

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Moapar 11.25 mg powder and solvent for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 11.25 mg of triptorelin, as triptorelin embonate.

After reconstitution in the 2 ml solvent, the reconstituted solution contains 11.25 mg of triptorelin, as triptorelin embonate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection (Powder for injection).

- Powder: White to off-white powder.

- Solvent: Clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Moapar is indicated for the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations.

The treatment with Moapar is to be initiated and controlled by a psychiatrist. The treatment should be given in combination with psychotherapy, in order to decrease deviating sexual behaviour.

4.2. Posology and method of administration

The recommended dose of Moapar is 11.25 mg triptorelin (1 vial) administered every twelve weeks as a single intramuscular injection.

The lyophilised microgranules are to be reconstituted using 2 ml of water for injections (see section 6.6).

The injection site should be varied periodically.

Since Moapar is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

No dosage adjustment is necessary for patients with renal or hepatic impairment.

Moapar must be administered under the supervision of a medically qualified person (nurse or physician).

The therapeutic benefit should be monitored regularly, for example prior to any new injection.

4.3. Contraindications

- patients with serious osteoporosis

- patients with known hypersensitivity to triptorelin, GnRH (Gonadotropin-releasing hormone), other GnRH agonist analogues or to any of the excipients of Moapar.

4.4. Special warnings and precautions for use

Initially triptorelin causes a transient increase in serum testosterone levels. During the initial phase of treatment, the patient should be closely monitored by the treating psychiatrist and consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels in order to control possible increase in sexual drive if considered appropriate..

Following treatment interruption, there is a risk of an increased sensitivity to the restored testosterone, which can lead to a highly increased sexual drive. For this reason, the addition of an adequate antiandrogen before stopping Moapar treatment should be considered.

Once the castration levels of testosterone have been achieved by the end of the first month, they are maintained for as long as the patients receive their injection every twelve weeks.

The evaluation of the treatment effect is essentially clinical. A clinical assessment of the treatment effect should be done regularly, e.g. before each 3-month injection of triptorelin. Serum testosterone levels may be measured in case there is a doubt of treatment effect, which could be related to compliance to triptorelin treatment or to a technical problem with the injection.

Caution is required in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

Administration of triptorelin in therapeutic doses results 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 a GnRH agonist may therefore be misleading.

The long term use of synthetic GnRH analogues may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture.

Bone Mineral Density may be assessed before the treatment start and may be followed regularly during the treatment.

In order to prevent the treatment-related bone loss, lifestyle modification including smoking cessation, moderation of alcohol consumption and regular weight bearing exercise are recommended. Adequate dietary calcium and vitamin D intake should also be maintained.

Treatment with GnRH analogues may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. Pituitary apoplexy is characterised by sudden headache, visual impairment and ophthalmoplegia.

Increased lymphocytes count has been reported with patients undergoing GnRH analogue treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

4.5. Interaction with other medicinal products and other forms of interaction

No controlled interactions studies have been performed.

4.6. Pregnancy and lactation

Moapar is not indicated for use in females.

Animal studies have shown effects on reproductive parameters (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However certain undesirable effects such as dizziness, somnolence and visual disturbance could impair the ability to drive and use machines.

4.8. Undesirable effects

As seen with other GnRH agonist therapies or after surgical castration, the most commonly observed adverse events related to triptorelin treatment were due to its expected pharmacological effects: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects include hot flushes (observed in 46% of the patients), impotence, and decreased libido (observed in 1% to 10% of the patients). With the exception of hypersensitivity reactions (uncommon) and injection site pain (<5%), all adverse events are known to be related to testosterone changes. The long-term use of synthetic GnRH analogues may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture.

The following adverse reactions considered as at least possibly related to triptorelin treatment were reported. Most of these events are known to be related to biochemical or surgical castration.

The frequency of the adverse reactions is classified as follows: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000).

System organ class	Very common	Common	Uncommon
Blood and lymphatic system disorders			Purpura
Ear and labyrinth disorders			Tinnitus
Endocrine disorders			Diabetes mellitus
Eye disorders			Abnormal sensation in eye Visual disturbance
Gastrointestinal disorders		Nausea	Abdominal distension Abdominal pain Constipation Diarrhoea Dry mouth Dysgeusia Flatulence Vomiting
General disorders and administration site conditions		Asthenia Injection site pain Oedema peripheral	Chest pain Dysstasia (difficulties to stand) Fatigue Influenza like illness Bruises, burning sensation, erythema or induration at the injection site Oedema Pain Fever Rigors Somnolence
Immune system disorders			Anaphylactic reaction Hypersensitivity
Infections and infestations			Nasopharyngitis

System organ class	Very common	Common	Uncommon
Investigations Metabolism and nutrition disorders			Increases in alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, blood creatinine, urea. Increased body temperature, weight loss, weight increased Anorexia Gout Increased appetite
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity	Arthralgia Joint stiffness Joint swelling Muscle cramp Muscular weakness Myalgia Neck pain
Nervous system disorders		Dizziness Headache	Paraesthesia Vertigo
Psychiatric disorders			Affect lability Confusion Decreased activity Depression Euphoric mood Insomnia Irritability Mood swings
Reproductive system and breast disorders		Erectile dysfunction Libido decreased	Breast pain Breast tenderness Ejaculation failure Gynaecomastia Nipple pain Testicular pain
Respiratory, thoracic and mediastinal disorders			Dyspnoea Orthopnoea
Skin and subcutaneous tissue disorders			Acne Alopecia Blister Pruritus
Vascular disorders	Hot flush		Epistaxis Hypertension Hypotension

4.9. Overdose

The pharmaceutical form of Moapar and its route of administration make accidental or intentional overdose unlikely. There is no experience of overdose. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Moapar. If overdose occurs, this should be managed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin releasing hormone analogues.

