GONAPEPTYL® CR

FERRING
PHARMACEUTICALS

NAME OF THE MEDICINAL PRODUCT
GONAPEPTYL CR
3.75 mg
Powder and solvent for suspension for injection
QUALITATIVE AND QUANTITATIVE COMPOSITION
One pre-filled syringe contains 3.75 mg triptorelin (as acetate) to be suspended in one ml sodium containing suspension agent.
PHARMACEUTICAL FORM
Powder and solvent for suspension for injection
prolonged release in pre-filled syringes.
Visual description:
Before mixing: White to faintly yellow powder and a clear colourless aqueous liquid.
After mixing: Homogeneous milky white to faintly yellow suspension.
CLINICAL PARTICULARS
Therapeutic indications
Men:
-Treatment of hormone dependent locally advanced or metastatic prostate cancer.
-Hormone sensitivity-assessment of a prostate carcinoma.
Women:
-Preoperative reduction of myoma size to reduce the symptoms of bleeding and pain in women with symptomatic uterine myomas.
-Symptomatic endometriosis confirmed by laparoscopy when suppression of the ovarian hormonogenesis is indicated to the extent that surgical therapy is not primarily indicated.
-Down regulation and prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation for assisted reproductive technologies (ART).
Children:
-Treatment of confirmed central precocious puberty (girls under 9 years, boys under 10 years).
Posology and method of administration
The product should only be used under the supervision of an appropriate specialist having requisite facilities for regular monitoring of response.
It is important that the injection of the sustained release form be performed strictly in accordance with the instructions given below.
Following reconstitution, the suspension has to be injected immediately.
Dosage and method of administration
The dosage of one syringe, equivalent to 3.75 mg Triptorelin, is injected either subcutaneously (e.g. into the skin of the abdomen, the buttock or thigh) or deep intramuscularly. The injection site should be changed each time.
Men:
-Once every four weeks an injection with one syringe, equivalent to 3.75 mg Triptorelin. In order to continually suppress testosterone levels, it is important to comply with a 4-weekly administration.
-As a diagnostic: Once every four weeks an injection with one syringe, equivalent to 3.75 mg Triptorelin. Generally it can be clarified after 3 months treatment whether the prostate cancer is androgen dependent or not, if so, administration can be continued.
Women:
- Uterine myomas and endometriosis:
Once every four weeks an injection with one syringe, equivalent to 3.75 mg triptorelin. In pre-menopausal women, the treatment must be initiated in the first 5 days of the cycle.
-Assisted reproduction techniques:
Single administration on cycle days 2 or 3 (follicular phase) or cycle day 22 (luteal phase).
Children:
-At the beginning of treatment one injection with one syringe, equivalent to 3.75 mg Triptorelin, on days 0, 14, and 28. Thereafter one injection every 4 weeks.
Should the effect be insufficient, the injections may be given every 3 weeks.
Dosing should be based on body weight. Children weighing less than 20 kg are injected with 1.875 mg (half dose), children between 20 and 30 kg receive 2.5 mg (2/3 dose), and children with more than 30 kg body weight are injected with 3.75 mg Triptorelin (full dose).
Note for specific patient groups:
-There is no need to adjust the dose for the elderly.
-According to current data, dose reduction or prolongation of the dosage interval in patients with impaired renal function is not necessary.
Duration of administration:
Men:
-Prostate carcinoma:
Treatment with GONAPEPTYL CR is usually a long-term therapy.
Women:
-Uterine myomas and endometriosis:
The duration of treatment depends on the initial degree of severity of endometriosis and on the evolution of its clinical manifestations (functional and anatomical) and on the evolution of the volume of the uterine myomas, determined by ultrasonography during treatment. Normally, the maximum attainable result is achieved after 3 to 4 injections.
In view of the possible effect on bone density, GONAPEPTYL CR therapy without add-back therapy should not exceed duration of 6 months.
Children:
-Central precocious puberty (CPP):
Treatment should be stopped if a bone maturation of older than 12 years in girls and older than 13 years in boys has been achieved.
Contraindications
General:
-Known hypersensitivity to triptorelin, poly-(d,l lactide coglycolide), dextran, or to any of the excipients.
-Hypersensitivity to gonadotrophin-releasing hormone (GnRH) or any other GnRH analogue.
In men:
-Hormone independent prostate carcinoma
-As sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastasis.
-After orchiectomy (in case of surgical castration GONAPEPTYL CR does not cause further decrease of serum testosterone)
In women:
-Pregnancy or lactation.
-Severe osteoporosis
In children:
-Progressive brain tumours
Special warnings and precautions for use
4.4 Special warnings and precautions for use
General:
The use of GnRH agonists may cause reduction in bone mineral density.
In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss.
Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).
Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.
Mood changes, including depression have been reported. Patients with known depression should be monitored closely during therapy.
Men:
Initially, triptorelin, like other GnRH agonists, causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.
A small number of patients may experience a temporary worsening of signs and symptoms of their prosate cancer (tumour flare) and temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.
As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction.
After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels.
Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and may lead to osteoprosis and increased risk of bone fracture.
In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.
Administration of triptorelin in therapeutic doses result in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.
Women:
GONAPEPTYL CR should only be prescribed after careful diagnosis (e.g. laparoscopy).
It should be confirmed that the patient is not pregnant before prescription of triptorelin.
Since menses should stop during GONAPEPTYL CR treatment, the patient should be instructed to notify her physician if regular menstruation persists.
Loss of bone mineral density
The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk. For this reason, therapy without addback treatment should not exceed a duration of 6 months. After withdrawal of treatment, the bone loss is generally reversible within 6 - 9 months.
In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of therapy.
No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuses, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.
Uterine myomas and endometriosis:
A supervening metrorrhagia in the course of treatment is abnormal (apart from the first month), and should lead to verification of plasma estrogen level. Should this level be less than 50 pg/ml, possible associated organic lesions should be sought. After withdrawal of treatment, ovarian function resumes, e.g. menstrual bleeding will resume after 7-12 weeks after the final injection.
