CBG MEB

Public Assessment Report

Scientific discussion

Menopur 150 IE, powder and solvent for solution for injection

(highly purified menotrophin)

NL License RVG 118466

Date: 28 December 2017

This module reflects the scientific discussion for the approval of Menopur 150 IE, powder and solvent for solution for injection. The marketing authorisation was granted on 15 July 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ART	Assisted Reproductive Technologies
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
COH	Controlled Ovarian Hyperstimulation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
FSH	Follicle-stimulating Hormone
GIFT	Gamete Intra-fallopian Transfer
hCG	human Chorionic Gonadotropin
HP-hMG	Highly Purified - human Menopausal Gonadotrophin
ICH	International Conference of Harmonisation
ICSI	Intracytoplasmic Sperm Injection
IE	*Internationale Eenheid* (International Unit)
IU	International Unit
IVF/ET	In Vitro Fertilisation/Embryo Transfer
LH	Luteinising Hormone
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
PCOD	Polycystic Ovarian Disease
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
WHO	World Health Organization

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Menopur 150 IE, powder and solvent for solution for injection from Ferring B.V.

The product is approved for the following indications:

- Fertility disorders due to insufficient stimulation of the gonads:
  In women
  - Anovulation, including polycystic ovarian disease (PCOD), in women who have been unresponsive to treatment with clomiphene citrate.

  In men:
  - selected cases of impaired spermatogenesis.

- Controlled ovarian hyperstimulation (COH) to induce the development of multiple follicles for assisted reproductive technologies (ART), e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI).

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

Menopur is a urinary derived highly purified human menopausal gonadotrophin (HP-hMG) preparation. The product contains follicle-stimulating hormone (FSH) activity and luteinising hormone (LH) activity in a 1:1 ratio.

This national application concerns a line extension to Menopur 75 IE, powder and solvent for solution for injection (NL License RVG 24536), which has been registered in the Netherlands by Ferring B.V. since 13 July 1999. The only difference between the 150 IU product and the marketed 75 IU product is the amount of drug substance. The indications and dosing schedule for the 75 IE and 150 IE formulations are similar.
The rationale of the development of the new formulation is to provide a product that is more convenient to use when doses higher than 225 IU are administered. Up to three vials of Menopur 150 IU can be dissolved in 1 mL solvent. With the Menopur 150 IU formulation the maximum daily dose (i.e. 450 IU) can be administered with one injection, instead of two injections (2 x 225 IU) with Menopur 75 IU, thereby reducing the stress and discomfort of injection for the patient. The new formulation is particularly of interest in the indication 'Controlled ovarian hyperstimulation', where the maximum daily dose is 450 IU.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

No new non-clinical or clinical studies were submitted with this application, which is acceptable given that the product is a line extension of an approved product license containing a well-known active substance. To support that the difference in concentration between the 150 IU formulation applied for and the marketed 75 IU formulation does not have any impact on the overall absorption rate, the company referred to a bioequivalence study with Menopur 75 IU and 1200 IU which has been assessed (see section IV.2 of this report).

II. QUALITY ASPECTS

II.1 Introduction

Menopur 150 IE is a white to off-white freeze-dried powder. The solvent is clear and colourless.
Each vial contains highly purified menotrophin (human Menopausal Gonadotrophin (hMG)), corresponding to 150 IU FSH and 150 IU LH. After reconstitution each ml solution contains 150 IU FSH and 150 IU LH.

The powder is packed in a colourless, type I glass vial with a halobutyl rubber stopper fitted with an aluminium flip-off seal.
The solvent is packed in a colourless, type I glass vial with a chlorobutyl rubber stopper fitted with an aluminium flip-off seal. The filling volume is 2 mL.

The excipients are:
Powder for solution for injection: lactose, polysorbate 20, sodium hydroxide and hydrochloric acid for pH adjustment
Solvent: isotonic sodium chloride solution, diluted hydrochloric acid for pH adjustment

II.2 Drug Substance

The active substance is menotrophin, an established active substance described in the British Pharmacopoeia (BP). It is an almost white or slightly yellow powder containing not less than 2000 IU of FSH and LH bioactivity per mg substance. It is soluble in water.
The quality dossier on the drug substance is largely in line with that approved for the 75 IU presentation, as the same substance is used. Cross-reference is made to the previously assessed dossier.

The active substance is purified from the urine of postmenopausal women, which is obtained from Argentina. The MAH has identified the steps contributing to viruses and prion removal. The theoretical overall reduction factor is considered sufficient. The validation demonstrates that the manufacturing process of the drug substance provides assurance of the safety of the overall manufacturing process in relation to potential virus as well as prion contamination.

II.3 Medicinal Product

Pharmaceutical development
The development of Menopur powder for solution for injection, 150 IU, is based on the experience gained from the development and manufacturing of the MAH's registered product Menopur 75 IU. The only difference between the two formulations is the amount of drug substance. The amounts of excipients are the same and the same solvent is used for both strengths.
Terminal sterilisation in the final container using steam or dry heat is not appropriate for the powder for solution for injection, since the drug substance menotrophin is sensitive to heat. The choice of sterile filtration is justified.
To ensure the extractable volume a 10% overfill is applied to Menopur 150 IU instead of an overage as for Menopur 75 IU. The shift from overage to overfill does not affect the amount of active ingredients. It has been concluded that although there are some small differences in the amounts of the other components, it is considered very unlikely that this will affect the activity of FSH and LH.
In comparison with Menopur 75 IU the ratio between the active substance menotrophin HP and polysorbate is different in the reconstituted solution of Menopur 150 IU. In addition the pH is likely to show a minor shift. Both parameters could affect the solubility. However, it is demonstrated that results of the dissolution test remain well within specification. The filling volume of 2 mL solvent remains the same. This is sufficient to withdraw the 1 mL needed for reconstitution of Menopur 150 IU. The needles and syringes provided in the package are CE marked.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines, and includes the following steps: preparation of the solution, sterile filtration, filling, freeze drying, stoppering and capping, visual inspection. Documented evidence is provided that the manufacturing process consistently produces the product, meeting its predefined specifications and quality characteristics

Control of excipients
The excipients comply with Ph.Eur. quality standards. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, purity, sterility, bacterial

endotoxins, and for the following parameters of the reconstituted solution of 1 vial in 1 ml solvent: dissolution time, clarity of solution, coloration of solution, pH of solution and particulate matter.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data on three batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Menopur powder: A stability study in accordance with the relevant ICH guidelines was conducted to investigate the stability of Menopur 150 IU powder for solution for injection. The first three full scale batches have been put on long term and accelerated stability. The available data cover 24 months storage for one batch and 18 months storage for two batches at long term conditions (25 ± 2°C/60 ± 5 % RH) and 6 months at accelerated conditions (40 ± 2°C/75 ± 5 % RH). All parameters tested are well within the shelf-life limits. The following shelf-life and storage conditions have been approved for the drug product: 24 months when not stored above 25°C.

Solvent: A stability study in accordance to the relevant ICH guideline was conducted to investigate the stability of 0.9 % sodium chloride solvent. Three constituted full scale processes validation batches have been placed on a long term and accelerated stability study. An update of the stability data is provided. The available data cover 18 months storage for the three batches at long term conditions (5± 3°C and 25 ± 2°C/60 ± 5% RH) and 6 months at accelerated conditions (40 ± 2°C/75 ± 5 % RH). All test results are well within the shelf-life limits. Shelf-life and storage conditions for the solvent: 36 months when stored at not more than 25°C.

The procedure for reconstitution, dose withdrawal and storage is provided. Reconstitution was performed according to the package leaflet. One batch of Menopur 150 IU was reconstituted to both 150 IU/ml and 450 IU/ml. Dissolution time was measured for each reconstitution. The reconstituted solution was stored at room temperature for 5 hours in the vial and administration syringe. The vials were stored up side down. The reconstituted solutions comply with the specifications.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Menopur does not contain or use in the manufacturing process materials covered by the scope of the TSE guideline. Lactose monohydrate is produced from bovine milk.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Menopur 150 IU has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH has committed to perform an evaluation of the release and shelf life specification of Menopur 150 IU after the data of 15 batches are available.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacodynamics and toxicology

The pharmacological, pharmacokinetic and toxicological properties of menotrophin are well-known. This product is a line extension of an approved product license. The MEB agreed that no further non-clinical studies are required, as cross-reference to the Menopur 75 IU dossier is justified.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Proteins are exempted in the EMEA/CHMP/SWP/4447/00 guideline along with e.g. aminoacids and peptides because they are unlikely to result in significant risk to the environment. Nevertheless, the guideline has been applied to Menopur 150 IU.

