FIRST=0;
KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
RUN;


        *STEP 12:        DESCRIBE TITLES FOR TABLES;

%LET TITLE1=Mean Plasma Abacavir Levels;
%LET TITLE2=Mean Plasma Abacavir Levels for Test & Reference Products;

        *DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH;
%LET TITLE3=     Plasma Abacavir Levels;
%LET TITLE4=     Abacavir Tablets, 300 mg, Matrix, ANDA 78742;
%LET TITLE5=     Fed Study;
%LET TITLE6=     Dose=1 x 300mg;
%LET FOOTNOT1=   1=TEST  2=REF;
%LET FOOTNOT2=   UNIT: Plasma Level=ng/mL  Time=hrs;
%LET FOOTNOT3=   UNIT: AUC=ng hr/mL  CMAX=ng/mL  TMAX=hr;
%LET FOOTNOT4=   Log-transformed Data Were Converted To Anti-log In The Table;
%LET LABEL1=     Plasma Level, ng/mL;
%LET LABEL2=     Time, Hrs;
%LET LABEL3=     Test;
%LET LABEL4=     Reference;

        *PRINT THE ORIGINAL DATASET SUBMITTED;
%PRINT(ORIGIN, ORIGINAL DATA SUBMITTED)
RUN;

        *TO CHECK >0 CONC FOR C1;
*PROC PRINT data=origin;
*       where c1 > 0;
*       var sub per seq c1 cmax;
*RUN;

%COPYDS(ORIGIN, NEW)
RUN;

        *STEP 13:        OPEN IF YOU WANT TO REMOVE, ADD OR EDIT;

*%REMUVSUB(NEW, NEW)
RUN;

%ADDVARIA(NEW, NEW)
RUN;

%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST)              /* TO EDIT KE-FIRST AND KE-LAST */
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
        *TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE NAMES;
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;
```

ORIGINAL DATA SUBMITTED

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	24	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of observations	48

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	64448396.58	2577935.86	7.59	<.0001
Error	22	7474439.92	339747.27		
Corrected Total	47	71922836.50			

R-Square	Coeff Var	Root MSE	AUCT Mean
0.896077	9.819582	582.8784	5935.879

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	5913002.03	5913002.03	17.40	0.0004
SUB(SEQ)	22	58211826.99	2645992.14	7.79	<.0001
PER	1	271055.40	271055.40	0.80	0.3814
TRT	1	52512.17	52512.17	0.15	0.6980

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	5913002.03	5913002.03	17.40	0.0004
SUB(SEQ)	22	58211826.99	2645992.14	7.79	<.0001
PER	1	271055.40	271055.40	0.80	0.3814
TRT	1	52512.17	52512.17	0.15	0.6980

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	5913002.034	5913002.034	2.23	0.1491

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-66.1514477	168.262510	-0.39	0.6980

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	64263290.21	2570531.61	7.48	<.0001
Error	22	7557217.43	343509.88		
Corrected Total	47	71820507.65			

R-Square	Coeff Var	Root MSE	AUCI Mean
0.894776	9.733728	586.0972	6021.302

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	5790685.98	5790685.98	16.86	0.0005
SUB(SEQ)	22	58151557.87	2643252.63	7.69	<.0001
PER	1	262570.52	262570.52	0.76	0.3914
TRT	1	58475.84	58475.84	0.17	0.6839

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	5790685.98	5790685.98	16.86	0.0005
SUB(SEQ)	22	58151557.87	2643252.63	7.69	<.0001
PER	1	262570.52	262570.52	0.76	0.3914
TRT	1	58475.84	58475.84	0.17	0.6839

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	5790685.975	5790685.975	2.19	0.1530

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-69.8067821	169.191677	-0.41	0.6839

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: CMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	16910601.30	676424.05	4.73	0.0002
Error	22	3146478.11	143021.73		
Corrected Total	47	20057079.41			

R-Square	Coeff Var	Root MSE	CMAX Mean
0.843124	16.44723	378.1821	2299.367

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1889814.38	1889814.38	13.21	0.0015
SUB(SEQ)	22	14809173.42	673144.25	4.71	0.0003
PER	1	178847.57	178847.57	1.25	0.2755
TRT	1	32765.92	32765.92	0.23	0.6369

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1889814.38	1889814.38	13.21	0.0015
SUB(SEQ)	22	14809173.42	673144.25	4.71	0.0003
PER	1	178847.57	178847.57	1.25	0.2755
TRT	1	32765.92	32765.92	0.23	0.6369

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1889814.384	1889814.384	2.81	0.1080

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-52.2541250	109.171781	-0.48	0.6369

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	2.29627307	0.09185092	8.80	<.0001
Error	22	0.22971747	0.01044170		
Corrected Total	47	2.52599054			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.909058	1.179363	0.102185	8.664392

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.21451217	0.21451217	20.54	0.0002
SUB(SEQ)	22	2.06347671	0.09379440	8.98	<.0001
PER	1	0.01557740	0.01557740	1.49	0.2349
TRT	1	0.00270679	0.00270679	0.26	0.6157

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.21451217	0.21451217	20.54	0.0002
SUB(SEQ)	22	2.06347671	0.09379440	8.98	<.0001
PER	1	0.01557740	0.01557740	1.49	0.2349
TRT	1	0.00270679	0.00270679	0.26	0.6157

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.21451217	0.21451217	2.29	0.1447

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.01501884	0.02949817	-0.51	0.6157

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	2.20968536	0.08838741	8.65	<.0001
Error	22	0.22473908	0.01021541		
Corrected Total	47	2.43442444			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.907683	1.164482	0.101071	8.679508

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.20299659	0.20299659	19.87	0.0002
SUB(SEQ)	22	1.98862231	0.09039192	8.85	<.0001
PER	1	0.01504522	0.01504522	1.47	0.2378
TRT	1	0.00302123	0.00302123	0.30	0.5920

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.20299659	0.20299659	19.87	0.0002
SUB(SEQ)	22	1.98862231	0.09039192	8.85	<.0001
PER	1	0.01504522	0.01504522	1.47	0.2378
TRT	1	0.00302123	0.00302123	0.30	0.5920

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.20299659	0.20299659	2.25	0.1482

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.01586723	0.02917678	-0.54	0.5920

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	3.96229385	0.15849175	4.92	0.0002
Error	22	0.70804736	0.03218397		
Corrected Total	47	4.67034121			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.848395	2.331240	0.179399	7.695429

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.53368890	0.53368890	16.58	0.0005
SUB(SEQ)	22	3.34146470	0.15188476	4.72	0.0003
PER	1	0.06257862	0.06257862	1.94	0.1771
TRT	1	0.02456163	0.02456163	0.76	0.3918

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.53368890	0.53368890	16.58	0.0005
SUB(SEQ)	22	3.34146470	0.15188476	4.72	0.0003
PER	1	0.06257862	0.06257862	1.94	0.1771
TRT	1	0.02456163	0.02456163	0.76	0.3918

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.53368890	0.53368890	3.51	0.0742

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.04524160	0.05178801	-0.87	0.3918

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5902.80278	118.97956	<.0001	-0.39	0.6980
2	5968.95423	118.97956	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5986.39874	119.63658	<.0001	-0.41	0.6839
2	6056.20552	119.63658	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2273.23967	77.19611	<.0001	-0.48	0.6369
2	2325.49379	77.19611	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.65688269	0.02085835	<.0001	-0.51	0.6157
2	8.67190153	0.02085835	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.67157480	0.02063110	<.0001	-0.54	0.5920
2	8.68744202	0.02063110	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.67280811	0.03661965	<.0001	-0.87	0.3918
2	7.71804971	0.03661965	<.0001		

The GLM Procedure
Least Squares Means

SEQ	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6286.85933	118.97956	<.0001	4.17	0.0004
2	5584.89767	118.97956	<.0001		

SEQ	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6368.63380	119.63658	<.0001	4.11	0.0005
2	5673.97046	119.63658	<.0001		

SEQ	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2497.78833	77.19611	<.0001	3.64	0.0015
2	2100.94513	77.19611	<.0001		

SEQ	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.73124271	0.02085835	<.0001	4.53	0.0002
2	8.59754150	0.02085835	<.0001		

SEQ	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.74453991	0.02063110	<.0001	4.46	0.0002
2	8.61447691	0.02063110	<.0001		

SEQ	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.80087329	0.03661965	<.0001	4.07	0.0005
2	7.58998452	0.03661965	<.0001		

PER	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6011.02494	118.97956	<.0001	0.89	0.3814
2	5860.73206	118.97956	<.0001		

The GLM Procedure
Least Squares Means

PER	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6095.26306	119.63658	<.0001	0.87	0.3914
2	5947.34120	119.63658	<.0001		

PER	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2360.40763	77.19611	<.0001	1.12	0.2755
2	2238.32583	77.19611	<.0001		

PER	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.68240680	0.02085835	<.0001	1.22	0.2349
2	8.64637741	0.02085835	<.0001		

PER	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.69721271	0.02063110	<.0001	1.21	0.2378
2	8.66180411	0.02063110	<.0001		

PER	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.73153599	0.03661965	<.0001	1.39	0.1771
2	7.65932183	0.03661965	<.0001		

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5902.80278	118.97956	<.0001	-0.39	0.6980
2	5968.95423	118.97956	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5986.39874	119.63658	<.0001	-0.41	0.6839
2	6056.20552	119.63658	<.0001		

The GLM Procedure
Least Squares Means

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	2273.23967	77.19611	<.0001	-0.48	0.6369
2	2325.49379	77.19611	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.65688269	0.02085835	<.0001	-0.51	0.6157
2	8.67190153	0.02085835	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.67157480	0.02063110	<.0001	-0.54	0.5920
2	8.68744202	0.02063110	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	7.67280811	0.03661965	<.0001	-0.87	0.3918
2	7.71804971	0.03661965	<.0001		

F. Additional Attachments

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-742 APPLICANT: Matrix Laboratories

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The DBE acknowledges your acceptance of the following dissolution method and specification:

USP Apparatus:	II (Paddle) @ 75 rpm
Medium:	0.1 N HCl (at 37°C)
Volume:	900 mL
Specification:	NLT (Q) 80% at 15 min.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely Yours,

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 78-742

BIOEQUIVALENCE – Acceptable Submission date: 12/27/06

1. FASTING STUDY (STF) Strength: 300 mg
Outcome: **AC**
Clinical Study Site: Veeda Clinical Research Pvt. Ltd., India
Analytical Site: (b) (4)

2. FED STUDY (STP) Strength: 300 mg
Outcome: **AC**
Clinical Study Site: Veeda Clinical Research Pvt. Ltd., India
Analytical Site: (b) (4)

Outcome Decisions: **AC = acceptable**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091294

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Outcome Page
ANDA: 091294

COMPLETED ASSIGNMENT FOR 91294 ID: 10376

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10376	1/28/2009	Bioequivalence Study	BE Study	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Typical BE Study Applications

BE Study Fasting and Fed Referenced to ANDA 78742	
BE study data Review	1
Total	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MYLAN PHARMACEUTICALS INC	ABACAVIR SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA H LEE
02/19/2010

MOHEB H MAKARY
02/19/2010

ETHAN M STIER on behalf of BARBARA M DAVIT
02/19/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	91-294	
Drug Product Name	Abacavir Sulfate Tablets	
Strength (s)	300mg	
Applicant Name	Mylan Pharmaceuticals Inc.	