Non-hormonal contraception should be used during the initial month of treatment as ovulation may be triggered by the initial release of gonadotrophins. It should also be used from 4 weeks after the last injection until resumption of menstruation or until another contraceptive method has been established.
During treatment of uterine myomas the size of uterus and myoma should be determined regularly, e.g. by means of ultrasonography. Disproportionally fast reduction of uterus size in comparison with the reduction of myoma tissue has in isolated cases led to bleeding and sepsis.
There have been a few reports of bleeding in patients with submucous fibroids following GnRH analogue therapy. Typically the bleeding has occurred 6 - 10 weeks after the initiation of therapy.
Children:
The chronological age at the beginning of therapy should be under 9 years in girls and under 10 years in boys.
In girls initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.
After finalising the therapy, development of puberty characteristics will occur. Information with regards to future fertility is still limited. In most girls menses will start on average one year after ending the therapy, which in most cases is regular.
Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.
Slipped capital femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.
The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.
Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.
Allergic and anaphylactic reactions have been reported in adults and children. These include both local site reactions and systemic symptoms. The pathogenesis could not be elucidated. A higher reporting rate was seen in children.
Interaction with other medicinal products and other forms of interaction
Estrogen containing medicinal products should not be used during treatment with GONAPEPTYL CR.
Pregnancy and lactation
Very limited data on the use of triptorelin during pregnancy do not indicate an increased risk of congenital malformations. However, Long-term follow-up studies on development are far too limited. Animal data do not indicate direct or indirect harmful effects with respect to pregnancies or postnatal developments, but there are indications for foetotoxicity and delayed parturition. Based on the pharmacological effects disadvantageous influence on the pregnancy and the offspring cannot be excluded and GONAPEPTYL CR should not be used during pregnancy.
Women of childbearing potential should use effective non-hormonal contraception except when undergoing ART. It is not known whether triptorelin is excreted in human milk. Because of the potential for adverse reactions from triptorelin in nursing infants, breastfeeding should be discontinued prior to and throughout administration.
Effects on ability to drive and use machines
GONAPEPTYL CR has no or negligible influence on the ability to drive and use machines.
Undesirable effects
Adverse experiences reported among patients treated with triptorelin during clinical trials and from post-marketing surveillance are shown below.
Men (all indications)
- Very common (> 1/10): Hot flushes, Bone pain, Dysuria, Impotence, decreased libido.
- Common (>1/100 and <1/10): Gynecomastia, Nausea, Perspiration, excessive, tiredness, sleep disorders, injection site reactions, injection site pain, Hypersensitivity (itching. skin rash, fever), Myalgia, arthralgia, Headache, Depressive mood irritability
- Uncommon (> 1/1000 and < 1/100) Hypertension, Decreased appetite: gastralgia, dry mouth anaphylactic reaction, Elevated enzyme levels (LDH, yGT, SGOT, SGPT), weight changes, Testicular atrophy, Asthma, aggravated, decreased facial hair, body hair loss, Thrombo-embolism.
Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation.
Dizziness and tremor can be seen in some of the patients.
Women (except ART indication, see below)
- Very common (> 1/10): Hot flushes, perspiration excessive, Bone pain, Mood changes Libido decreased, vaginal bleeding/spotting, vaginal dryness, dyspareunia
- Common (> 1/100 and < 1/10): Nausea, Tiredness, sleep disorders Injection site reaction, Injection site pain Hypersensitivity (itching. skin rash, fever), Myalgia, arthralgia, Depressive mood, irritability
- Uncommon (> 1/1000 and < 1/100) Visual disturbances: Anaphylactic reaction Elevated enzyme levels (LDH, yGT, SGOT, SGPT), cholesterol level raised, Back ache, Paraesthesia ,Weight changes have been reported following administration of GONAPEPTYL CR Dizziness and tremor can be be seen in some of the patients. Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation.
Very common (>1/10): Abdominal pain, Headache
Common (>1/100 < 1/10): Nausea. Diarrhoea, Vomiting, Abdominal distension, Injection site reactions/ injection site pain, Fever, Postoperative pain, Pain ,Upper respiratory tract infection, Pharyngitis, Migraine, Dizziness, Abortion, Vaginal haemorrhage, Intermenstrual bleeding, Pelvic pain, Ovarian hyperstimulation syndrome, Dysmenorrhoea, Breast pain, Coughing, Hot flushes.
Very rare cases of allergic reactions, localized or generalized, including anaphylactic reactions have been reported after injection of GONAPEPTYL
Children
Uncommon (>1/1000 and< 1/100): vomiting, nausea, Anaphylactic reaction, Vaginal bleeding and dryness.
A few cases of epiphysiolysis capitis femoris have been reported during use with triptorelin. Whether or not a causal relationship exists is unknown.
Overdose
There is insufficient experience of overdosing with triptorelin to draw conclusions on possible adverse effects.Considering the package form and the pharmaceutical form,overdosing is not expected.
PHARMACEUTICAL PARTICULARS
List of excipients
One pre-filled syringe with powder contains:
Poly-(d,l lactide coglycolide)
Propyleneglycol octanoate decanoate
One pre-filled syringe with one ml suspension agent contains:
Dextran 70
Polysorbate 80
Sodium chloride
Sodium hydrogen phosphate dihydrate
Sodium hydroxide
Water for injection
Incompatibilities
In the absence of compatibility studies this medicinal product should not be mixed with other medicinal products.
Shelf life
See outer carton. Reconstituted suspension: 3 minutes
Special precautions for storage
Store at 2°C - 8°C (in a refrigerator). Keep the container in the outer carton.
Instructions for use and handling
GONAPEPTYL CR is for single use only and any unused suspension shouldbe discarded.
Preparation:
Instructions for the physician how to prepare the suspension.
Since successful treatment depends upon correct preparation of the suspension,
the following instructions must be strictly followed.
- Take the package of GONAPEPTYL CR from the refrigerator.
- Remove the cap from the disposable syringe containing the powder. Keep upright to prevent spilling.
- Open the package with the connector without removing the connector.
- Screw the syringe containing the powder onto the connector in the package,and then remove it.
- Screw the syringe containing the solvent tightly onto the free end of the connector and ensure that it fits tightly.

Reconstitution of the suspension:
- Empty the solvent into the syringe with the powder, then shoot it back and forth into the first syringe - the first two or three times without pushing the injection rod all the way in. Repeat this about 10 times or until you have a homogeneous milky-like suspension. While preparing the suspension, you might possibly create some foam. It is important that the foam be dissolved or removed from the syringe before giving the injection.

Mixing

Mix approximately 10 times

Injection:
- Remove the connector together with the empty syringe.
- Mount the injection needle on the syringe with the ready-to-use suspension.
- Inject subcutaneously or deep into the muscle immediately.

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Manufacturer & MAH:
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THIS IS A MEDICINE
- A MEDICINE IS A PRODUCT WHICH AFFECTS YOUR HEALTH. AND ITS CONSUMPTION CONTRARY TO INSTRUCTIONS IS DANGEROUS FOR YOU.
- STRICTLY FOLLOW THE DOCTOR'S PRESCRIPTION, THE METHOD OF USE AND THE INSTRUCTIONS OF THE PHARMASIST WHO SOLD THE MEDICINE.
- THE DOCTORS AND THE PHARMACIST ARE EXPERTS IN MEDICINE, ITS BENEFITS AND RISKS.
- DO NOT BY YOURSELF INTERRUPT THE PERIOD OR TREATMENT PRESCRIBED FOR YOU.
- DO NOT REPEAT THE SAME PRESCRIPTION WITHOUT CONSULTING YOUR DOCTOR.
-KEEP THE MEDICINE OUT OF REACH OF CHILDREN.

Council of Arab Health Ministers
Union of Arab Pharmacists