Since Menopur 150 IU is a line extension which is expected to substitute an available product, this will not lead to an increased exposure to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Menotrophin is a well-known active substance with established efficacy and tolerability.

FSH in combination with LH (hMG) is available on the European market, in purified forms derived from human menopausal urine (e.g. Menopur) or as recombinant peptide produced by cultured cells. These different formulations are equally effective in achieving pregnancy[1,2]. The currently approved recombinant FSH formulations by a centralised procedure are Gonal-F (EU/1/95/001/001-035, MAH: Serono Europe Ltd.) and Puregon (EU/1/96/008/001-041, MAH: Merck Sharp & Dohme Ltd.).

IV.2 Pharmacokinetics

To support that the difference in concentration between the 150 IU formulation applied for and the marketed 75 IU formulation does not have any impact on the overall absorption rate, the company referred to a bioequivalence study with Menopur 75 IU and 1200 IU which has been assessed in 2009 in the line extension application for Menopur 600 and 1200 IE powder and solvent for solution for injection.

Bioequivalence study - Menopur 75 IU vs 1200 IU
In this study a former Menopur multidose formulation of 1200 IU (600 IU/mL) was compared to the registered Menopur 75 IU single dose formulation. A subcutaneous injection of 450 IU (0.75 mL) of the 1200 IU formulation was compared to 450 IU of the 75 IU formulation; the latter was administered as two 1 mL subcutaneous injections of 225 IU each (3 vials reconstituted in 1 ml of solvent). The two formulations were demonstrated to be bioequivalent.

The formulation tested in the bioequivalence study was not identical to the final Menopur 600 IU and 1200 IU formulations: the solvent for reconstitution in the final formulation does not contain sodium chloride. This reduces the osmolarity of the formulation, but the activities of FSH and LH per volume are the same.

The composition of Menopur 150 IU is very comparable to the currently marketed Menopur 75 IU, only the pH adjustment has been done with different buffers and the achieved concentration of the active ingredient can be higher. As the differences between the formulations are considered smaller than the differences between the formulations tested in the bioequivalence study, the new formulation is expected to be bioequivalent as well.

Further, the MAH argues that the rate limiting step in the vascular absorption of FSH is the lymphatic flow rate and transportation of FSH, and not concentration driven diffusion from the site of injection to the lymph capillaries. Consequently, it is highly unlikely that the very small difference in concentration in the current 150 IU formulation compared to the marketed 75 IU formulation will have any impact on the overall absorption rate into the vascular system and the expected bioequivalence of the two formulations.

IV.3 Pharmacodynamics

No pharmacodynamic studies were submitted for the new strength. Reference is made to the Clinical Expert Report and Clinical Overview for Menopur 75 IU. The impact of Menopur treatment on the established pharmacodynamic markers of gonadotrophin treatment, i.e. follicle size and estradiol levels, has been described for downregulated women undergoing controlled ovarian hyperstimulation

[1] Nugent D, Vandekerckhove P, Hughes E, et al. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2000;(4):CD000410.
[2] Bayram N, van Wely M, van Der Veen F. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2001;(2):CD002121.

(COH) for IVF/ICSI and for follicle induction in anovulatory women who are unresponsive to clomiphene citrate.

IV.4 Clinical efficacy

No new efficacy data have been submitted. The lack of efficacy studies is acceptable for this line extension. The efficacy of Menopur for treatment of women with WHO group II anovulatory infertility who previously had failed to ovulate or conceive on clomiphene citrate, and the efficacy of Menopur for multiple ovarian follicular development in patients undergoing ART was described in the Clinical Overview.