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310	
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs	
Contact's Phone Number	(304) 599-2595	
Contact's Fax Number	(304) 285-6407	
Submission Date(s)	January 28, 2009 August 27, 2009	
First Generic	No	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	06-VIN-132	06-VIN-133
Study Type (s)	Fasting	Fed
Strength(s)	300 mg	300 mg
Clinical Site	veeda clinical research Pvt. Ltd.	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi Ahmedabad – 380 015, India	
Analytical Site	(b) (4)	
Analytical Address		
OVERALL REVIEW RESULT	**ADEQUATE**	

Review of a Dissolution Amendment

1 EXECUTIVE SUMMARY

In this dissolution amendment, the firm, Mylan, submitted its response to the deficiency letter dated July 22, 2009 from the Division of Bioequivalence (DBE) for its proposed drug product, Abacavir Sulfate Tablets, 300 mg. In response to the deficiency letter, the firm has submitted clarification on all the discrepancies identified by the reviewer concerning the incompleteness of the data submitted. The firm also submitted supportive documents. The firm's responses to the deficiency comments are acceptable. The dissolution testing is now considered acceptable.

Note: The 356 form submitted with the original application was under the applicant Matrix Laboratories Limited; however, the 356 form submitted with the amendment was under the applicant Mylan Pharmaceuticals Inc.

The DBE will review the fasted and fed BE studies at a later date.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. The clinical and analytical site was last inspected on (b) (4) for NDA 22-459 and the outcome was VAI.

Background[1]

On January 28, 2009, the firm submitted *in vitro* dissolution testing comparing its test product, Abacavir Sulfate Tablets, 300 mg, to the RLD product, Ziagen ® (abacavir sulfate) Tablets, 300 mg. The *in vitro* dissolution testing was incomplete due to the following reasons.

1. The firm should be advised to provide the raw data for the 12 units of both test and reference products for review.

DBE Comment No. 01
Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Firm's Response:
None

DBE Deficiency Comment No. 01
You did not provide the raw data for the 12 units of both test and reference in dissolution testing.

Firm's Response:

[1] DARRTS: 91-294.

COMPARATIVE DISSOLUTION PROFILES
Abacavir Sulfate Tablets 300mg vs Ziagen Tablets 300 mg

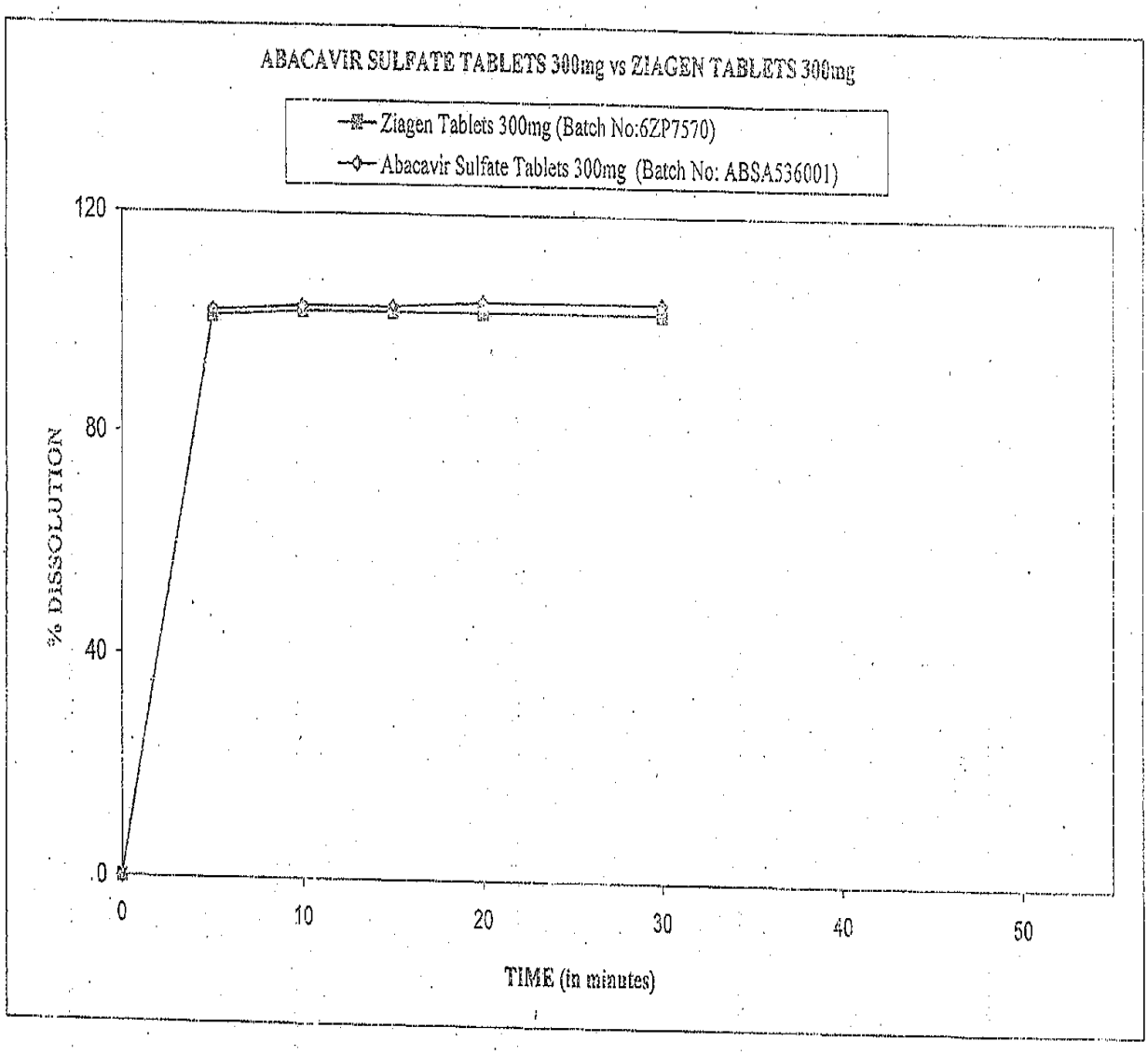
Product : Ziagen Tablets 300mg
Batch Number : 6ZP7570

Tablet No.	% drug dissolved at different time intervals				
	5 min	10 min	15 min	20 min	30 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MIN.					
MAX.					
MEAN	101	102	102	102	102
% RSD	0.9	1.2	1.1	0.8	0.8

Product: Abacavir Sulfate Tablets 300 mg
Batch Number : ABSA536001

Tablet No.	% drug dissolved at different time intervals				
	5 min	10 min	15 min	20 min	30 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MIN.					
MAX.					
MEAN	102	103	103	104	104
% RSD	2.6	2.6	2.2	2.5	2.2

Dissolution Parameters: 0.1 N HCl, 900 mL, USP Apparatus #II Paddle,75 RPM,37± 0.5°C



Reviewer's Comments:

1. The firm's dissolution testing data with the FDA method are acceptable. The firm's proposed specification of NLT 80% (Q) in 15 minutes is the same as that recommended by the FDA for this drug product.

Deficiency Comments:

None

Recommendations:

The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals Inc , on its test product, Abacavir Sulfate Tablets, 300 mg, comparing it to GlaxoSmithKline, Ziagen® (abacavir sulfate) Tablets, 300 mg, respectively, is acceptable.

The firm should be informed of the above recommendations.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-294

APPLICANT: Mylan Pharmaceuticals Inc

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

Your dissolution testing using the FDA-recommended method is acceptable. We acknowledge that you will conduct dissolution testing for the test product using the FDA-recommended method and specification.

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

1.1 Outcome Page

ANDA: 91-294

Enter Review Productivity and Generate Report

2 *COMPLETED ASSIGNMENT FOR 91294 ID: 9566*

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Abacavir Sulfate Tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9566	8/27/2009	Other	Dissolution Amendment	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE

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/s/

GLENDOLYNN S JOHNSON
10/27/2009

YIH CHAIN HUANG
10/27/2009

BARBARA M DAVIT
10/30/2009

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW- ADDENDUM

ANDA No.	91-294	
Drug Product Name	Abacavir Sulfate Tablets	
Strength (s)	300mg	
Applicant Name	Matrix Laboratories Limited, India	
Address	Matrix Laboratories Inc. 76,South Orange Ave, Suite 301, South Orange, NJ 07079, USA	
Applicant's Point of Contact	Keith Guinta	
Contact's Phone Number	973 761 1600	
Contact's Fax Number	973.761.1680	
Submission Date(s)	January 28, 2009	
First Generic	No	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	06-VIN-132	06-VIN-133
Study Type (s)	Fasting	Fed
Strength(s)	300 mg	300 mg
Clinical Site	veeda clinical research Pvt. Ltd.	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi Ahmedabad – 380 015, India	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	**Incomplete**	

I. EXECUTIVE SUMMARY

This addendum is to revise the following typographical error in the deficiency letter provided to the firm.

The typographical error in the original DBE letter provided to the firm is listed below with the corrected comment:

Original Comment

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of water, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

Corrected Comment:

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

*The dissolution testing should be conducted in 900 mL of **0.1 N HCl**, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.*

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

A letter with the corrections shown above will be sent to the firm to amend the previous DBE deficiency letter dated July 15, 2009.

ADDENDUM TO PREVIOUS BIOEQUIVALENCE DEFICIENCY LETTER

ANDA: 91-294

APPLICANT: Matrix Laboratories Limited

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The previous letter dated July 15, 2009 sent by the Division of Bioequivalence (DBE) contained a typographical error. The current letter is to correct the error and should supercede the previous letter. We regret the error and apologize for any inconvenience it may have caused.

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submissions acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

The following deficiencies have been identified:

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

2. You did not provide the raw data for the 12 units of both test and reference in dissolution testing.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

II. OUTCOME

ANDA: 91-294

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

III. *Completed Assignment for 91294 ID: 8689*

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Abacavir Sulfate Tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8689	1/28/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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/s/

GLENDOLYNN S JOHNSON
08/07/2009

YIH CHAIN HUANG
08/07/2009

CHANDRA S CHAURASIA on behalf of BARBARA M DAVIT
08/07/2009

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-294	
Drug Product Name	Abacavir Sulfate Tablets	
Strength (s)	300mg	
Applicant Name	Matrix Laboratories Limited, India	
Address	Matrix Laboratories Inc. 76,South Orange Ave, Suite 301, South Orange, NJ 07079, USA	
Applicant's Point of Contact	Keith Guinta	
Contact's Phone Number	973 761 1600	
Contact's Fax Number	973.761.1680	
Submission Date(s)	January 28, 2009	
First Generic	No	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	06-VIN-132	06-VIN-133
Study Type (s)	Fasting	Fed
Strength(s)	300 mg	300 mg
Clinical Site	veeda clinical research Pvt. Ltd.	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi Ahmedabad – 380 015, India	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	**Incomplete**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. The firm's proposed specification is the same as that the FDA-recommended specification of NLT 80% (Q) in 15 minutes. The dissolution data meet the specification at S1 level. However, the submission is incomplete since the firm did not submit the raw data for 12 units of both test and reference products for review.

The DBE will review the fasted and fed BE studies at a later date.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. The clinical and analytical site was last inspected on (b) (4) for NDA 22-459 and the outcome was VAI.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☐	☒	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Method Listed in Internal OGD Database
Abacavir

Dosage Form: Tablet

Medium: 0.1 N HCl

Apparatus: II (paddle)

Speed/RPMs: 75

Modify Date: 3/22/2006

Sampling Times: 5, 10, 15, and 30 min

Volume: 900

Notes:

Specification:

Note: The OGD database does not have specifications set for the single treatment of abacavir; however, there are specifications for the combination treatments of abacavir. The combination treatment of Abacavir Sulfate 300 mg and Lamivudine 150 mg/Zidovudine 300 mg tablets and Abacavir Sulfate/Lamivudine tablets have the following specifications: Lamiv and Zido: NLT 80% (Q) in 30, Abaca: NLT 80% (Q) in 15 min and both components: NLT 80% (Q) in 30 min, respectively. The specifications set for this application are consistent with the OGD database and allows the firm to meet the S1 level.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP - II (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	0.1M Hydrochloric acid
	Volume:	900 mL
	Temperature:	37°C ± 0.5 °C
Firm's Proposed Specifications	Complies with USP General Chapter <711> Not less than 80% (Q) of the labeled amount of Abacavir is dissolved in 15 minutes.	
Dissolution Testing Site (Name, Address)	Matrix Laboratoires Ltd., F-4 & F-12. Malegaon MIDC, Sinnar Nashik-422 113, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						5	**10**	**15**	**20**	**30**	
06-VIN-132 and 06-VIN-133	Aug 2006	ABSA536001 Mfg date: July 2006	300 mg Tablet	12	Mean	102	103	103	104	104	Module 5
					Range	(b) (4)					
					%CV	2.6	2.6	2.2	2.5	2.2	
	Aug 2006	6ZP7570 Exp date: Nov 2008	300 mg Tablet	12	Mean	101	102	102	102	102	
					Range	(b) (4)					
					%CV	0.9	1.2	1.1	0.8	0.8	

II. COMMENTS:

1. The firm's dissolution testing data with the FDA method are acceptable. The firm's proposed specification of NLT 80% (Q) in 15 minutes is the same as that recommended by the FDA for this drug product.

2. However, the firm did not provide the raw data for the 12 units of both test and reference in dissolution testing.

III. DEFICIENCY COMMENTS:

1. The firm should be advised to provide the raw data for the 12 units of both test and reference products for review.

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Matrix Laboratories Limited, on its test product, Abacavir Sulfate Tablets, 300 mg, comparing it to GlaxoSmithKline, Ziagen® (abacavir sulfate) Tablets, 300 mg, respectively, is incomplete due to the deficiency listed above.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-294

APPLICANT: Matrix Laboratories Limited

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submissions acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

The following deficiencies have been identified:

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of water, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

2. You did not provide the raw data for the 12 units of both test and reference in dissolution testing.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 91-294

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

VI. *Completed Assignment for 91294 ID: 8689*

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Abacavir Sulfate Tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8689	1/28/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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/s/

Glendolynn S Johnson
7/14/2009 03:58:52 PM
BIOPHARMACEUTICS

Yih Chain Huang
7/14/2009 04:02:45 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
7/15/2009 08:21:35 AM
BIOPHARMACEUTICS
Signing for Dr. Barbara M. Davit, Acting Director, DBE-2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

Other Review(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Amy M. Taylor MD, MHS, Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Linda L. Lewis, MD, Acting Deputy Director
Division of Pediatric and Maternal Health

DPMH PM Denise Pica-Branco, PhD

ANDA: 206725 (Lead Application)

Drug: abacavir

RLD: Ziagen® (abacavir) tablets
Ziagen® (abacavir) oral solution

Drug Class: antiretroviral

Date of Meeting: August 7, 2015

Consult Request: The Office of Generic Drugs (OGD) requested that DPMH review and comment on the carve-out or retention of protected pediatric information from generic abacavir.

