CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Triptofem 0.1 mg/ml, solution for injection in pre-filled syringe Karmed HandelsgesmbH, Austria

triptorelin (as acetate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2441/001/DC
Registration number in the Netherlands: RVG 110636

22 April 2013

Pharmacotherapeutic group:	gonadotropin releasing hormone analogues
ATC code:	L02AE04
Route of administration:	subcutaneous
Therapeutic indication:	downregulation and prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation for assisted reproductive technologies (ART)
Prescription status:	prescription only
Date of authorisation in NL:	30 January 2013
Concerned Member States:	Decentralised procedure with AT, BE, DE, DK, ES, FI, FR, IT, NO, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Triptofem 0.1 mg/ml, solution for injection in pre-filled syringe, for subcutaneous use, from Karmed HandelsgesmbH. The date of authorisation was on 30 January 2013 in the Netherlands.

The product is indicated for downregulation and prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation for assisted reproductive technologies (ART).

In clinical trials Triptofem 0.1 mg/ml has been used in cycles where urinary and recombinant human follicle stimulating hormone (FSH) as well as human menopausal gonadotrophin (HMG) were used for stimulation.

A comprehensive description of the indications and posology is given in the SPC.

Triptorelin (acetate) is a synthetic decapeptide and an analog of the natural hypothalamus hormone GnRH. Triptorelin has a longer duration of action than the natural GnRH and has a biphasic effect at the pituitary level. After an initial large sudden increase in LH and FSH levels (flare-up), circulating LH and FSH levels decrease due to the pituitary GnRH-receptor desensitization, with a consequent marked reduction in the gonadal stimulating hormones (LH and FSH) production. The Gonapeptyl induced down-regulation of the pituitary can prevent the LH surge and thereby premature ovulation and/or follicular luteinization. The use of the down-regulation with GnRH agonist reduces the cycle cancellation rate and improves the pregnancy rate in ART cycles. The exact duration of action of Triptofem 0.1 mg/ml has not been established, but pituitary suppression is maintained for at least 6 days after stopping administration. After discontinuation of Triptofem, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Decapeptyl 0.1 mg/ml, solution for injection (NL License RVG 11778) which has been registered in the Netherlands by Ferring B.V. since 26 September 1989 (original product). In addition, reference is made to Decapeptyl authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Triptofem 0.1 mg/ml is a product for parenteral use, it is exempted for bioequivalence study (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is triptorelin, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white powder, which is freely soluble in acetic acid, soluble in water, 0.1N hydrochloric acid, 0.1N sodium hydroxide, dimethylformamide and it is practically insoluble in acetone and chloroform.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacture requires 17 synthesis steps. Adequate in-process controls are applied for monitoring the progress c.q. completion of the reactions and/or the purity of the resulting products. Adequate specifications are provided for the solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets usual pharmaceutical standards and the ICH guidelines. Whenever possible and considered appropriate, Ph.Eur. methods have been employed. Batch analysis results are presented for 5 batches. All results comply with the set requirements.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines. The substance was stored at long-term conditions (< -15°C and 2-8°C for 60 months) and at accelerated conditions (25°C/60% RH for 24 months and 40°C/75% RH for 6 months).
Based on the provided normal testing data the proposed re-test period of 3 years in the proposed packaging (providing protection from light) for storage at < -15°C or 2-8°C is acceptable.

** Ph.Eur. is an official handbooks (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Triptofem 0.1 mg/ml is a clear colourless solution with pH 4.0-5.0 and osmolarity 284 – 287 mOsm/Kg.

1 ml aqueous solution for injection is packed in single use pre-filled disposable borosilicate type 1 glass syringes with integrated needle and rigid needle shield. The syringe is closed with a chlorobutyl rubber stopper with a polystyrene plunger rod.

Each pre-filled syringe of 1 ml solution for injection contains 100 micrograms triptorelin acetate equivalent to 95.6 micrograms triptorelin free base.

The excipients are: sodium chloride, glacial acetic acid (for pH adjustment), water for injections

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Because of the parenteral use, bioequivalence studies are not required. An initial overfill of 10% was removed, as it is not required.
A standard container closure system is used to fill the drug product into, clear glass syringe barrels, hydrolytic class I, according to Ph. Eur.
The drug product is intended for injection, therefore it has to be sterile. Sterility is part of the batch release and shelf life specification. Sterile filtration is necessary since heat sterilization methods in the finished container are not possible due to the heat sensitive nature of the peptide drug substance. The formulation of Triptofem is considered essentially similar to the originator triptorelin formulation, Decapeptyl 0.1 mg/ml, solution for injection from Ferring.

Manufacturing process
The manufacturing process consists of dissolution, mixing, sterile filtration and sterile filling. All relevant process steps and parameters were sufficiently described. As the procedure is very straight forward the provided information is sufficient. An adequate flow chart is included. Sterile filtration and filling of the syringes are performed under aseptic conditions. Sufficient information on control of critical steps is provided. Process validation has been performed on three batches.

Control of excipients
Sodium chloride, glacial acetic acid and water for injection comply with the corresponding monographs of Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form, and include tests for appearance, identification, extractable volume, related substances, triptorelin content, bacterial endotoxins, sterility test and subvisible particles. The set acceptance criteria are acceptable, and in line with provided data. Validations of the analytical methods have been presented. The stability indicating nature of the related substances method has been demonstrated. Batch analysis and process validation has been performed on three batches. The batch analysis results of the three validation batches show that the finished products meet the specifications. The control tests and specifications for drug product are adequately drawn up.

Stability of drug product
Stability data on the product have been provided for three full-scale batches in accordance with applicable European guidelines during storage at 5ºC ± 3°C (18 months), 25ºC/60%RH (6 months) and 40ºC/75%RH (6 months). On the basis of the presented stability data a shelf-life of 24 months was granted with the storage conditions ‘Store in a refrigerator (2°C – 8°C). Do not freeze’. Photostability testing showed no significant changes, and therefore the drug product can be considered to be photostable. Nevertheless the SPC includes ‘Store in the original package in order to protect from light’, as has been included in the SPC of the reference product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Decapeptyl, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to

generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of triptorelin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Triptorelin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Triptofem 0.1 mg/ml, solution for injection is a parenteral aqueous formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required in case of parenteral routes other than intravenous, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Triptofem 0.1 mg/ml, solution for injection is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Triptorelin was first approved in 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of triptorelin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC is similar to the SPC of Gonapeptyl (NL/H/1427/MR), the Core Safety Profile (CSP) (agreed March 2011, DE/H/PSUR/0038/001) and the agreed wording on GnRH agonists has been implemented, as well as the wording on depression.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The vast majority of the participants are women in child-bearing age (between 18 and 39). No weaknesses have been identified. This could be expected since the PL is similar to the PL of the innovator. Also the results show that the answers to all questions were (very) easily found and understood. Overall the test meets the criteria for a successful readability test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Triptofem 0.1 mg/ml, solution for injection in pre-filled syringe has a proven chemical-pharmaceutical quality and is a generic form of Decapeptyl 0.1 mg/ml, solution for injection. Decapeptyl is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Triptofem 0.1 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 November 2012. Triptofem 0.1 mg/ml, solution for injection in pre-filled syringe is authorised in the Netherlands on 30 January 2013.

The date for the first renewal will be: 28 November 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to re-evaluate the shelf-life limit for total impurities after the stability studies have been finalized.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached