MENOTROPINS (Systemic)

Category

Gonadotropin; infertility therapy adjunct.

Indications

Accepted

Infertility, female (treatment)¾Menotropins are indicated, in conjunction with chorionic gonadotropin, for stimulation of ovulation and pregnancy in patients with ovulatory dysfunction not due to primary ovarian failure 1, 10, 12, 23, 24, 28, 40, 44, 45.

In general, menotropins are the treatment of choice for induction of ovulation in patients with hypothalamic hypogonadism or those who do not respond to clomiphene 12, 23, 24, 28, 29, 40, 41, 42, 44, 45, 59, 64.

Reproductive technologies, assisted *¾Menotropins are indicated, in conjunction with chorionic gonadotropin (hCG), to stimulate the development of multiple oocytes in ovulatory patients who are attempting to conceive by means of assisted reproductive technologies, such as gamete intrafallopian transfer (GIFT) or in vitro fertilization (IVF). 10, 12, 19, 25, 26, 29, 33, 36, 46, 64

Infertility, male (treatment)¾Menotropins are also indicated in combination with chorionic gonadotropin for stimulation of spermatogenesis in men with primary or secondary hypogonadotropic hypogonadism. 1, 10, 24, 32

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Menotropins contain follicle-stimulating hormone (FSH) and luteinizing hormone (LH) 58, 64.

For induction of ovulation and assisted reproductive technologies (ART)¾
Menotropins prepare the ovarian follicle for ovulation 10, 29.

The combination of FSH and LH stimulates follicular growth and maturation. 10, 29, 35, 64 Chorionic gonadotropin, whose actions are nearly identical to those of LH, is administered following menotropins treatment to mimic the naturally occurring surge of LH that triggers ovulation. 10, 29, 33, 35, 39, 43

For treatment of male infertility¾
Following administration of chorionic gonadotropin to increase testosterone concentrations in men with hypogonadotropic hypogonadism, administration of menotropins induces spermatogenesis 10.

Precautions to Consider

Carcinogenicity

Long-term studies have not been done in animals to evaluate the carcinogenic potential of menotropins 10, 64.

Pregnancy/Reproduction

Fertility¾Use of menotropins to induce ovulation is associated with a high incidence of multiple gestations and multiple births 10, 14, 15, 16, 17, 18, 21, 24, 28, 29, 64.

As a result, this may increase the risk of neonatal prematurity, as well as other complications associated with multiple gestations 10, 14, 15, 16, 17, 18, 21, 24, 28, 29, 46, 64.

Pregnancy¾Although problems in humans have not been documented, use of menotropins during pregnancy is unnecessary 64.

Ovarian hyperstimulation syndrome (OHS), which may be induced by menotropins therapy, is more common, more severe, and protracted in patients who conceive. 3, 10, 28

FDA Pregnancy Category X 1, 10.

Breast-feeding

It is not known whether menotropins are distributed into breast milk 10.

However, menotropins are not indicated during the course of breast-feeding 59, 64.

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

For females only

>> Abnormal vaginal bleeding, undiagnosed 10, 65

(may indicate the presence of endometrial hyperplasia or carcinoma, which may be exacerbated by menotropins-induced increases in estrogen serum concentrations; other possible endocrinopathies should also be ruled out)

>> Ovarian cyst or enlargement not associated with polycystic ovarian syndrome 10, 41, 65

(risk of further enlargement)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
For females only

>> Estradiol 5, 8, 10, 19, 23, 24, 28, 29, 39, 40, 41, 42, 43, 44, 64, 66

(measurement of serum concentrations is recommended as needed, continuing through the day of chorionic gonadotropin administration 5, 64 ; recommended to determine optimal dose and to lessen the risk of ovarian hyperstimulation 5, 8, 10, 61, 64, 69)

>> Ultrasound examination 5, 8, 10, 19, 23, 24, 28, 29, 38, 39, 40, 41, 42, 43, 44, 64

(recommended during menotropins therapy and prior to administration of chorionic gonadotropin to provide information on the number and size of mature follicles, to follow follicular development, and to lessen the risk of ovarian hyperstimulation syndrome and multiple gestation 3, 5, 8, 10, 64)

Daily basal body temperature 5, 10, 42, 64

(can be used in ovulation induction to determine if ovulation has occurred 5, 6, 64 ; if basal body temperature following a cycle of treatment is biphasic and is not followed by menses, a pregnancy test is recommended 5)

Progesterone 5, 10, 64

(measurement of serum or urine concentrations can be used prior to menotropins therapy to confirm anovulation 5, 6, 34, 37, 42, 64 ; serum concentrations can be used after therapy to detect luteinized ovarian follicles 5, 6, 10, 64)

For males only

Sperm count and determinations of sperm motility 32

(to evaluate success of treatment 32)