BACKGROUND

Ziagen® (abacavir) Regulatory History

- Ziagen® oral tablet and oral solution (NDA 20-977 and 20-978) were originally approved for marketing on December 17, 1998. The original approval included

patients aged 3 months to 13 years. The pediatric dosing regimen was for twice daily dosing.

- A Written Request was issued on August 20, 1998 requesting studies in pediatric patients aged 3 months to 12 years with HIV infection. Pediatric exclusivity was granted on December 14, 1998.
- On July 18, 2008, twice daily dosing for adolescents was approved.
- On March 23, 2015, Ziagen® received 3 years of Waxman-Hatch marketing exclusivity for once daily dosing in pediatric patients 3 months of age and older in combination with other agents for the treatment of HIV-1 infection which expires March 23, 2018. Protected pediatric use information was added to:
  - Highlights
    - Dosage and Administration
  - Dosage and Administration
  - Adverse Reactions
  - Clinical Pharmacology
  - Clinical Studies

Pediatric Studies of Drugs

Although an ANDA seeking approval for a duplicate of a listed drug that has remaining exclusivity for an approved indication or condition of use must either carve out that indication or condition of use (which it is permitted to do if the drug remains safe and effective for the remaining non-protected conditions of use) or await expiration of that exclusivity before seeking approval, the Best Pharmaceuticals for Children Act (BPCA) (section 505A of the Food, Drug and Cosmetic Act) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) provides additional authority to permit the approval of drugs under 505(j) when pediatric information protected by exclusivity [three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the labeling and cannot be safely carved out. It also expressly authorizes FDA to include a disclaimer in ANDA labeling when such labeling is carved out.

505A(o)(l)(2) states:
PEDIATRIC INFORMATION IS ADDED TO LABELING.—‘‘(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(F).

‘‘(2) LABELING.— Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(F), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include — ‘‘(A) a statement that, because of marketing exclusivity for a manufacturer — ‘‘(i) the drug is not labeled for pediatric use; or ‘‘(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the

pediatric use under paragraph (1); and ‘‘(B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.”

In addition, FDA added a provision on pediatric risk information in § 201.56(d)(5) of the January 24, 2006, Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products to avoid any possible confusion as to what information the agency may require in generic labeling that otherwise omits a pediatric indication or other aspect of labeling pertaining to pediatric use protected by patent or exclusivity. § 201.56(d)(5) states:

“Any risk information that is required under § 201.57(c)(9)(iv) is considered appropriate pediatric contraindications, warnings, or precautions within the meaning of 505A(1)(2) of the Federal Food Drug and Cosmetic Act (the act) (21 U.S.C. 355A(1)(2)), whether such information appears in the Contraindications, Warnings and Precautions, or Use in Specific Populations section of labeling.”

Reviewer comments:
These provisions under BPCA outlined above require the generic labeling to:

1) *Provide a standard disclaimer when new pediatric information in labeling is protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] and “carved out,” (i.e., not included in generic labeling).*

2) *Retain important pediatric safety information protected by three-year Hatch-Waxman exclusivity that is necessary for safe use.*

Disclaimers generally are not used for other protected information, including indications protected by Orphan Drug Exclusivity (ODE), that is omitted from generic labeling. Pediatric indications and uses with ODE may be omitted from generic drug labeling ((21 U.S.C. 355(j)(2)(A)(v); see also 21 CFR 314.92(a)(1), 314.94(a)(8)(iv) and 314.127(a)(7)) and 21 CFR 316.31) as long as the drug product remains safe and effective for the remaining non-protected conditions of use.

DPMH Summary
OGD, DPMH, and DAVP (in consultation with OCC) agreed that generic abacavir could be approved without the protected pediatric use information related to the Ziagen® March 23, 2015, approval of a once daily dosing regimen in pediatric patients with HIV-1 infection as no unique or unexpected safety concerns were observed in the clinical trials. All information related to the Ziagen® March 23, 2015, approval of a once daily dosing regimen in pediatric patients with HIV-1 infection can be carved out from generic abacavir labeling until Waxman-Hatch Exclusivity expires on March 23, 2018 except for information comparing plasma concentration of abacavir in pediatric patients to adults in Section 12 Clinical Pharmacology subsection 12.3 Pharmacokinetics. This information

combines data related to both the once daily and twice daily dosing and separating out the data related to once daily dosing would be difficult.

The following general disclaimer was agreed upon:

> **Additional pediatric use information for patients aged 3 months and older is approved for ViiV Healthcare Company's Ziagen® (abacavir sulfate) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.**

DPMH concurs with the model labeling included in the OGD meeting minutes (Reference ID 3816709) for generic versions of abacavir that carve out exclusivity-protected information. DPMH concludes that a generic drug with this labeling would not be less safe or effective than Ziagen® for the remaining non-protected conditions of use.

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/s/

AMY M TAYLOR
10/15/2015

HARI C SACHS
10/16/2015

LINDA L LEWIS
10/19/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091294

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pediatric Use Labeling Package

Innovator Product Name:
ZIAGEN® (abacavir) tablets
ZIAGEN® (abacavir) oral solution

Background

The Reference Listed Drug, **ZIAGEN®** (abacavir) (NDA 020977 and 020978) of ViiV Healthcare UK Limited received 3 years of Hatch-Waxman marketing exclusivity for once daily dosing in pediatric patients 3 months of age and older in combination with other antiretroviral agents for the treatment of HIV-1 infection (D-147), which expires March 23, 2018.

On, December 18, 2001, Congress passed the "Best Pharmaceuticals for Children Act" (BPCA). Section 11 allows for prompt approval of an ANDA that omits a pediatric indication or other aspect of labeling pertaining to pediatric use when that labeling is protected by patent or exclusivity. A labeling statement indicating the ANDA is not labeled for pediatric use because of marketing exclusivity is required. In addition, the statute directs FDA to include in the ANDA labeling a statement of any appropriate pediatric contraindications, warnings, precautions or other information considered necessary to assure safe use.

1. Are there any issues of safety or effectiveness for the remaining conditions of use when the protected pediatric information is removed from the labeling?
2. Are the proposed labeling statements acceptable?
3. Are there any statements of appropriate pediatric contraindications, warnings, or precautions that should be included in the generic drug labeling?

Consult Request Form (Form FDA 3291)	Ziagen consult form.doc
CDER Office of Chief Counsel Tracking Information Form	OCC Consult Form Abacavir.docx
Previously approved innovator labeling: NDA 020977/S-028 and 020978/S-032 approved February 19, 2015	ZiagenOLDLABELING .pdf
New innovator labeling with protected pediatric information: NDA 020977/S-027 and 020978/S-031 approved March 23, 2015	ZiagenNEWLABELING .pdf

Proposed model labeling for ANDAs	 Ziagen Proposed Model Labeling.doc
Innovator's exclusivity information from the Orange Book	 Ziagen Patents and Exclusivities.doc

Esther Kim
Labeling Reviewer
Office of Generic Drugs
(240) 402-5897
Esther.Kim@fda.hhs.gov

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/s/

CARRIE L LEMLEY
07/07/2015

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: II	Team: 23	PM: Sean Belouin

Electronic ANDA: Yes ☒ No ☐

ANDA #: 091294
Firm Name: Mylan Pharmaceuticals, Inc.
ANDA Name: Abacavir Tablets USP, 300 mg
RLD Name: Ziagen Tablets, 300 mg

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 23\Electronic AP Summary

AP/TA Letter Located:
V:\Chemistry Division II\Team 23\APPROVAL LTRS and cGMP LETTERs

Project Manager Evaluation: **Date: 6/12/12 Initials:** SJB

☒ Previously reviewed and tentatively approved --- Date 2/15/11
☐ Previously reviewed and CGMP Complete Response issued -- Date N/A

Original Rec'd date 1/28/09	Date of Application 1/28/09	Date Acceptable for Filing 5/4/09
Patent Certification (type) PIV, PIII	Date Patent/Excl. expires 6/18/12	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** 18229 (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: N/A Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date: N/A	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 6/15/12* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 6/14/12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 10/30/09 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 6/11/12 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) N/A

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☒ Labeling Endorsement, Date emailed: 6/12/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 6/13/12

☒ Division

☒ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 6/14/2012**
Chief, Reg. Support Branch **Initials:** IM for MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Ziagen NDA# 20-977 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☒ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day Yes	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary 6/11/2012	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:BOS = 20-977 (Ziagen) Submission date 1/28/2009 with PIII to '394 and '500 patants and PIV to '540 patent. Ack LO 5/4/2009. Copies of PIV RR sent via (b) (4) 5/21/2009 to GlaxoSmithKline (NC, GB) and SmithKline Beecham (PA) and rc'd 5/22, 5/26 and 5/22/2009, respectively. No litigation was filed within the 45 day time period. On 8/26/2009, transfer of ownership of the ANDA from Matrix to Mylan ocurred. Application TA'd 2/15/2011.
ANDA 91-294 is the first application to be received for Abacavir with a PIV certification. All the previous ANDA's were submitted under the PEPFAR program. The one exception is ANDA 77-844 from Aurobindo, which was originally submitted as a PEPFAR application with PIII certs to all patents, but was amended 12/14/2011 with a PIV to the '540 patent. Aurobindo was not sued.
By virtue of being the first applicant with a PIV certification pre-MMA, Mylan is eligible for 180-day exclusivity and is eligible for Full Approval after the expiration of the '394 patent 6/18/2012.

2. ***Labeling Endorsement***

Reviewer, Chan H. Park:
Date 6/12/12
Initials CHP

Labeling Team Leader, Koung U. Lee:
Date 6/12/12
Initials CHP

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:
From: Lee, Koung U
Sent: Wednesday, June 13, 2012 2:57 PM
To: Belouin, Sean; Park, Chan H
Subject: RE: 91294 LABELING ENDORSEMENT (FULL AP, Monday, June 18th)

Gentlemen,

I concur. Thanks.

Koung

From: Belouin, Sean
Sent: Wednesday, June 13, 2012 2:53 PM
To: Park, Chan H

Cc: Lee, Koung U
Subject: RE: 91294 LABELING ENDORSEMENT (FULL AP, Monday, June 18th)

Thanks Chan. I've updated the letter accordingly.

-Sean

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 14Jun2012**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 6/14/2012**
Chemistry Div. **II (Smith)** **InitialsGJS**
Comments:CMC Acceptable.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 6/18/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Multiple ANDAs have been tentatively approved (including this one) for this drug product.

OGD Office Management Evaluation

6. Peter Rickman **Date 6/18/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: This ANDA was granted tentative approval on February 15, 2011. Final approval was blocked at that time by Mylan's paragraph III certification to the '394 patent due to expire on June 18, 2012 (with pediatric exclusivity extension). Refer to the administrative summary created at the time of the tentative approval. With the expiration of the '394 patent, this ANDA is eligible for final approval. Note: This ANDA is not part of the PEPFAR program.

Final-printed labeling (FPL) found acceptable for approval 6/11/12, as endorsed 6/13/12.

CMC found acceptable for approval (Chemistry Review #5) 6/14/12.

AND/OR

7. Robert L. West **Date 6/18/12**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 6/15/12 (Verified 6/18/12). No "OAI" Alerts noted.

Mylan provided a paragraph IV certification to the '540 patent, but was not sued within the 45-day period. Mylan also provided a paragraph III cetification to the '394 patent. The '394 patent (with pediatric exclsuivity extension) expired on 6/18/12. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This first-generic ANDA is recommended for final approval. The agency has agreed that with this approval, Mylan is eligible for 180-day generic drug exclusivity for this drug product.

8. ***OGD Director Evaluation***

Keith Webber
Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D. 6/18/12.
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager

Date 6/18/12
Initials SJB

Check Communication and Routing Summary into DARRTS

EER DATA:

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

- 
-  [1]
-  [2]

- FDA Home[3]
- Drug Databases[4]
- Orange Book[5]

-

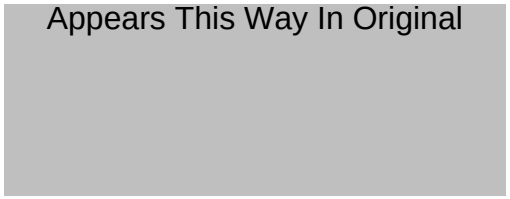
Patent and Exclusivity Search Results from query on Appl No 020977 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020977	001	5034394	Dec 18, 2011	Y	Y		
N020977	001	5034394*PED	Jun 18, 2012				
N020977	001	6294540	May 14, 2018	Y	Y	U - 65	
N020977	001	6294540*PED	Nov 14, 2018			U - 65	

Exclusivity Data

There is no unexpired exclusivity for this product.


Appears This Way In Original

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/s/

SEAN J BELOUIN
06/18/2012

TELEPHONE CONFERENCE FAX

ANDA 091294

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Mylan Pharmaceuticals Inc TEL: (304) 599-2595

ATTN: S. Wayne Talton FAX: (304) 285-6407

FROM: Sukhamaya (Sam) Bain, Ph.D. FDA CONTACT PHONE: (240) 276-8579

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 28, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Abacavir Sulfate Tablets, 300 mg.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Tina Nhu at (240) 276-8548. Please submit documentation by fax to the attention of the Project Manager at (240) 276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

List of Deficiencies to Be Communicated to the Applicant

ANDA: 091294 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Abacavir Sulfate Tablets USP, 300 mg.

Reference is made to your amendment dated April 5, 2012.

The following deficiencies represent minor deficiencies:

1. (b) (4)

2.

Sincerely yours,

Glen J. Smith, Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

SUKHAMAYA BAIN
06/04/2012

From: Shimer, Martin
To: "Keith Giunta";
cc: "Nitin.Bhattad@matrixlabsindia.com"; Shimer, Martin;
Subject: RE: ANDA 91-294 Abacavir Sulfate - PIV Notice Request
Date: Monday, May 04, 2009 4:15:25 PM

Mr. Giunta,

It is permissible to use [redacted] (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 91-294.

Regards,

Martin Shimer

From: Keith Giunta [mailto:Keith.Giunta@matrixlabsus.com]
Sent: Monday, May 04, 2009 3:45 PM
To: Shimer, Martin
Cc: Nitin.Bhattad@matrixlabsindia.com
Subject: ANDA 91-294 Abacavir Sulfate - PIV Notice Request

Dear Mr. Shimer,

We have recently received filing acceptance for the above-referenced PIV ANDA. I'm writing to request permission to send the PIV Notice(s) to the NDA holder and/or any patent holders/assignees regarding ANDA 91-294 via courier [redacted] (b) (4) instead of U.S. registered/ certified mail.

Thank you,

Keith

KEITH GIUNTA
MATRIX LABORATORIES, INC.
SUITE 301
76 SOUTH ORANGE AVENUE
SOUTH ORANGE, NJ 07079
(T) 973.761.1600 [redacted] (b) (4)
(F) 973.761.1680
KEITH.GIUNTA@MATRIXLABSUS.COM

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE

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/s/

MARTIN H Shimer
12/31/2009

Telephone Fax

ANDA 91-294

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951

TO: Matrix Laboratories, Inc. TEL: 973-761-1600

ATTN: Keith Giunta FAX: 973-761-1880

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Abacavir Sulfate Tablets, 300 mg.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-294 Date of Submission: January 28, 2009 and April 27, 2009

Applicant's Name: Matrix Laboratories, Inc.

Established Name: Abacavir Sulfate Tablets, 300 mg

Labeling Deficiencies:

1. CONTAINER - 60s

   a. Please print the pharmacy directive in color, preferably in red to enhance the prominence. In addition, relocate this to the principal display panel for better attention.

   b. It is preferable to revise to read "Each film-coated tablet…".

   c. The text on your label looks too cluttered. Please allow one space line between sections.

   d. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe that this package should comply with the Act. Please comment.

2. CARTON - 1 x 60s

   See comments under CONTAINER above.

(b) (4)

5. WARNING CARD

   a. Revise the first paragraph of the front side to read as follows:

   b.

(b) (4)

6. PACKAGE INSERT LABELING

a. GENERAL

i. Please note that the labeling for the reference listed drug, Ziagen® Tablets, was updated December 19, 2008. Please revise your labeling accordingly.

ii. Please be advised that the half page requirement for the highlight section **is only applicable if it** was printed in 2 columns on a standard size piece of typing paper (8 1/2 x 11), single spaced, in 8 point type with 1/2 inch margins on all sides and between columns. Please ensure that the highlight sections and the entire insert can easily be read and that the point type not be smaller than 6

iii Please include the margin markers designating the recent changes appearing in your proposal. We refer you to the innovator's labeling.

iv. Abacavir Hypersensitivity Reaction Registry

We note that you included information regarding the Abacavir Hypersensitivity Reaction Registry. Please submit your commitment that you will put this registry in place prior to full approval of your application. You are required to join this registry for full approval.

b. HIGHLIGHTS of PRESCRIBING INFORMATION

i. BOXED WARNING

Add a bullet to the text "Discontinue abacavir sulfate…possible (5.1)" and relocate to be the 4th bulleted text.

ii. RECENT MAJOR CHANGES

Please include the dates appearing in the innovator's labeling, not your own.

iii. DOSAGE FORMS AND STRENGTHS

You indicated that your tablet is scored. However, the CMC information regarding your finished drug product does not support this. Please be advised that the innovator's 300 mg tablet is scored for pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage from is appropriate. It has been the Agency's policy that the generic firms' drug product should follow the same scoring configuration of the innovator's product. Please revise the scoring configuration of your drug product and revise the labeling accordingly, wherever necessary. In addition, please submit all CMC information associated with the scoring change.

c. FULL PRESCRIBING INFORMATION

i. 2.2 Pediatric Patients

A) See comment 6(b)(iii) above.

B) (b) (4)

ii. DOSAGE FORMS AND STRENGTHS

See comment 6(b)(iii) above.

iii. 6 ADVERSE REACTIONS

(b) (4)

iv. DESCRIPTION

We note that your drug product contains iron complexes. In accordance with the 21 CFR 73.1200(c), the amount of elemental iron contained in the formulation cannot exceed 5 mg per day at the maximum recommended dosage. Please provide calculations of the amount of elemental iron of this product if consumed at the maximum daily recommended dosage.

v. 16 HOW SUPPLIED/STORAGE AND HANDLING
See comment 6(b)(iii) above.

7. MEDICATION GUIDE

a. We note that you did not submit your proposal for a separate medication guide to be dispensed to patients. Please submit one.

b. Please note that the point type for the final printed medication guide may not be smaller than 10. We refer you to 21 CFR 208.20 for guidance.

c. You are responsible for ensuring that this medication guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24]. Please explain how you will comply with this requirement.

d. Include the disclaimer statement for the proprietary names appearing in the medication guide.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Dr. Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE
ANDA-91294	ORIG-1	MATRIX LABORATORIES INC	ABACAVIR SULFATE

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/s/

LILLIE D GOLSON
09/28/2009
Lillie Golson for Wm. Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 91-294

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Matrix Laboratories, Inc. TEL: (973) 761-1600

ATTN: Keith Guinta FAX: (973) 761-1680

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 28, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Abacavir Sulfate Tablets, 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ADDENDUM TO PREVIOUS BIOEQUIVALENCE DEFICIENCY LETTER

ANDA: 91-294

APPLICANT: Matrix Laboratories Limited

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The previous letter dated July 15, 2009 sent by the Division of Bioequivalence (DBE) contained a typographical error. The current letter is to correct the error and should supercede the previous letter. We regret the error and apologize for any inconvenience it may have caused.

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submissions acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

The following deficiencies have been identified:

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

2. You did not provide the raw data for the 12 units of both test and reference in dissolution testing.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BARBARA M DAVIT
08/14/2009

BIOEQUIVALENCE AMENDMENT

ANDA 91-294

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Matrix Laboratories, Inc. TEL: (973) 761-1600

ATTN: Keith Giunta FAX: (973) 761-1680

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 28, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Abacavir Sulfate Tablets, 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-294

APPLICANT: Matrix Laboratories Limited

DRUG PRODUCT: Abacavir Sulfate Tablets, 300 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submissions acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

The following deficiencies have been identified:

1. Your dissolution testing data with the FDA-recommended method are incomplete. Based on the data submitted, the DBE recommends the following:

The dissolution testing should be conducted in 900 mL of water, at 37°C, using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification: NLT 80% (Q) in 15 minutes for abacavir.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

2. You did not provide the raw data for the 12 units of both test and reference in dissolution testing.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Barbara Davit

7/22/2009 04:35:42 PM

Shimer, Martin

From: Shimer, Martin
Sent: Monday, May 04, 2009 4:15 PM
To: 'Keith Giunta'
Cc: 'Nitin.Bhattad@matrixlabsindia.com'; Shimer, Martin
Subject: RE: ANDA 91-294 Abacavir Sulfate - PIV Notice Request

Mr. Giunta,

It is permissible to use (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 91-294.

Regards,

Martin Shimer

From: Keith Giunta [mailto:Keith.Giunta@matrixlabsus.com]
Sent: Monday, May 04, 2009 3:45 PM
To: Shimer, Martin
Cc: Nitin.Bhattad@matrixlabsindia.com
Subject: ANDA 91-294 Abacavir Sulfate - PIV Notice Request

Dear Mr. Shimer,

We have recently received filing acceptance for the above-referenced PIV ANDA. I'm writing to request permission to send the PIV Notice(s) to the NDA holder and/or any patent holders/assignees regarding ANDA 91-294 via courier (b) (4) instead of U.S. registered/certified mail.

Thank you,

Keith

KEITH GIUNTA
MATRIX LABORATORIES, INC.
SUITE 301
76 SOUTH ORANGE AVENUE
SOUTH ORANGE, NJ 07079
(T) 973.761.1600 (b) (4)
(F) 973.761.1680
KEITH.GIUNTA@MATRIXLABSUS.COM

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/s/

Martin Shimer
6/26/2009 10:27:17 AM
CSO

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-294 **FIRM NAME**: MATRIX LABORATORIES INC.

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ABACAVIR SULFATE

DOSAGE FORM: TABLETS, 300 MG

Random Queue: 9

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Chem Team Leader: Smith, Glen J Chem PM: Laura Longstaff Labeling Reviewer: Chan Park
Bio PM: Diane Nhu

Letter Date: JANUARY 28, 2009 **Received Date**: JANUARY 28, 2009

Comments: EC- 1 YES **On Cards:** YES

Therapeutic Code: 7030241 ANTIETROVIRAL/SYSTEMIC/HIV/NUCLEOSIDE REVERSE TRAN

Archival copy: CTD FORMAT PAPER **Sections** I

Review copy: YES E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Rebekah Granger	**Recommendation:**
Date 4/30/2009	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

This ANDA contains the same data as the one presented in the Tentatively Approved ANDA 78-742. Formulation and all BE studies are also similar.

4/21 – Keith Giunta (973) 761-1600
Revise 356h to reflect Finished Product as the Established Name – ok
(b) (4) cited but LOA was not included – ok
Address Sec 3.2.R on Drug Substance
Sec 1.14 states that labeling container and PI submitted electronically. Info not included in CD. Please resubmit
Provide schematics for (b) (4)

DBE Contact Entered on 4/30/2009

Per correspondence submitted by sponsor dated 4/27 the above is adequate for filing

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JANUARY 28, 2009	☒
1.2.1	**Form FDA 3674 (PDF)** YES Box B	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5

1.3.5.1 Patent Information ☒

Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations

1.3.5.2 Patent Certification

1. Patent number(s) PIII – '394 and '500
   PIV – '540
2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☐
   PIV ☒ (Statement of Notification) ☐
3. Expiration of Patent(s): 11-14-2018
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES

Patent and Exclusivity Search Results from query on Appl No 020977 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020977	001	5034394	Dec 18, 2011	Y	Y		
020977	001	5034394*PED	Jun 18, 2012				
020977	001	5089500	Jun 26, 2009			U-248	
020977	001	5089500*PED	Dec 26, 2009				
020977	001	6294540	May 14, 2018	Y	Y	U-65	
020977	001	6294540*PED	Nov 14, 2018			U-65	

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-248	TREATMENT OF HIV
U-65	METHOD OF TREATMENT OF A PATIENT INFECTED WITH HIV

1.4.1

References ☒

Letters of Authorization

1. DMF letters of authorization
   a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES
   b. Type III DMF authorization letter(s) for container closure YES
2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])

1.12.11	**Basis for Submission** NDA# : 20-977 Ref Listed Drug: ZIAGEN Firm: GLAXO SMITH KLINE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) **HOW SUPPLIED** Bottles of 60 tablets NDC 65015-XXX-17 (b) (4)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** N/A **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** YES **3.2.S.1.2 Structure** YES **3.2.S.1.3 General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (Includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES – DMF #18229 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** Refer to DMF #18229	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES in Sec 3.2.P.5 b. Same lot number(s) **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification** YES	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** Refer to DMF #18229	☒
3.2.S.7	**Stability** Refer to DMF #18229	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** Batch Formulation YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** YES **3.2.P.3.5 Process Validation and/or Evaluation** YES 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) **PROPOSED COMMERCIAL BATCH SIZE:** (b) (4)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** USP/NF Testing **3.2.P.4.3 Validation of Analytical Procedures** USP/NF Testing **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** YES **3.2.P.5.6 Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 24 MONTHS **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES – Lot # ABSA536001	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

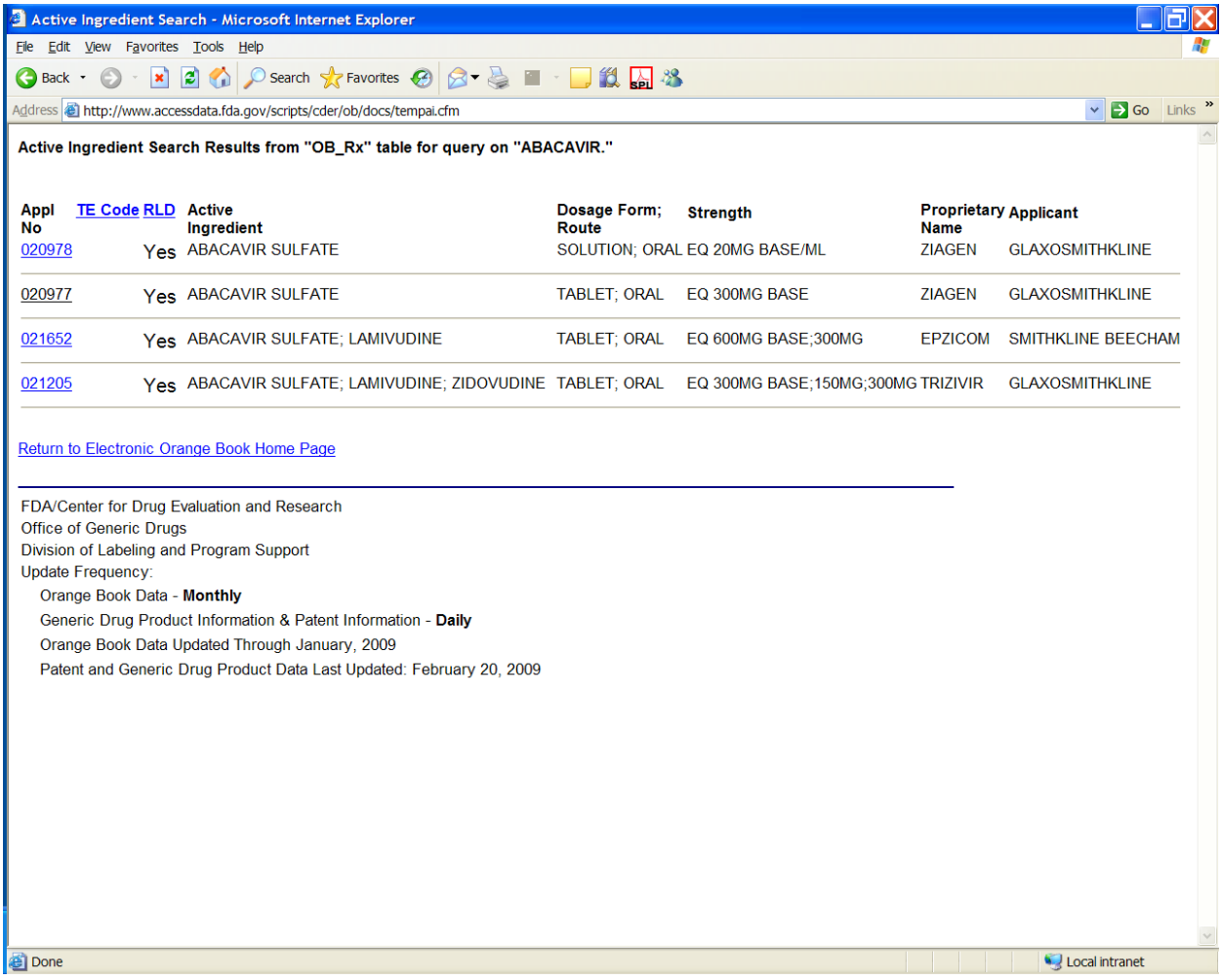
3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES Product Name: Abacavir Sulfate Tablets 300 mg. Batch #: ABSA536001 Batch Size: (b) (4) (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** RLD: 6ZP7570 ANDA: ABSA536001 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information YES Table 13. Protocol Deviations YES **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples YES Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 300 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008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Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
020978 Yes ABACAVIR SULFATE SOLUTION; ORAL EQ 20MG BASE/ML ZIAGEN GLAXOSMITHKLINE
020977 Yes ABACAVIR SULFATE TABLET; ORAL EQ 300MG BASE ZIAGEN GLAXOSMITHKLINE
021652 Yes ABACAVIR SULFATE; LAMIVUDINE TABLET; ORAL EQ 600MG BASE;300MG EPZICOM SMITHKLINE BEECHAM
021205 Yes ABACAVIR SULFATE; LAMIVUDINE; ZIDOVUDINE TABLET; ORAL EQ 300MG BASE;150MG;300MG TRIZIVIR GLAXOSMITHKLINE
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FDA/Center for Drug Evaluation and Research
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Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through January, 2009
Patent and Generic Drug Product Data Last Updated: February 20, 2009
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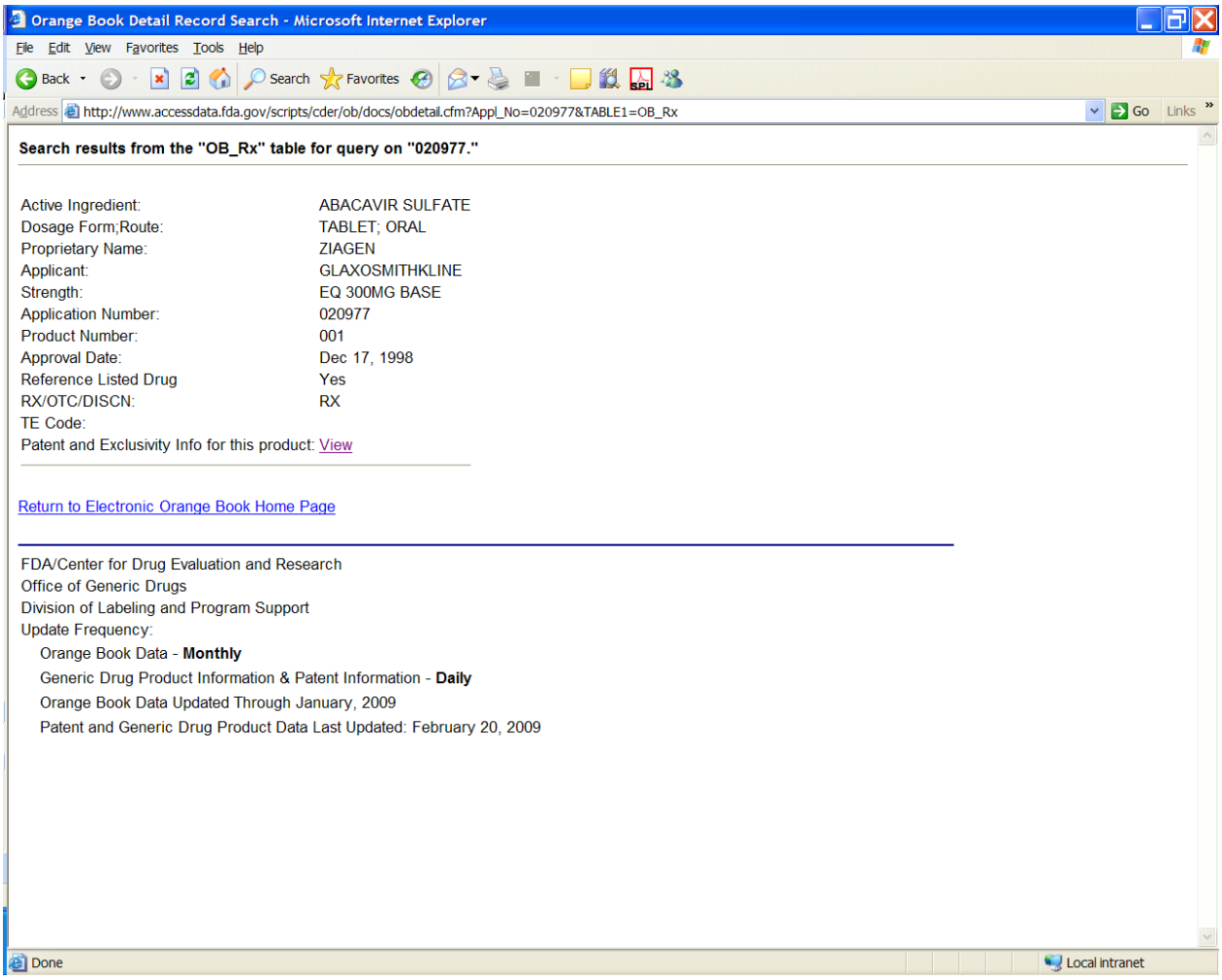
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File Edit View Favorites Tools Help
Back Search Favorites
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Go Links
Search results from the "OB_Rx" table for query on "020977."
