LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Moapar, 11.25 mg, powder and solvent for suspension for injection
(triptorelin embonate)

SE/H/663/01/MR

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This module reflects the scientific discussion for the approval of Moapar. The procedure was finalised at 2007-05-21. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Debioclinic S.A. applied for a marketing authorisation for Moapar, 11.25 mg, powder and solvent for suspension for injection, the active substance being triptorelin embonate. Triptorelin, a GnRH agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. 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, after chronic and continuous administration of triptorelin to men, decreased LH and FSH secretion is seen as well as 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.

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

One CMS raised potential serious risk to public health relating to the proposed indication as they considered that the documentation of efficacy of Moapar in decreasing sexual drive in men with sexual deviations was scarce. Other CMS and the RMS SE found the proposed indication acceptable based on the surrogate endpoint - reduction of testosterone to castrate levels. There is limited evidence from studies that the sexual drive in men with sexual deviations will decrease as a result of testosterone reduction to castrate levels, as they do in men without sexual deviations. Thereby, the frequency of possibly offensive sexual acts is expected to be reduced. This was considered a reasonable justification for the applied indication.

The CMS that had potential serious risk to public health withdrew its request before the second CMD meeting.

The apparent lack of well designed studies on Moapar in patients with sexual deviations has been acknowledged, however acceptable due to the difficulty in performing these studies in the actual patient population.

II. QUALITY ASPECTS

II.1 Introduction

Moapar is presented in the form of powder for suspension for injection, containing the equivalent of 11.25 mg of triptorelin free base in the form of triptorelin embonate. The triptorelin embonate is incorporated into lyophilised microgranules of the biodegradable polymer poly(d,l-lactide-co-glycolide) to get a slow release formulation. The powder is to be reconstituted with water for injections prior to intramuscular injection.

Triptorelin embonate does not have a monograph in the Ph Eur. Information on the drug substance has been supplied in the form of an ASMF.

The powder is packed in 6 ml Type I colourless glass vials with grey bromobutyl stoppers and aluminium flip-off capsules.

II.2 Drug Substance

The active substance in Moapar is triptorelin embonate, a decapeptide manufactured by Bachem AG, Switzerland. The structural formula is:

[(L-Pyr)-(L-His)-(L-Trp)-(L-Ser)-(L-Tyr)-(D-Trp)-(L-Leu)-(L-Arg)-(L-Pro)-(Gly-NH_2)]

The peptide is synthesised using standard methods used in conventional solution-phase peptide synthesis. Relevant specifications for the drug products are given. Data is presented confirming the manufacturer's ability to consistently produce a product fulfilling the specifications. The structure of the drug substance has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Moapar 11.25 mg, powder for suspension for injection is formulated using excipients described in the current Ph Eur, except for Poly (d,l-lactide-co-glycolide) which is controlled according to acceptable in house specifications.

All raw materials used in the product is in compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Triptorelin embonate 11.25 mg, powder and solvent for suspension for injection has already been approved through the MRP (DE/H/492/01) on the 28th of September, 2004, in the prostate cancer indication with Germany as RMS. The scientific rationales for using triptorelin embonate for the prostate cancer indication and the proposed indication "the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations" are similar. The preclinical parts of the Moapar 11.25 mg dossier are essentially the same as the dossier which was submitted in 2004. The suggested SPC for Moapar is also essentially the same SPC, except for the indication, as already approved for the prostate cancer indication.

III.2 Pharmacology

The active ingredient, triptorelin, is a synthetic decapeptide agonist analog to the naturally occurring luteinizing hormone-releasing hormone (LHRH). LHRH is also known as a gonadotropin-releasing hormone (GnRH). The pharmacological activity of triptorelin and its increased potency as compared to LHRH/GnRH has been demonstrated in *in vitro* and *in vivo* studies. In vitro, triptorelin was 100 fold more active than native LHRH in stimulating LH release in primary cultures of anterior pituitary cells from female rats. In vivo studies in immature male rats showed that triptorelin induced an increase in circulating LH and FSH activities after subcutaneous administration of 50 or 100 ng triptorelin/rat. Triptorelin has also been shown to have direct effects on the testis and ovary of rats.

Triptorelin has stimulatory effect on steroidogenesis during short-term exposure of the preovulatory follicle, reflected by stimulation of estradiol, progesterone, and andosterone release, but exerts a direct inhibitory action on the rat ovarian follicle after prolonged exposure (> 24 hours), as reflected by inhibition of estradiol, progesterone and andosterone release, inhibition of cell differentiation and a reduction in LH receptors. In addition, binding to testicular luteinizing hormone/human chorionic gonadotrophin (LH/hCG) receptor sites was demonstrated following seven daily s.c. administrations of triptorelin in mature (2 μg/day) and immature hypophysectomized (0.2 or 2 μg/day) male rats.