Testosterone 10

(measurement of baseline serum concentrations recommended prior to therapy, to rule out other causes of infertility 10, 34 and following therapy to evaluate success of treatment; should increase)

Side/Adverse Effects

Note: Arterial thromboembolism has been reported in patients who have received menotropins and chorionic gonadotropin, both in association with and separate from ovarian hyperstimulation syndrome. 1, 3, 10 Complications resulting from thromboembolism have included venous thrombophlebitis,

pulmonary embolism, pulmonary infarction, stroke, arterial occlusion necessitating limb amputation, and (rarely) death. 3, 10, 11

Serious respiratory complications have occurred with menotropins therapy. 3 These conditions included atelectasis and acute respiratory distress syndrome. 3, 10 Rarely, death has resulted. 3, 10, 67

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent¾about 20%
For females only

Uncomplicated, mild to moderate, ovarian enlargement or 10, 39, 44 ovarian cysts 10, 12, 23, 38, 39, 44 12, 29 (mild bloating, abdominal or pelvic pain)¾usually mild to moderate and abate within 7 to 10 days 10, 23, 29; pain, swelling, or irritation at injection site 1, 10, 29; rash at injection site or on body 10, 29
Incidence less frequent or rare

For females only

Severe ovarian hyperstimulation syndrome 1, 3, 10, 11, 23, 24, 28, 29, 38, 39, 44, 61 1, 3, 10, 13, 23, 28, 29, 44, 61, 63 (severe abdominal or stomach pain; feeling of indigestion; moderate to severe bloating; decreased amount of urine; continuing or severe nausea, vomiting, or diarrhea; severe pelvic pain; rapid weight gain; swelling of lower legs; shortness of breath)

Note: In clinical trials, ovarian hyperstimulation syndrome (OHS) occurred in 0.4% of patients treated with 150 Units or less each of FSH and LH and in 1.3% of patients treated with higher doses of menotropins. 1, 3, 10, 44 OHS may often occur 7 to 10 days after ovulation or completion of therapy. 1, 3, 10, 13, 23, 44 OHS differs from uncomplicated ovarian enlargement and can progress rapidly to cause serious medical problems. 3 With OHS, a marked increase in vascular permeability results in rapid accumulation of fluid in the peritoneal, pleural, and pericardial cavities (third spacing of fluids). 3, 10, 13, 23, 28, 29, 44 Medical complications ultimately arising from this increased vascular permeability may include hypovolemia, hemoconcentration, electrolyte imbalance, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events. 3, 10, 13, 23, 28, 29, 39, 44 OHS is more common, more severe, and protracted in patients who conceive. 1, 3, 10, 13, 28

For males only

Erythrocytosis (shortness of breath; irregular heartbeat; dizziness; loss of appetite; headache; fainting; more frequent nosebleeds)¾has been reported in one patient 4, 10

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

For males only

Gynecomastia (enlargement of breasts) 1, 10

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Menotropins (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to menotropins or gonadotropins
Other medical problems, especially abnormal vaginal bleeding or ovarian cyst or enlargement
Proper use of this medication

>> Proper dosing
Precautions while using this medication

>> Importance of close monitoring by physician

For females only

>> Importance of recording of basal body temperature and timing of intercourse, when recommended by physician

Side/adverse effects

Signs of potential side effects, especially ovarian cysts, enlargement, or hyperstimulation syndrome or skin reactions (for ovulation induction) and erythrocytosis (for males)

General Dosing Information

Patients receiving menotropins should be under supervision of a physician experienced in the treatment of gynecologic or endocrine disorders. 1, 3

For females only

Dosage varies considerably and must be adjusted to meet the individual requirements of each patient, on the basis of clinical response 3, 29, 33, 41.

Conception should be attempted within 48 hours of ovulation 28.

It is recommended that the couple have intercourse or insemination performed daily beginning the day after chorionic gonadotropin is administered until ovulation is thought to have occurred 28, 38, 64.

If ovulation does not occur after any cycle of therapy, the therapeutic regimen employed should be re-evaluated 3, 38, 41.

If ovulation does not occur after 3 cycles of menotropins therapy, the appropriateness of continuing use of menotropins for ovulation induction should be reconsidered. 3, 20, 24, 38, 41, 64

For treatment of adverse effects

Ovarian enlargement or ovarian cyst formation

· Discontinuing therapy until ovarian size has returned to baseline. 3, 23 Human chorionic gonadotropin should also be withheld for that cycle 1, 3, 10, 12, 23, 28, 29, 38, 40, 41, 44, 62.

· Prohibiting intercourse until ovarian size has returned to baseline to prevent cyst rupture. 3, 10

· Reducing dosage in next course of therapy. 3

Ovarian hyperstimulation syndrome (OHS)¾

Acute phase:

· Discontinuing therapy. 3, 10, 28

· Prohibiting intercourse until ovarian size has returned to baseline to prevent cyst rupture. 3, 28, 31

· Most cases of OHS will spontaneously resolve when menses begins. 3, 10 In selected cases, hospitalization of the patient with bed rest may be necessary. 3, 10, 28, 61

· Utilizing therapy to prevent hemoconcentration and minimize risk of thromboembolism and renal injury. 10, 39

· Correcting (cautiously) electrolyte imbalance while maintaining acceptable intravascular volume 3, 10, 23 ; in the acute phase, intravascular volume deficit cannot be completely corrected without increasing third space fluid volume. 3, 10

· Monitoring fluid intake and output, body weight, hematocrit, serum and urine electrolytes, urine specific gravity, blood urea nitrogen (BUN), creatinine, and abdominal girth daily or as often as required. 3, 10, 23, 39, 44, 70

· Monitoring serum potassium concentrations for development of hyperkalemia. 3, 10

· Limiting performance of pelvic examinations since they may result in rupture of ovarian cysts and hemoperitoneum. 3, 10, 23, 28, 30, 44, 70

· Administering intravenous fluids, electrolytes, and human serum albumin as needed to maintain adequate urine output and to avoid hemoconcentration. 3, 10, 23, 28, 61

· Administering analgesics as needed. 3, 10

· Avoiding diuretic use since it reduces intravascular volume further. 3, 10, 23, 28, 44

· Removing ascitic, pleural, or pericardial fluid only if it is imperative for relief of symptoms such as respiratory distress or cardiac tamponade; to do so may increase risk of injury to the ovary. 3, 10, 23, 44

· In patients who require surgery to control bleeding from ovarian cyst rupture, employing surgical measures that also maximally conserve ovarian tissue. 3, 10

Intermediate phase:

· Once patient is stabilized, minimizing third spacing of fluids by cautiously replacing potassium, sodium, and fluids as required, based on monitoring of serum electrolyte concentrations. 3, 10, 61

· Avoiding diuretic use. 3, 10, 28, 44

Resolution phase:

· The third space fluid shifts to intravascular compartment, resulting in decreased hematocrit value and increased urinary output. 3, 10

· Peripheral and/or pulmonary edema may result if third space fluid volume mobilized exceeds renal output. 3, 10

· Administering diuretics when required, to manage pulmonary edema. 3, 10

Parenteral Dosage Forms

MENOTROPINS FOR INJECTION USP

Usual adult dose

Induction of ovulation¾
Intramuscular, 75 Units of FSH and 75 Units of LH activity once a day for usually seven or more days, followed by 5000 to 10,000 Units of chorionic gonadotropin one day after the last dose of menotropins 10, 28, 29, 41, 45, 68.

If necessary, the dose of menotropins may be increased by 75 to 150 Units FSH and 75 to 150 Units LH every four or five days 10, 28, 29, 38, 40, 41.

Up to 450 Units FSH and 450 Units LH a day may be required. 43

Assisted reproductive technologies *¾
Intramuscular, 150 Units of FSH and 150 Units of LH activity once a day for usually seven or more days, followed by 5000 to 10,000 Units of chorionic gonadotropin one day after the last dose of menotropins 10, 68.

If necessary, the dose of menotropins may be increased by 75 to 150 Units FSH and 75 to 150 Units LH every four or five days. 10, 25, 26, 27

Note: Dosage regimen may vary according to physician preference or patient response. 3, 10, 28, 29, 68

If the ovaries are abnormally enlarged or the serum estradiol concentration is excessively elevated on the last day of menotropins therapy, human chorionic gonadotropin should not be given for that cycle. 1, 3, 10, 12, 23, 28, 29, 38, 40, 41, 44

Male infertility (hypogonadotropic hypogonadism)¾
Intramuscular, 75 Units of FSH and 75 Units of LH activity three times a week (plus chorionic gonadotropin 2000 Units twice a week) for at least four months following pretreatment with chorionic gonadotropin (5000 Units three times a week for up to four to six months) 10.

If an increase in spermatogenesis has not occurred after four months, the dose may be increased to 150 Units FSH and 150 Units LH three times a week (with no change in dose of chorionic gonadotropin) 10.

Size(s) usually available:

U.S.¾75 Units of FSH and 75 Units of LH activity (Rx)[Humegon 3] [Pergonal 1, 10]

150 Units of FSH and 150 Units of LH activity (Rx)[Humegon 3] [Pergonal 1, 10]

Canada¾75 Units of FSH and 75 Units of LH activity (Rx)[Humegon 7] [Pergonal 2]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:

Using standard aseptic technique, reconstitute by adding 1 to 2 mL of 0.9% Sodium Chloride Injection USP to each ampul of Menotropins for Injection USP 10.

Stability:

Use immediately after reconstitution 10 ; discard any unused portion 10.