Active Ingredient: ABACAVIR SULFATE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: ZIAGEN
Applicant: GLAXOSMITHKLINE
Strength: EQ 300MG BASE
Application Number: 020977
Product Number: 001
Approval Date: Dec 17, 1998
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
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Orange Book Data Updated Through January, 2009
Patent and Generic Drug Product Data Last Updated: February 20, 2009
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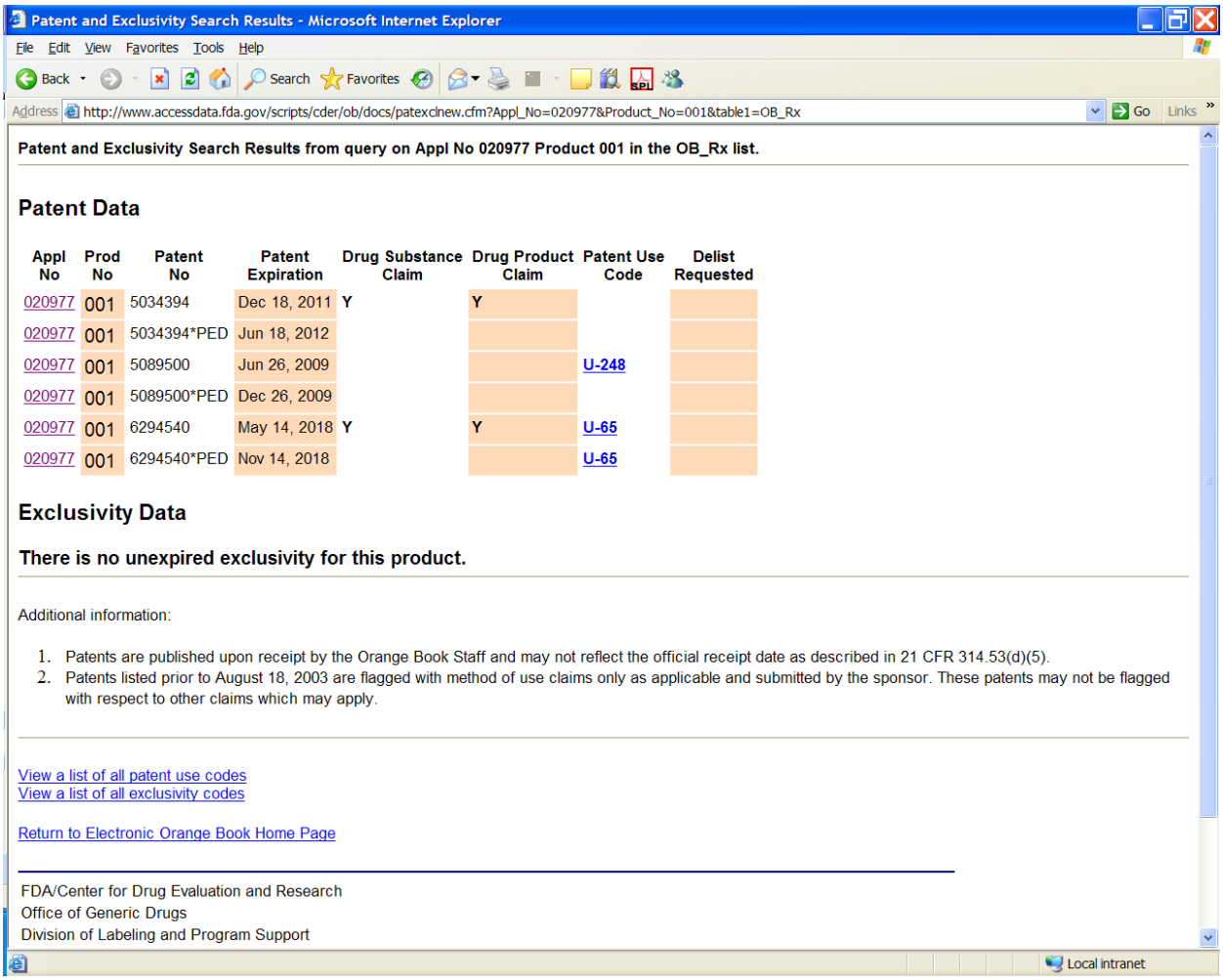

Patent and Exclusivity Search Results from query on Appl No 020977 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020977	001	5034394	Dec 18, 2011	Y	Y		
020977	001	5034394*PED	Jun 18, 2012				
020977	001	5089500	Jun 26, 2009			U-248	
020977	001	5089500*PED	Dec 26, 2009				
020977	001	6294540	May 14, 2018	Y	Y	U-65	
020977	001	6294540*PED	Nov 14, 2018			U-65	

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

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Table 3 Statistical Summary of the Comparative Bioavailability Data

Abacavir 300mg Tablet Dose (1x 300 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. 06-VIN-132)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	6060.151	6211.255	97.57	94.25 – 101.00
AUC∞	6161.041	6300.900	97.78	94.41 – 101.27
Cmax	2798.991	2943.524	95.09	86.54 – 104.49
Fed Bioequivalence Study (Study No. 06-VIN-133)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	5749.583	5836.587	98.51	93.64 – 103.63
AUC∞	5834.681	5927.999	98.43	93.62 – 103.48
Cmax	2149.108	2248.570	95.58	87.44 – 104.47

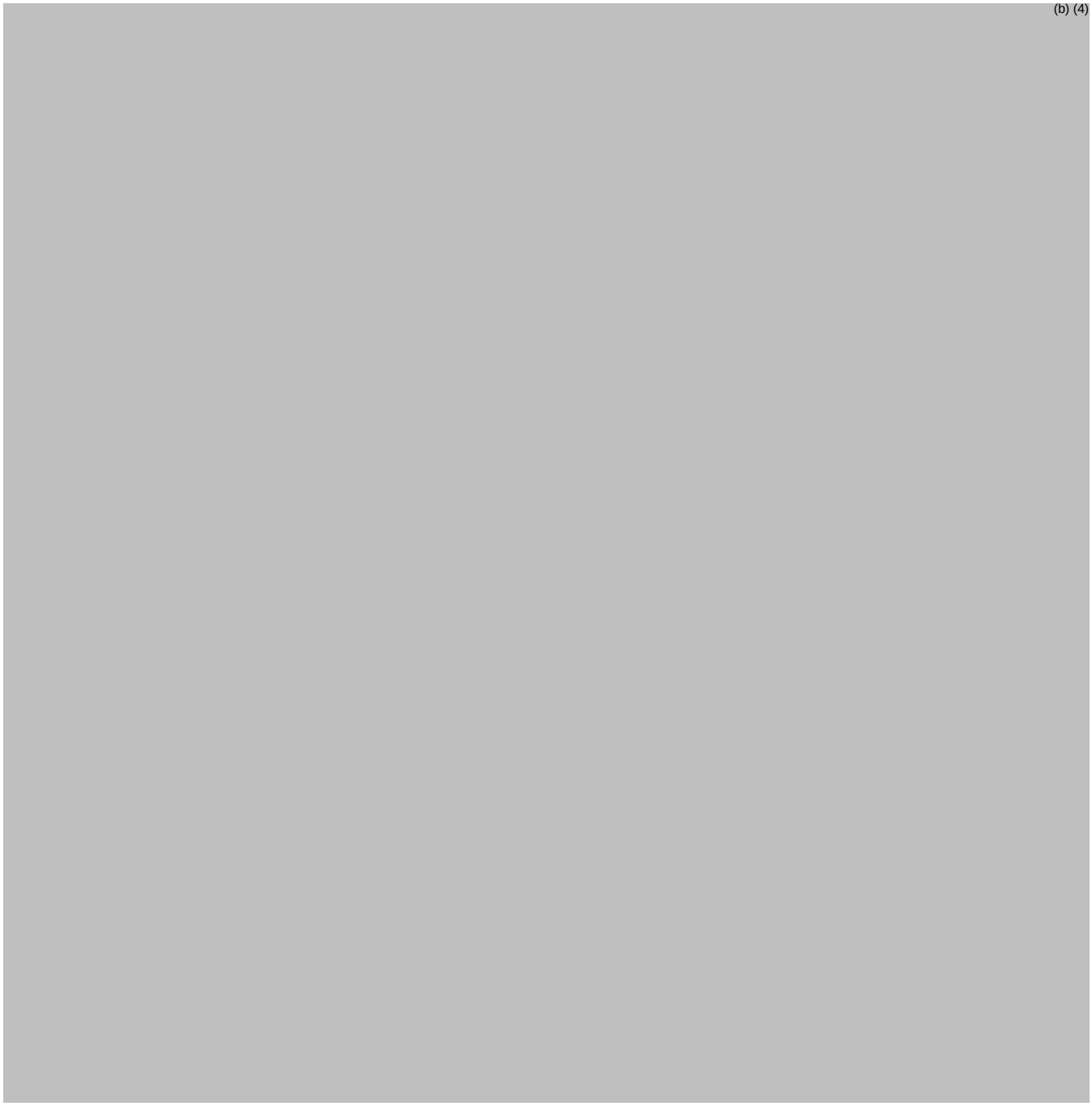
Table 6 Formulation Data

#	Ingredients	mg/tablet	% w/w
1	Abacavir Sulfate (Eqv. to 300mg of Abacavir)	(b) (4)	(b) (4)
2	Microcrystalline Cellulose		
3	Colloidal Silicon Dioxide		
4	Magnesium Stearate		
5	(b) (4)		
6			
7	Sodium Starch Glycolate		
8	(b) (4)		
(b) (4)			
Coated tablet weight		**820.00**	**100.00**

Please include the formulation of all strengths.

INACTIVE INGREDIENTS SEARCH FOR ANDA 91-294
MATRIX LABORATORIES INC – ABACAVIR SULFATE TABLETS, 300 MG

(b) (4)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Martin Shimer

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