İNHALE İNSÜLİNLER

Gen2 delivery device-MannKind Corporation

DR. FERHAT DENİZ
GATA HAYDARPAŞA EĞİTİM HASTANESİ
ENDOKRİNOLOJİ VE METABOLİZMA HASTALIKLARI


afrezza
(insulin human) Inhalation Powder
FDA ONAYI 2014
HAZİRAN
Dosing Guide
for Afrezza®
(insulin human) Inhalation Powder
How to use and store Afrezza®
Packaging and dosing
Titration
Dosing configuration chart

NİÇİN

Intensive insulin therapy has not gained widespread clinical acceptance for several reasons:

1. Multiple daily injections are inconvenient,
2. Adherence is a concern,
   Many patients with T2DM are reluctant to start insulin because of perceived misconceptions and barriers, including
   - risks of hypoglycemia,
   - weight gain,
   - fear of injections
3. The time-activity profile may not mimic normal insulin secretion.

Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA, - Ann. Intern. Med. - 2001; 134 (3); 203-7

İnsulin uygulama ve dağılımı hakkında **Yeni stratejiler** **araştırılmaya devam etmektedir:**

inhalasyon,

oral,

buccal,

nasal,

transdermal.

Insulin human inhalation powder in DM: A Summary

Orally inhaled rapid-acting Technosphere® insulin (TI) administered via a thumb-sized, breath-powered inhaler

Shown to have superior HbA_{1c} lowering compared with inhaled placebo and noninferior HbA_{1c} lowering compared with subcutaneous insulin aspart

Associated with significantly lower fasting plasma glucose levels and significantly less hypoglycaemia and bodyweight gain compared with insulin aspart

The only inhaled insulin available for the treatment of adults with T1DM and T2DM

Generally well tolerated, with hypoglycaemia, cough and throat pain/irritation occurring most commonly

Esther S. Kim & Greg L. Plosker **Drugs** (**2015**) 75:1679–1686

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Advanced DRUG DELIVERY Reviews
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Clinical evaluation of inhaled insulin ☆

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2.1.5. Kos inhaled insulin. . . . . .

Inhaled device produced by Nektar Therapeutics

Exubera:

- Lyophilized regular insulin delivered via a pulmonary inhalation device
- This formulation was developed through a partnership between Pfizer, Sanofi , and Nektar Therapeutics.
- Exubera is packaged in blisters containing 1 or 3 mg of dry powdered insulin, equivalent to approximately 3 units and 8 units of short –acting insulin respectively.
- The blister packets can be stored at room temperature.

2.1. Inhaled insulin devices . . . . . .
2.1.1. Exubera. . . . . .
2.1.2. AERx Insulin Diabetes Management System (iDMS)
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AERx delivery system, developed by a partnership of **Aradigm Corporation** with **Novo Nordisk**.

AERx Insulin Diabetes Management System (iDMS):

- This system uses a microprocessor-controlled piston to extrude liquid insulin under pressure through laser-generated perforations yielding **droplets 2 –3 micrometers** in diameter.
- Once the droplets have been generated, the device, using a green light as a visual cue, **guides the patient to breathe at the optimal speed and depth for deep lung delivery** by means of a " Breath Check "system.
- In addition, a chaser volume of fresh air (400 ml) follows the patient's breath to deliver the aerosolized insulin to the deep lung in a reproducible fashion.

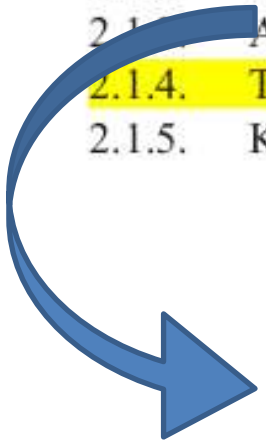
2.1. Inhaled insulin devices . . . . . .
2.1.1. Exubera. . . . . .
2.1.2. AERx Insulin Diabetes Management System (iDMS)
2.1.3. AIR® system . . . . . .
2.1.4. Technosphere® system . . . . . .
2.1.5. Kos inhaled insulin. . . . . .

AERx delivery system, developed by a partnership of **Aradigm Corporation** with **Novo Nordisk**.

AERx Insulin Diabetes Management System (iDMS):-devam

- The insulin (Novo Nordisk) is contained in **strips**, and the AER x device can deliver between 1– 10 AERx units of insulin at a time in increments of one unit. This allows titration of insulin dose for carbohydrate dose, similar to CSII or other subcutaneous insulin regimens.
- **One inhaled AER x unit** is expected to mimic the effect of *one IU of subcutaneously delivered insulin*,
- Finally, the device offers electronic download capability to monitor dosing, frequency of use, and breathing patterns.
- This technology is useful to monitor adherence to the prescribed insulin regimen as well as to empower patients through information regarding their diabetes management and treatment.

2.1. Inhaled insulin devices . . . . . .
2.1.1. Exubera. . . . . .
2.1.2. AERx Insulin Diabetes Management System (iDMS)
2.1.3. AIR® system . . . . . .
2.1.4. Technosphere® system . . . . . .
2.1.5. Kos inhaled insulin. . . . . .



AIR® system:

- Alkermes in conjunction with Eli Lilly are developing a device to deliver Regular insulin as large porous particles 5 – 30µm in diameter.
- This technology is based on findings that porous particles of small mass density, but with large size, are delivered efficiently to the deep lung and exert systemic effects.
- The device is breath-activated and may be useful for the delivery of both short - and long-acting insulin regimens.
- Patients using the system had greater treatment satisfaction and insulin deliver satisfaction when compared to subcutaneous insulin delivery

2.1. Inhaled insulin devices . . . . . .
- 2.1.1. Exubera. . . . . .
- 2.1.2. AERx Insulin Diabetes Management System (iDMS)
- 2.1.3. AIR® system . . . . . .
- 2.1.4. Technosphere® system . . . . . .
- 2.1.5 Kos inhaled insulin. . . . . .

KOS Insulin RRS Aerosol devise produced by KOS Pharmaceuticals

KOS inhaled İnsulin:

- Kos Pharmaceuticals, Inc. is developing a breath-actuated inhaler for delivery of insulin.
- The device incorporates an electronic dose counter to encourage adherence and allow for monitoring of insulin delivery.
- The product is in Phase II of clinical development

Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 58 (2006) 1061–1075
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Clinical evaluation of inhaled insulin ☆

Abstract

Diabetes affects over 18.2 million individuals in the United States alone. Current therapy to treat type 1 diabetes relies on subcutaneous insulin administration either by injection or continuous infusion. In addition, patients with type 2 diabetes who fail lifestyle intervention and oral therapy require subcutaneous insulin. Optimal injection protocols to achieve tight metabolic control often prove burdensome to patients. Thus, development of pulmonary insulin delivery to supplement and/or replace subcutaneous insulin injections may be an effective alternative, allowing patients to achieve intensive diabetes management. This review will discuss the devices in development for the delivery of inhaled insulin. In addition, the efficacy of inhaled insulin in both type 1 and type 2 diabetic populations will be discussed. Finally, the available safety data with respect to the unique pulmonary effects of inhaled insulin will be covered.

INDICATIONS AND USAGE FOR AFREZZA® (INSULIN HUMAN) INHALATION POWDER

- Afrezza®, the only man-made rapid acting inhaled insulin, for adults with diabetes who need mealtime blood sugar control.
- Afrezza® is delivered through a specially designed inhaler.
- Afrezza® is used to control high blood sugar in adults with type 1 and type 2 diabetes.

LIMITATIONS OF USE:

- Do not use Afrezza® in place of long-acting insulin; Afrezza® must be used with a long-acting insulin in patients with type 1 diabetes.
- Do not use Afrezza® to treat diabetic ketoacidosis.
- It is not known if Afrezza® is safe and effective for use in people who smoke. Afrezza® is not for use in patients who smoke or who have recently stopped smoking (less than 6 months).
- It is not known if Afrezza® is safe and effective in children under 18 years of age.

IMPORTANT SAFETY INFORMATION FOR AFREZZA® (INSULIN HUMAN) INHALATION POWDER

WARNING: RISK OF SUDDEN LUNG PROBLEMS (BRONCHOSPASM) IN PATIENTS WITH LONG-TERM (CHRONIC) LUNG DISEASE

- **Sudden lung problems (acute bronchospasm) have been seen in patients with asthma and COPD (chronic obstructive pulmonary disease) using Afrezza®.**
- **Afrezza® is not to be used in patients with long-term lung disease such as asthma or COPD.**
- **Before initiating Afrezza®, your doctor will perform a detailed medical history, physical examination, and a breathing test (called spirometry) to identify potential lung problems.**

IMPORTANT SAFETY INFORMATION FOR AFREZZA® (INSULIN HUMAN) INHALATION POWDER

- CONTRAINDICATIONS:
- Do not use Afrezza® if you have problems with your lungs, such as asthma or COPD (chronic obstructive pulmonary disease)
- Do not use Afrezza® during a low blood sugar reaction (hypoglycemia).
- If you are allergic to regular human insulin or to any of the ingredients in Afrezza®, do not use Afrezza® as this may cause a significant and severe allergic reaction.

- Before using Afrezza®, it is important to tell your doctor about all your medical conditions, including
  - if you have a history of lung problems,
  - if you smoke or have recently quit smoking,
  - if you are pregnant or plan to become pregnant, or
  - if you are breast feeding or planning to breast-feed.
  - All other medicines and supplements you take.

IMPORTANT SAFETY INFORMATION FOR AFREZZA® (INSULIN HUMAN) INHALATION POWDER

- Your doctor will:
  - take a medical history, and
  - do a physical exam and
  - a breathing test (spirometry) to determine if you have lung problems.

- Patients with lung problems should not use Afrezza®.
  - If your doctor finds you have lung problems, use of Afrezza®may cause a severe asthma-like breathing problem.
  - Afrezza®can reduce lung function, so your doctor will also want to test your breathing 6 months after starting Afrezza®, and then each year after that, even if you have no lung symptoms. More frequent testing should be done if you have symptoms such as wheezing or coughing.

- You must test your blood sugar levels while using insulin, such as Afrezza®.
- Do not make any changes to your dose or type of insulin without talking to your healthcare provider.
- Any change of insulin should be made carefully and only under your doctor's care.

There are certain serious side effects that are associated with the use of Afrezza®

- Severe allergic reaction (including whole body reaction).
  - Get medical help right away if you have any signs or symptoms of a severe allergic reaction, including :
    - a rash over your whole body,
    - trouble breathing,
    - a fast heartbeat, or
    - sweating.
- Low blood sugar (hypoglycemia) which can be serious and life-threatening.

  Common symptoms of hypoglycemia are :
  - dizziness or light-headedness,
  - sweating,
  - confusion,
  - headache,
  - blurred vision,
  - slurred speech,
  - shakiness,
  - fast heartbeat,
  - anxiety, irritability or mood change, or hunger.
  - ➢ It may cause harm to your heart or brain.
  - ➢ It is important for you to understand how to manage the use of Afrezza®, and to understand how to lessen the risk of hypoglycemia events.
- Lung cancer occurred in more people who were taking Afrezza® compared to other diabetes medications.
  - ➢ There were too few cases to know if lung cancer was related to Afrezza®.
  - ➢ Tell your doctor if you currently have lung cancer, have had it in the past, or if you have an increased risk of developing lung cancer.
- Heart failure can occur if you are taking insulin together with TZDs, even if you have never had heart failure or other heart problems. If you already have heart failure it may get worse while you take TZDs with Afrezza®. Tell your doctor if you have any new or worsening symptoms of heart failure including shortness of breath, swelling of your ankles or feet or sudden weight gain. Your treatment with Afrezza® and TZDs may need to be changed or stopped if you have new or worsening heart failure.

There are certain serious side effects that are associated with the use of Afrezza®

- Severe allergic reaction (including whole body reaction).
- Low blood sugar (hypoglycemia) which can be serious and life-threatening.
- Lung cancer occurred in more people compared to other diabetes medications
- Heart failure can occur if you are taking insulin together with TZDs

- Get emergency help if you have
  - trouble breathing,
  - shortness of breath,
  - fast heartbeat,
  - swelling of your face, tongue, or throat,
  - sweating,
  - extreme drowsiness (uyku hali),
  - dizziness, or confusion.
- The most common side effects of Afrezza® :
  - Low blood sugar (hypoglycemia),
  - Cough,
  - Sore throat,
  - Headache,
  - Diarrhea,
  - Tiredness,
  - Nausea.

While using Afrezza®

- Do not drive or operate heavy machinery until you know how Afrezza® affects you.
- You should not drink alcohol or use other medicines that contain alcohol and
- You should not smoke.

Respiratory AEs Reported in Technosphere Insulin Trials.

	Technosphere Insulin			Technosphere Placebo			
Respiratory Symptom	MedTone, n = 2647, n (%)	Gen2, n = 370, n (%)	Total, n = 3017, n (%)	MedTone, n = 114, n (%)	Gen2, n = 176, n (%)	Total, n = 290, n (%)	Comparator, n = 2198, n (%)
Any respiratory AE	1205 (45.5)	158 (42.7)	1363 (45.2)	44 (38.6)	60 (34.1)	104 (35.9)	682 (31.0)
Cough	710 (27.3)	101 (27.3)	811 (26.9)	21 (18.4)	36 (20.5)	57 (19.7)	114 (5.2)
URI	257 (9.7)	27 (7.3)	284 (9.4)	9 (7.9)	5 (2.8)	14 (4.8)	239 (10.9)
Nasopharyngitis	200 (7.6)	20 (5.4)	220 (7.3)	16 (14.0)	8 (4.5)	24 (8.3)	172 (7.8)
Bronchitis	79 (3.0)	11 (3.0)	90 (3.0)	3 (2.6)	7 (4.0)	10 (3.4)	58 (2.6)
Oropharyngeal pain	66 (2.5)	11 (3.0)	77 (2.6)	4 (3.5)	4 (2.3)	8 (2.8)	25 (1.1)
Throat irritation	59 (2.2)	9 (2.4)	68 (2.3)	2 (1.8)	2 (1.1)	4 (1.4)	3 (0.1)
Productive cough	56 (2.1)	1 (0.3)	57 (1.9)	3 (2.6)	0	3 (1.0)	18 (0.8)
Sinusitis	50 (1.9)	5 (1.4)	55 (1.8)	1 (0.9)	2 (1.1)	3 (1.0)	49 (2.2)
Dyspnea	33 (1.2)	8 (2.2)	41 (1.4)	0	2 (1.1)	2 (0.7)	6 (0.3)
Viral respiratory infection	4 (0.2)	5 (1.4)	9 (0.3)	0	5 (2.8)	5 (1.7)	5 (0.2)

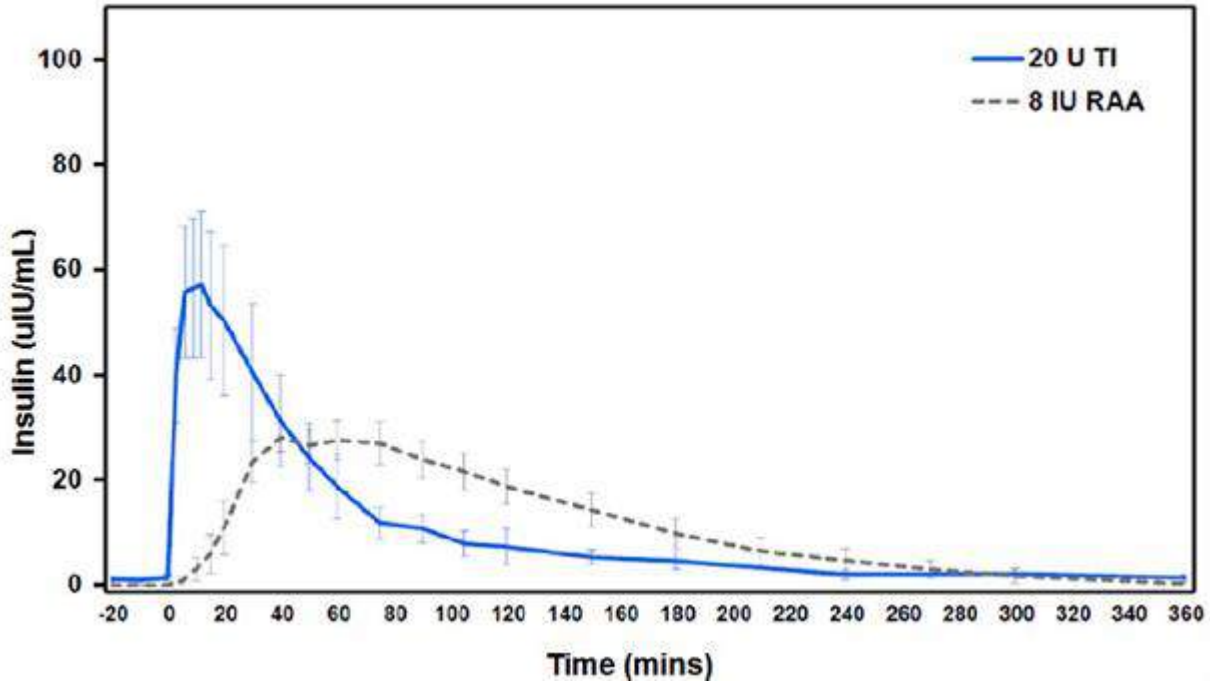
Abbreviations: AE, adverse event; URI, upper-respiratory infection.

Wesley Nuffer, , Jennifer M. Annals of Pharmacotherapy 2015, 49(1) 99–106

FARMAKOLOJİ

- TI is a dry powder of human (recombinant DNA) insulin formulated to absorb onto Technosphere microparticles for pulmonary administration.
- The powder dissolves immediately on inhalation to deliver insulin quickly, reaching peak concentrations within about 15 minutes of administration.8
- The **carrier** of these insulin particles, Fumaryl diketopiperazine (FDKP), is an inert **excipient** that encapsulates peptides and proteins into microspheres.
- These particles dissolve in the neutral pH environment of the lungs, with the small size facilitating efficient distribution and absorption into circulation.
- Whereas this absorption into systemic circulation is more rapid, the insulin used with TI is regular human insulin.
- Once the insulin enters **circulation**, metabolism and elimination are **similar** to that of regular human insulin.
- The FDKP is absorbed into the bloodstream and is excreted intact primarily through the kidneys.

Farmakokinetik



Abbreviations:
IU, international units;
RAA, rapid-acting analogue;
SE, standard error;
TI, Technosphere Insulin;
U, units (fill content of TI cartridges).

Mean (SE) baseline-corrected TI concentration-time profiles with Gen2 inhaler

- TI achieved median maximum concentrations (Tmax) in 12 to 15 minutes, compared with approximately 40 minutes with SC rapid-acting insulin analog
- İnsülin exposure & Overall insulin exposure was also dose proportional, with insulin concentrations returning to near baseline by 180 minutes, markedly earlier than SC formulations.

➢ Despite faster absorption, studies did not demonstrate a difference in onset of action between TI and insulin lispro.

➢ Both insulin and FDKP excipient levels rapidly decline from the lung (lavage studies: 4.h: % 31, 12.h: % 0.3-0.4 Gotfried M, et al. Lung deposition and absorption of insulin from technosphere insulin (abstract 955). Diabetologia. 2009;52:S375)

Design Features and Efficacy End Points for Major Efficacy Trials for Technosphere Insulin

	T1DM		T2DM	
Design Features	MKC-TI-009[16]	MKC-TI-171[17]	MKC-TI-102[18]	MKC-TI-175[19]
Primary analysis statistical measure	Noninferiority	Noninferiority	Noninferiority	Superiority
Treatment duration	52 weeks	24 weeks	52 weeks	24 weeks
Treatment blinding	Open-label	Open-label	Open-label	Double-blind
Background treatment	Insulin glargine	Basal insulin (varied by patient)	Insulin glargine	OAD
Randomized trial treatment	Prandial TI	Prandial TI	Prandial TI	Prandial TI
Randomized control treatment	Prandial RAA aspart	Prandial RAA	BPR 70/30	Prandial TP (placebo)
Titration of TI based on BG measurements	Premeal and postprandial	Postprandial	Premeal & post-prandial	Post-prandial
Inhaler	MedTone	Gen2 and MedTone	MedTone	Gen2
Maximum TI dose/meal	90 U/meal	4 U/kg/d	90 U/meal	4 U/kg/d
A1C inclusion range (%)	>7 and ≤11	≥7.5 and ≤10.0	>7 and ≤11	≥7.5 and ≤10.0
Baseline A1C TI (%)/Baseline A1C comparator (%)	8.41/8.48	7.94/7.92	8.69/8.68	8.25/8.27
Adjusted mean Δ from baseline, TI group % (SE) [95% CI]	−0.13 (0.058) [−0.24, −0.01]	−0.21 (0.062) [−0.33, −0.09]	−0.59 (0.063) [−0.71, −0.47]	−0.82 (0.061)
Adjusted mean Δ from baseline, comparator percentage (SE) [95% CI]	−0.37 (0.059) [−0.49, −0.25]	−0.40 (0.060) [−0.52, −0.28]	−0.71 (0.061) [−0.83, −0.59]	−0.42 (0.062)
Treatment difference TI, comparator percentage (SE) [95% CI]	0.24 (0.082) [0.08, 0.40]	0.19 (0.086) [0.02, 0.36]	0.12 (0.085) [−0.05, 0.29]	−0.40 (0.087) [−0.57, −0.23], $P < 0.0001$

Insulin aspart group demonstrated superior A1C lowering compared with the TI group, which failed to achieve the prespecified upper confidence interval limit of <0.4% needed to demonstrate noninferiority

Both groups attained an A1C reduction, with a between-group treatment difference of 0.19% in favor of insulin aspart. Based on these data, **TI achieved noninferiority**

Abbreviations: A1C, hemoglobin A1C; **BG**, blood glucose; **BPR**, biphasic insulin aspart mixture; **MKC**, MannKind Corporation; **RAA**, rapid-acting analog (insulin); **TI**, Technosphere insulin; T1DM, type 1 diabetes; T2DM, type 2 diabetes; **TP**, Technosphere placebo.

* Mannkind Corporation Briefing Document: Endocrinology and Metabolic Drug Advisory Committee. AFREZZA: (insulin human [rDNA origin]) inhalation powder. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf. Accessed August 25, 2014.

Design Features and Efficacy End Points for Major Efficacy Trials for Technosphere Insulin

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Background treatment	Insulin glargine	Basal insulin (varied by patient)	Insulin glargine	OAD
Randomized trial treatment	Prandial TI	Prandial TI	Prandial TI	Prandial TI
Randomized control treatment	Prandial RAA aspart	Prandial RAA	BPR 70/30	Prandial TP (placebo)
Titration of TI based on BG measurements	Premeal and postprandial	Postprandial	Premeal & post-prandial	Post-prandial
Inhaler	MedTone	Gen2 and MedTone	MedTone	Gen2
Maximum TI dose/meal	90 U/meal	4 U/kg/d	90 U/meal	4 U/kg/d
A1C inclusion range (%)	>7 and ≤11	≥7.5 and ≤10.0	>7 and ≤11	≥7.5 and ≤10.0
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Both groups demonstrated A1C reductions, with a between group treatment difference of 0.12% in favor of the BPR 70/30 group

This successfully met noninferiority criteria with TI tx.

The TI group demonstrated a statistically superior A1C reducti at 24 weeks, with a between-group difference of −0.40%

The TI group also had a higher percentage of patients attaini an A1C of <7%

Abbreviations: A1C, hemoglobin A1C; **BG**, blood glucose; **BPR**, biphasic insulin aspart mixture; **MKC**, MannKind Corporation; **RAA**, rapid-acting analog (insulin); **TI**, Technosphere insulin; T1DM, type 1 diabetes; T2DM, type 2 diabetes; **TP**, Technosphere placebo.

* Mannkind Corporation Briefing Document: Endocrinology and Metabolic Drug Advisory Committee. AFREZZA: (insulin human [rDNA origin]) inhalation powder. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf. Accessed August 25, 2014.

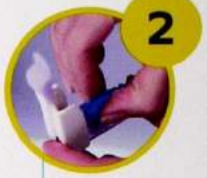
DOZAJ

Yemek başlangıcında veya başlamasından 20 dk içinde uygula.

4-step administration instructions

1 SELECT
the Afrezza® cartridge

- Blue cartridge=4 units; green cartridge=8 units; yellow cartridge=12 units
- Multiple cartridges required for doses exceeding 12 units



2 LOAD
cartridge into the Afrezza® inhaler

- Open inhaler by lifting mouthpiece
- Load cartridge into inhaler—making sure it lies flat
- Keep inhaler level—do not turn upside down, shake, or drop, as this may cause a loss of insulin
- Lower mouthpiece to close inhaler until you hear a snap

3 INHALE
Afrezza®

- Remove mouthpiece cover, hold inhaler away from mouth, and exhale fully
- Place mouthpiece in mouth with head and inhaler level, then tilt inhaler down toward chin
- Inhale deeply and hold breath for as long as is comfortable before exhaling

4 DISCARD
used cartridge

- Put mouthpiece cover back onto inhaler
- Lift mouthpiece, then remove cartridge
- Dispose of used cartridge in household trash

Repeat as necessary to obtain the prescribed dose.

The Afrezza® inhaler can be used for up to **15 days from the date of first use.** After 15 days of use, the inhaler must be discarded and replaced with a new inhaler.

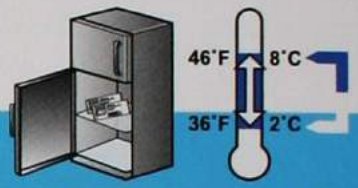
Storage and handling[1]

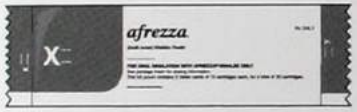
Afrezza® inhalers

Keep the Afrezza® inhaler in a clean, dry place with the mouthpiece cover on. Wipe it with a clean, dry cloth if needed, instead of washing it. **To obtain a new inhaler, patients should call sanofi-aventis US at 1-800-633-1610.**

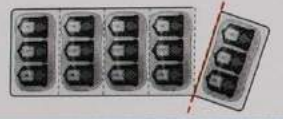
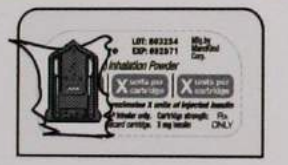
	**Opened package**	May be used for up to **15 days**

Afrezza® cartridges



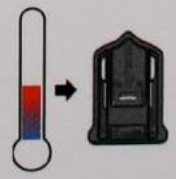
Not in use: Refrigerated storage		**Refrigerated**
	**Sealed** (unopened)	May be stored until the **expiration date**[a]
Blister cards and strips 	**Sealed** (unopened)	May be stored for **1 month**[a]

[a] If a foil package, blister card, or strip is not refrigerated, the contents must be used within 10 days.

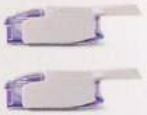
In use: Room temperature storage		Room temperature
Blister cards and strips 	**Sealed** (unopened)	Must be used **within 10 days**
Strips 	**Opened**	Must be used **within 3 days**

Do not put a blister card or strip back into the refrigerator after being stored at room temperature.

Before use, cartridge and inhaler should be at room temperature for 10 minutes.



10 minutes

	Afrezza® box contents			
NDC	0024-5874-90	0024-5884-63	0024-5882-36	0024-5894-63
Box		 (combination)	 (combination)	 (combination)
2 inhalers in every box				
4-unit cartridges	 x 90	 x 60	 x 30	
8-unit cartridges		 x 30	 x 60	 x 60
12-unit cartridges				 x 30
Total number of cartridges	90	90	90	90
Total units of insulin	360	480	600	840

Two inhalers are included in every box of Afrezza®.

Write 1 prescription for either:

4- and 8-unit combination doses

OR

8- and 12-unit combination doses.