ATC code: L02A E04

Mechanism of action and pharmacodynamic effects

Triptorelin, a GnRH agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. Studies in men show that after the administration of triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone.

However, chronic and continuous administration of triptorelin to men results in decreased LH and FSH secretion and suppression of testicular steroidogenesis. A reduction of serum testosterone levels into the range normally seen after surgical castration occurs approximately 2 to 4 weeks after initiation of therapy. This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product.

Testosterone plays a major role in the regulation of sexuality, aggression, cognition, emotion, and personality. In particular, it is a major determinant of sexual desire, fantasies and behaviour, and basically controls the frequency, duration and magnitude of spontaneous erections. The effects of testosterone (and of its reduced metabolite 5α -dihydrotestosterone [DHT]) are mediated through their actions on the intracellular androgen receptor.

Clinical efficacy

Administration of Moapar as an intramuscular injection for a total of 3 doses (9 months) resulted in achievement of castration levels of testosterone in 97.6% of patients with advanced prostate cancer after four weeks of treatment, which was maintained from month 2 through month 9 of treatment in 94.1% of the patients.

5.2. Pharmacokinetic properties

Absorption:

Following a single intramuscular injection of Moapar, t_{max} was 2 (2-6) hours and C_{max} (0-85 days) was 37.1 (22.4-57.4) ng/ml. Triptorelin did not accumulate over 9 months of treatment.

Distribution:

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0.5 mg triptorelin is approximately 30 l in healthy men.

Biotransformation:

Metabolism of triptorelin has not been determined in humans.

Elimination:

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of 0.5 mg triptorelin to healthy male volunteers, 42% of the dose was excreted in urine as intact triptorelin. In these healthy volunteers, the true terminal half-life of triptorelin was 2.8 hours and total clearance of triptorelin 212 ml/min.

Special populations:

Triptorelin clearance decreases with impaired renal or liver function. Following intravenous administration of 0.5 mg triptorelin to subjects with moderate renal insufficiency (Cl_{creat} 40 ml/min), triptorelin had a clearance of 120 ml/min; 88.6 ml/min in subjects with severe renal insufficiency (Cl_{creat} 8.9 ml/min) and 57.8 ml/min in patients with mild to moderate impaired hepatic function (Cl_{creat} 89.9 ml/min).

Because of the large safety margin of Moapar, no dose adjustment is recommended in patients with renal or hepatic impairment.

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied.

5.3. Preclinical safety data

The toxicity of triptorelin towards extragenital organs is low.

The observed effects were mainly related to the excessive pharmacological effects of triptorelin.

In chronic toxicity studies at clinically relevant doses, triptorelin induced macro- and microscopic changes in the reproductive organs of male rats, dogs and monkeys. These were considered to reflect the suppressed gonadal function caused by the pharmacological activity of the compound. The changes were partly reversed during recovery. After subcutaneous administration of 10 micrograms/kg to rats on days 6 to 15 of gestation, triptorelin did not elicit any embryotoxicity, teratogenicity, or any effects on the development of the offspring (F1 generation) or their reproductive performance. At 100 micrograms/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

Triptorelin is not mutagenic *in vitro* or *in vivo*. In mice, no carcinogenic effect has been shown with triptorelin at doses up to 6000 micrograms/kg after 18 months of treatment. A 23 month carcinogenicity study in rats has shown an almost 100% incidence of benign pituitary tumours at each dose level, leading to premature death. The increased incidence in pituitary tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder:

poly (d, l-lactide-co-glycolide)
mannitol
carmellose sodium
polysorbate 80.

Solvent:

Water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

3years.

After reconstitution, chemical and physical in use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

Powder in 6 ml Type I colourless glass vial with grey bromobutyl stopper and aluminium flip-off capsule and 2 ml of solvent in Type I colourless glass ampoule, and a kit of 1 empty injection syringe of polypropene and 2 injection needles.

6.6. Special precautions for disposal and other handling

For SE:

The solvent should be drawn into the injection syringe and transferred to the vial containing the powder. The vial should be gently shaken to thoroughly disperse particles and obtain a uniform suspension. The suspension will appear milky. The suspension obtained should be drawn back into the injection syringe. The injection needle has to be changed and the produced suspension for injection should be administered immediately.

The suspension should be discarded if not used immediately after reconstitution.

Moapar is only intended for single use and any unused suspension should be discarded.

Used injection needles should be disposed in a designated sharp container. Any remaining medicinal product should be discarded.

For all countries except SE:

Using the simple injection needle, all of the solvent should be drawn up into the injection syringe and transferred to the vial containing the powder. The vial should be gently shaken to thoroughly disperse particles and obtain a uniform suspension. The suspension will appear milky. The suspension obtained should be drawn back into the injection syringe. The injection needle has to be changed and the produced suspension for injection should be administered immediately. This injection needle is equipped with a safety system.

The suspension should be discarded if not used immediately after reconstitution.

Moapar is only intended for single use and any unused suspension should be discarded.

Used injection needles should be disposed in a designated sharp container. Any remaining medicinal product should be discarded.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

21964

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2006-06-09

10. DATE OF REVISION OF THE TEXT

26 December, 2008