Long-term treatment with triptorelin inhibits or suppresses the growth of various tumours including prostate tumours.

To summarise, triptorelin, when given continuously and in therapeutic doses, is a potent inhibitor of gonadotropin secretion with subsequent suppression of testicular and ovarian function after an initial transient stimulation of LH and FSH production. In conclusion, prolonged treatment with LHRH agonists can result in testicular inhibition and thus, biochemical castration.

III.3 Pharmacokinetics

The pharmacokinetic studies with sustained release formulations of triptorelin, as either embonate or acetate formulations, were performed in rats and dogs after a single dose by i.m. administration.

A pivotal study was conducted in rats to assess if a single i.m. injection (1125 mcg/kg) of the clinical formulation of triptorelin embonate was able to induce and maintain testosterone castration levels for 3 months. The results from this study showed that triptorelin serum levels increased rapidly and reached a peak within the first 3 hours after injection, after which, the concentrations decreased progressively during two weeks and remained at a plateau until day 84. After the injection, also serum testosterone levels increased rapidly in all animals to a mean peak concentration of about 15 nmol/l. The testosterone levels then decreased during the next weeks, and were followed by a transient rebound between day 20 and 30, and finally reached minimum levels between 3 and 5 weeks post injection. These low testosterone levels of 3-5 nmol/l were maintained for the next 2 months and were considered to be testosterone castration levels in rats. Similar effects with other triptorelin formulations, administered as single i.m. doses, were also seen when tested for 1 or 3 months in rats.

In dogs, the effects of a single i.m. injection of triptorelin embonate microgranules (up to 3000 mcg/kg) on testosterone levels were assessed up to 1-month. After initially high levels, the serum concentrations of triptorelin declined over the 30 day study period. For males, increased testosterone levels were seen at day 3 and 7, followed by decreased levels at day 14, and

reaching a minimum detectable level at day 28. No detectable levels were found in female dogs dosed at the same levels at any day over the 30-day period.

In conclusion, the pharmacokinetics of triptorelin has been limited but sufficiently studied in rats and dogs. After initially high levels of triptorelin and testosterone are induced, a steady state of low levels of testosterone, considered being castration levels, is maintained.

III.4 Toxicology

General toxicity including local tolerance and safety pharmacology

The toxicity studies were performed with either triptorelin embonate or triptorelin acetate which is considered acceptable considering that the active circulating moiety is the free peptide (triptorelin).

Safety pharmacology studies performed a long time ago were limited but showed that triptorelin has probably no major effects on behaviour and CNS, the cardiovascular and digestive systems. The safety pharmacology of triptorelin has not been fully addressed in animals. Transient increases in carotid artery blood pressure were observed for up to 30 minutes following bolus i.v. administration of triptorelin (300 or 1000 μg/kg) in anaesthetized male rats. However, no adverse effects were seen on the cardiovascular system in the toxicity studies performed with sc. and i.m. administrations of triptorelin. Since adequate clinical experience exists and information was available from the repeat dose toxicity studies no more safety pharmacology studies conducted in animals are required.

Acute toxicity of triptorelin was investigated 25 years ago in mice and rats following single i.p. and sc. administrations. Based on these studies the acute toxicity of triptorelin is considered low.

Repeat dose toxicity studies of triptorelin, triptorelin acetate microspheres and triptorelin embonate microgranules were conducted in male and female rats (up to 3000 μg/kg i.m. every month for 6 months), in male and female dogs (up to 3000 μg/kg i.m. every month for 6 months), and in male and female Cebus Apella monkeys (up to 200 μg/kg s.c. daily for 6 months). The only effects observed were expected consequences of exaggerated pharmacological activity of triptorelin. In relation to the intended clinical dose of triptorelin embonate microgranules (11.25 mg/3-month for a 70 kg man, i.e. 125 μg/day or 1.8 μg/kg/day), the doses used in the preclinical studies approximate from 0.1 to 100 times the intended therapeutic dose.

Serum levels of testosterone in males, estradiol and progesterone in females, and LH were suppressed in animals administered 2 μg/kg/day and higher doses of triptorelin by daily injection or administered the equivalent average daily dose by once monthly i.m. injection of the sustained release formulations. At the same dose levels, spermatogenic arrest and atrophy of the testes and accessory sex organs were observed in male animals (rats, dogs, monkeys) and inhibition of estrus and atrophy of the ovary and accessory sex organs were observed in female animals (rats, dogs, monkeys). The fundamental change in the testis was one of arrested spermatogenesis and sperm maturation without impairment of spermatogonia. This change was similar to those that occur following hypophysectomy and which can be reversed by administration of gonadotrophic hormones.