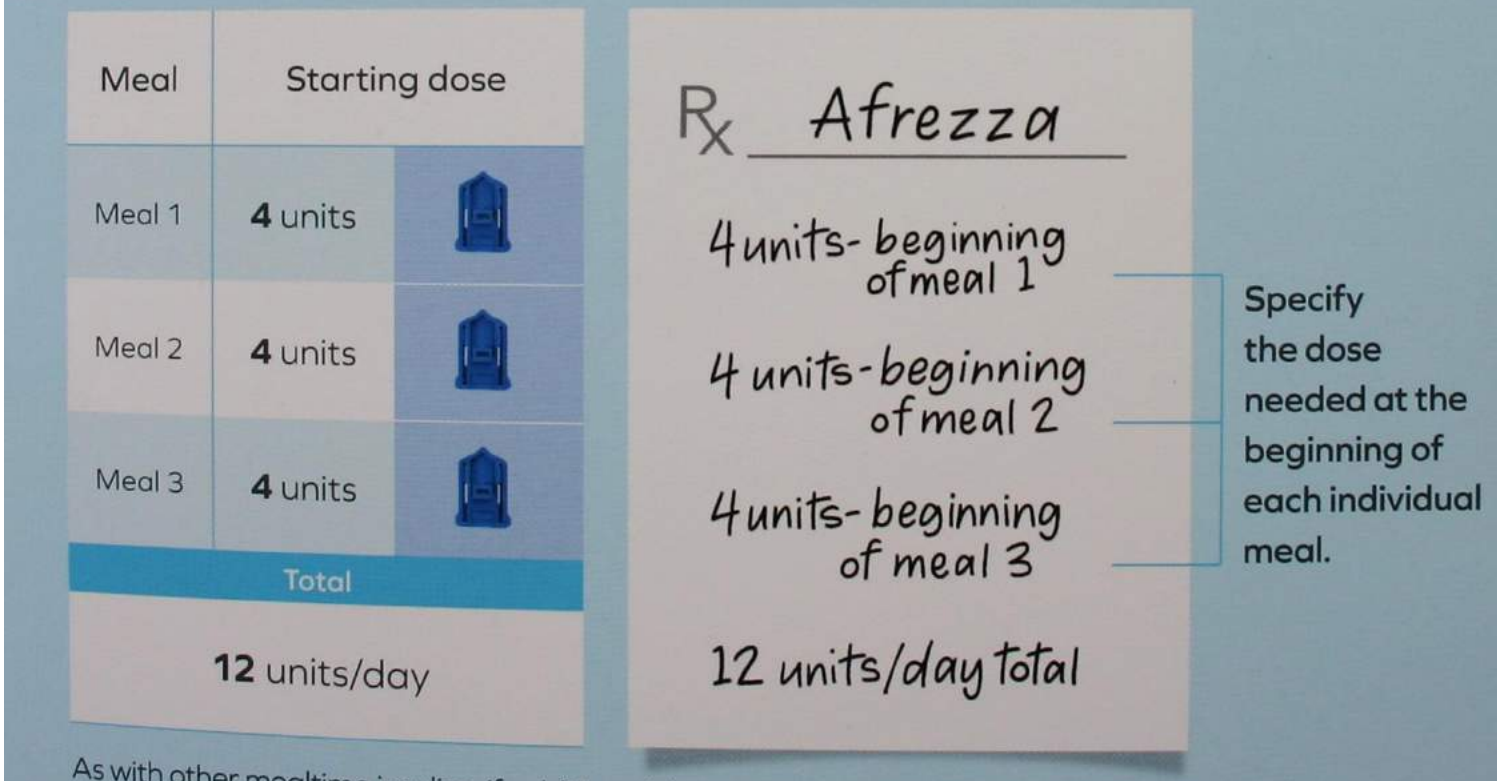
Prescribing Afrezza®

Start patients on 4 units per meal[1]

Example: For insulin-naive patients and patients currently using up to 4 units SC mealtime insulin. See full Prescribing Information for dose conversion.

Example 1: For illustrative purposes only

Meal	Starting dose
Meal 1	**4** units
Meal 2	**4** units
Meal 3	**4** units
Total	**12** units/day



As with other mealtime insulins, if additional doses are required, reflect appropriately on the script.

Titrating inhaled Afrezza®

(insulin human) Inhalation Powder

An option for titrating the mealtime dose, as demonstrated in a clinical trial[1,2]

PPG, postprandial glucose; SMBG, self-monitoring of blood glucose.

Example 2: For illustrative purposes only

Meal	Dose
Meal 1	**8** units
Meal 2	**4** units
Meal 3	**8** units
Total	
20 units/day	

Rx Afrezza

8 units - beginning of meal 1

4 units - beginning of meal 2

8 units - beginning of meal 3

20 units/day total

Specify the dose needed at the beginning of each individual meal.

As with other mealtime insulins, if additional doses are required, reflect appropriately on the script.

Prescribing Afrezza®

12 units or more per meal[3]

For Afrezza® doses exceeding 12 units, inhalations from multiple cartridges are necessary.[1]

Example 3: For illustrative purposes only

Meal	Dose
Meal 1	**16** units
Meal 2	**12** units
Meal 3	**20** units
Total	
48 units/day	

Rx Afrezza

16 units - beginning of meal 1

12 units - beginning of meal 2

20 units - beginning of meal 3

48 units/day total

Specify the dose needed at the beginning of each individual meal.

As with other mealtime insulins, if additional doses are required, reflect appropriately on the script.

Dosing conversion for Afrezza®

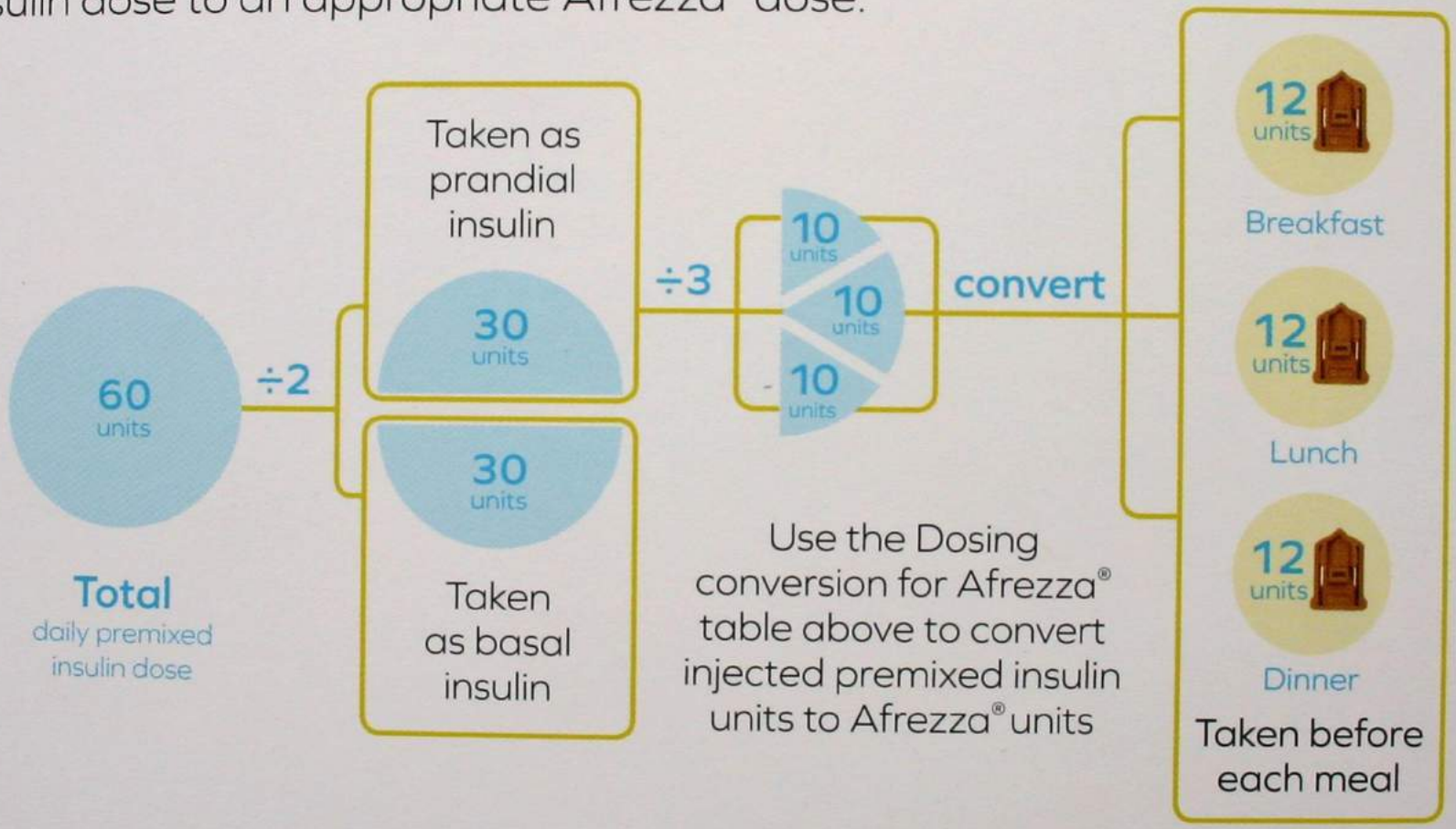
(insulin human) Inhalation Powder[1]

The appropriate Afrezza® dose for each meal can be determined by converting doses of injected mealtime insulin, as shown in the table below.

Injected mealtime insulin dose	Afrezza® dose	4 units (blue)	8 units (green)	12 units (yellow)
		Number of cartridges needed		
Up to 4 units	4 units	1		
5-8 units	8 units		1	
9-12 units	12 units	1 +	1	OR 1
13-16 units	16 units		2	
17-20 units	20 units		1 +	1
21-24 units	24 units			2

Example: Converting from injected premixed insulin to Afrezza®

The example below shows the conversion from an injected premixed insulin dose to an appropriate Afrezza® dose.



Really, it's inhaled?

"Yes, you now have an option."

Talk about Afrezza® with your appropriate adult diabetes patients who are uncontrolled on 2 or more oral antidiabetic drugs or are in need of insulin intensification.

afrezza.
(insulin human) Inhalation Powder

Important Information Regarding Afrezza® (insulin human) Inhalation Powder

Sanofi will no longer promote Afrezza® in the U.S. as of April 4, 2016 at 11:59 pm ET when all rights will be transferred back to MannKind Corporation. MannKind has publicly stated its commitment to ensuring the continued supply of Afrezza® and support for healthcare professionals and their patients.

Sanofi is prepared to fulfill orders for Afrezza® from wholesalers in the U.S. until October 1, 2016 as long as we have inventory or unless we are notified by MannKind to discontinue. MannKind will assume full responsibility for supply on October 1, 2016 (or earlier in the event we are notified by MannKind that they will assume responsibility for fulfilling orders for Afrezza® prior to this date). Therefore Afrezza prescriptions can continue to be filled at a pharmacy of choice under the existing Sanofi NDC numbers

From April 5, 2016 onwards all questions regarding Afrezza® should be directed to MannKind Corporation at **1-877-323-8505**.

As always, patients who are currently prescribed Afrezza® should speak to their healthcare professional regarding any treatment questions.

Please see full Prescribing Information for Afrezza®, including **Boxed WARNING** from your Sales Representative.

SANOFI

İlginize Teşekkürler!

Tedavi Değerlendirmeleri

- Existing data on TI has demonstrated that it is an effective option for managing prandial glucose excursions in patients with diabetes.
- Head-to-head comparisons suggest that it is inferior to rapid-acting insulins in lowering A1C, although it did prove noninferiority in some trials.
- The lower rates of hypoglycemia seen across TI trials is positive but could be a result of the lower comparable efficacy.
- One barrier facing TI is where it will ultimately fit within clinical guidelines. Current diabetes standards of care do not highlight a role for using bolus insulin alone or in combination with oral antihyperglycemic agents.
- T1DM patients use both basal and bolus insulin to manage their glucose or utilize an insulin pump. Similarly, bolus insulin is viewed as a later option in patients with T2DM, after basal insulin has already been initiated. This suggests that those patients who may be averse to injections or needles would likely still require basal insulin delivered by injection prior to receiving bolus TI insulin treatment. TI could reduce the number of injections from 4 or more down to 1 but would not avoid needle use altogether.
- The faster absorption and higher maximum concentrations seen with TI are interesting, but existing data do not demonstrate that these advantages lead to any clinical differences in overall insulin onset.

Tedavi Değerlendirmeleri

- More data are needed to determine whether these absorption advantages can translate to faster insulin action in the body, which could set TI apart from other insulins on the market.
- Many questions remain regarding the pulmonary administration of insulin and potential risks associated with this method of delivery.
- The requirement for regular pulmonary function testing (baseline, 6 months, and annually thereafter) represents another potential barrier for the use of this drug, particularly in offices where PFTs are not routinely conducted. The additional costs of these tests must be considered when determining the overall cost of therapy for TI.
- Pricing information is not yet available on the product, but the cost of routine PFT tests, along with potential formulary coverage, are important considerations when evaluating where this product could fit, particularly since the previous inhaled insulin product (Exubera) was removed from the market for financial and economic reasons.
- The required postmarketing studies TI is conducting will help clarify potential risks and product safety, particularly for long-term use.