In both males and females, triptorelin caused decreases in weights of reproductive organs. Changes in the pituitary (focal hyperplasia and benign microadenoma) were detected in male rats administered once monthly injections of triptorelin acetate microspheres or daily injections of triptorelin peptide for 6 months; these changes are commonly observed in rats in response to an altered hormonal environment. No changes were observed in the pituitary in dogs and

monkeys after 6 months of drug administration. No other abnormalities and no treatment related deaths were observed. The reversible nature of these changes was apparent from the investigations included in the recovery phases of the rat and monkey experiments. Relevant information has been included in the SPC.

The ***local tolerance*** of triptorelin was evaluated following i.m. injection in rats. Resorption of the injected acetate microspheres was completed between 40 and 45 days and was exclusively due to the macrophage response to the presence of foreign material and there were no permanent changes. The local tolerance due to the resorption of the microgranules (embonate) was similar to that of the microspheres (acetate).

There was no evidence that administration of high doses of triptorelin to laboratory animals results in any detectable manifestations of immunomodulation.

Reproductive toxicity

Reproductive toxicity was studied in rats (special fertility study, embryo-foetal development), mice (embryo-foetal development) and rabbits (special study). No adverse effects on fertility were seen in female rats receiving triptorelin acetate by sc. injection at doses up to 200 µg/kg daily for 60 days or in female rats receiving 600 µg/kg of triptorelin acetate microspheres (slow release) form by i.m. injection on days 1 and 31. Approximately half of the females per group were allowed to deliver for examination of the lactation and growth period including behavioural studies as well as examination of the reproduction performance of the F1 generation. There was no indication that parental treatment with triptorelin acetate affected fertility or general reproductive performance of the F1 animals selected to produce the F2 generation. Administration of triptorelin acetate to sexually mature female rabbits at 20 µg/kg/day by sc. administration over a period of 2 weeks prior mating induced no effects on the ovaries.

In the embryo-foetal development study in mice, no fetotoxic or teratogenic effects were seen in mated females administered up to the high dose of 200 µg/kg/day of triptorelin embonate formulation by sc. injection during gestation days 6 - 15. In rats, no teratogenic effects were seen. However, at the highest tested dose, daily sc. injections of 100 µg/kg/day, maternal toxicity was evident as reduced weight gains were seen. This high-dose level was also embryotoxic since a statistically significant increase in mean number of resorption sites and mean resorption/implant ratio were observed. No adverse affects were seen at the dose of 10 µg/kg/day. Relevant information has been included in the SPC.

Genotoxicity and carcinogenicity

The genotoxicity of triptorelin has been studied with respect to gene mutations in bacteria and in Mouse lymphoma L5178Y cells (HGPRT locus), chromosomal aberrations in vitro in CHO cells and clastogenicity in vivo in the mouse (micronucleus test, bone marrow). No genotoxic potential was evident at concentrations up to limit of toxicity or where signs of toxicity were observed or at concentrations where the test substance was soluble.

The potential carcinogenic effects of triptorelin embonate microgranules were investigated when administered monthly via i.m. injections for 18 months in CD-1 mice and 23 months in Sprague Dawley rats. The intended study period in rats was 24 months but due to mortality the study was terminated at month 23.

In mice tested up to the highest tested dose of 6000 µg/kg, no oncogenic effects were observed. In rats, an almost 100% incidence of adenomatous tumors in the pars distalis of rats treated with triptorelin embonate microgranules at doses of 120, 600 and 3000 µg/kg/month were observed. In rats, this is a known effect seen with castration or exposure to compounds causing gonadal atrophy and concomitant defects in gonadal hormone production leading to histopathological changes in adenohypophyseal gonadotrophs. In absence of negative feedback

control, hypothalamic hyperphysiotropic factors hyperstimulate the pituitary causing castration cells to appear in the pars distalis. The effect seems to be species-specific, and long-term clinical experience has shown that similar problems do not appear in humans.

Relevant information has been included in the SPC

IV. CLINICAL ASPECTS

IV.1 Introduction

As treatment with triptorelin embonate is associated with reduction of testosterone to castration levels, it was developed and evaluated for the treatment of advanced prostate cancer. Market authorisation then was sought for Moapar 11.25mg triptoreline powder and solvent for suspension for injection, given every 84 days, for the indication '*reversible reduction of serum testosterone to castrate levels in order to decrease sexual drive in adult men with sexual deviations*. During the procedure, the indication was changed to "*reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with **severe** sexual deviations."*

IV.2 Pharmacokinetics

The relative bioavailability of the 1-month and the 3-month formulation is comparable as studied in a subset of patients in study DEB-96-TRI-01.

After an intramuscular injection of 11.25 mg C_{max} was 37.1 (22.4-57.4) ng/ml and t_{max} 2 h (2-6). Triptorelin exposure (AUC) and C_{max} was shown to be similar when the results of two studies were compared (DEB-96-TRI-01 and DEB-99-TRI-01) in patients with advanced prostate cancer.

From a subset of patients in one study (DEB-96-TRI-01) there was no indication of accumulation, when the exposure were compared for the first, second and third period of three months.

Triptorelin is eliminated both by the liver and kidneys. In healthy subjects approximately 42 % of triptorelin itself is excreted renally, which increases to 62 % in patients with hepatic impairment (Child-Pugh A and B). The half-life after an intravenous bolus dose of 0.5 mg triptorelin acetate was 2.8 hours in healthy subjects and approximately 7 hours in patients with mild to moderate renal impairment and approximately 8 hours in patients with severe renal impairment and in patients with hepatic impairment (Child-Pugh A and B).

The impact of renal and hepatic impairment on the pharmacokinetics of triptorelin acetate (0.5 mg i.v.) was analysed in study DEB-95-TRI-03. The exposure was found to be higher in patients with hepatic and renal impairment, approximately 4-fold higher in patients with hepatic impairment. However, this does not have any influence on the safety or efficacy of Moapar, since very large increases in the exposure and maximal concentrations of triptorelin does not change the testosterone profile.

There is no information of the influence of race on the pharmacokinetics of triptorelin.

IV.3 Pharmacodynamics

No formal evaluation of the PK-PD correlation was made. From the observed data, however 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.

There is thereafter a decrease in LH and FSH secretion. After approximately 4 weeks, testosterone levels are reduced to the range normally seen in surgically castrated men.

IV.4 Clinical efficacy

Since some sexual deviations may result in severe problems for the individual and even lead to sexual offensive behaviour with violation of established laws with unacceptable consequences for the victims, there is a need for effective treatment. Currently available and ethically acceptable treatment options include hormonal treatment with antiandrogens as well as psychiatric drugs and psychotherapy, none of which, although potentially effective, has been shown to provide sufficient effect in severe cases. Pharmacotherapy is often associated with adverse effects, resulting in poor treatment compliance.

The studies performed in men with prostate cancer provide clear evidence that triptorelin will reduce testosterone production to castration levels which appear to be maintained throughout the period of treatment. The issue whether castration levels of testosterone provide sufficient effects on sex deviations could only be addressed from indirect evidence as the studies presented were small and, although apparently positive, only provided limited evidence of a treatment effect. It is, however, understandable that there are no well performed studies available in this group of patients.

Historical data suggest that the most drastic method to reduce testosterone, surgical castration, reduces paraphilic fantasies and behaviour as well as recidivism rates in sexual offenders versus before castration. Positive effects of leuprorelin, a synthetic analogue of GnRH, have been reported in case series of sexual deviations. Several uncontrolled case studies and a few controlled studies have reported the efficacy of both medroxyprogesterone acetate and cyproterone acetate in the treatment of sexual deviations. Thus, it could be concluded that testosterone reduction, as occurs during treatment with triptorelin, will reduce the frequency and intensity of deviant sexual behaviour in men with paraphilias and possibly also open a window for psychological behavioural treatment approaches.

IV.5 Clinical safety

The safety of triptorelin when used for advanced prostate cancer appears acceptable with regard to adverse events, serious adverse events and deaths in that often elderly and severely ill population. Most adverse events in those populations studied are related to testosterone suppression and, apart from decreased libido and erectile dysfunction, include hot flushes and headache. There is some concern with regard to negative effects of testosterone reduction on bone mineral density. Limited data suggest that treatment effects are reversible upon discontinuation.

The safety of triptorelin for long-term use in men with paraphilias has virtually not been studied.

IV.6 Discussion of clinical aspects

Considering the seriousness of some sexual deviations, in particular pedophilia, with regard to the risk of sex offence to young victims, it is reasonable to provide a variety of treatment options, one of which might be triptorelin. Treatment decision should be limited to doctors experienced in psychiatry and treatment should preferably be given as a back-up to other treatments, i.e. appropriate psychotherapy. From reports using other GnRH-analogues or other

hormonal treatments for paraphilias, it can be assumed that treatment has to continue for several years in order to prevent relapse and to allow appropriate time for additional psychotherapy. Although the duration of treatment cannot be established in advance, the effects need to be assessed at regular intervals at which the benefit of continuation should be evaluated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Moapar, 11.25 mg, powder and solvent for suspension for injection, was recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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