IV.5 Clinical safety

Literature
The literature describing the risks associated with Menopur and other preparations in this pharmacological class was reviewed in the previously assessed Clinical Expert Report and Clinical Overview.

Post-marketing experience
Menopur was first approved in Denmark on 18 November 1999. As of 31 December 2014 Menopur was approved in 121 countries worldwide, and a large number of patients has been exposed.

A safety database is maintained at the Pharmacovigilance department at Ferring Pharmaceuticals A/S comprising all adverse events cases reported spontaneously by healthcare professionals, consumers, regulatory authorities, from the scientific literature and serious adverse events occurring in clinical trials (development trials, local phase IV trials, investigator-initiated trials). The cases from the clinical trials included in the development of Menopur have been discussed in the previously assessed Clinical Expert Report and Clinical Overview.

The MAH has provided a report of adverse events that were not reported in clinical trials. The line listing contains all adverse events reported between 1 January 1990 and 29 February 2016. A total of 2723 adverse events were reported on Ferring menotrophins. Of these, 661 were serious and 2062 were non-serious. All adverse events were assessed as related to Menopur. There were 323 spontaneous reports of the drug being ineffective.

Most cases were reported for the following adverse events:
hypersensitivity (30), headache (43), dizziness (24), dyspnoea (26), abdominal distension (31), abdominal pain (29), nausea (54), ascites (27), skin reaction (62), rash (36), arthralgia (30), pain in extremity (24), ovarian hyperstimulation syndrome (214), injection site erythema (36), injection site inflammation (44), injection site pain (80), injection site reaction (180), injection site swelling (29), pyrexia (84), malaise (30), influenza like illness (57), drug effect decreased (34), drug ineffective (323), therapeutic response decreased (22), product preparation error (35), prescribed overdose (104).

The MEB agrees that no safety concerns have been identified and that the benefit-risk profile for their menotrophins remains favourable. The cumulative experience is in line with the information stated in the Company Core Data Sheet.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Menopur 150 IU.

- Summary table of safety concerns as approved in RMP

Important identified risks	Ovarian hyperstimulation syndrome (OHSS) Anaphylactic reaction
Important potential risks	Thromboembolic events Multiple pregnancy Pregnancy wastage

	Ectopic pregnancy Reproductive system neoplasm Congenital malformation Menopur 600 IU/1200 IU formulations (not registered in the Netherlands Overdosage due to inadvertent medication error during self-administration of Menopur 600 IU and 1200 IU formulations.
Missing information	Experience in patients with hepatic or renal impairment, and metabolic diseases (e.g. insulin dependent diabetes mellitus).

This summary of safety concerns was laid down in an updated RMP, which was approved in July 2017. The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The MAH referred to a previously assessed bioequivalence study comparing the Menopur 75 IU formulation to Menopur 1200 IU. Bioequivalence was demonstrated. The composition of Menopur 150 IU is very comparable to the currently marketed Menopur 75 IU. As the differences between these two formulations are considered smaller than the differences between the formulations tested in the bioequivalence study, the new formulation is expected to be bioequivalent as well.
The MEB concluded that, from a pharmacokinetic point of view, the small differences between the formulations are considered not to influence the bioavailability. The MEB agrees that the difference in concentration in the 150 IU formulation compared to the marketed 75 IU formulation is not expected to have any impact on the exposure to FSH/LH.

No new pharmacodynamic, efficacy or safety studies were performed. This is acceptable, as the only difference compared to the marketed Menopur 75 IU product is the amount of drug substance.
The MAH submitted its Clinical Expert Reports and Clinical Overviews regarding pharmacodynamics, efficacy and safety of Menopur. An updated overview of all adverse drug reactions reported post-marketing was provided. The adverse events ‘pyrexia’ and ‘dizziness’ have been added to the SmPC. Risk management is adequately addressed in the RMP.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH has submitted a bridging report making reference to the successfully user tested PL for Bravelle 75 IU powder and solvent for solution for injection. Bravelle is another gonadotrophin product by Ferring and is very similar to Menopur. The PL for Bravelle was assessed and approved in MRP variation procedure UK/H/0697/001/II/006. The two products belong to the same class of medicinal product, have the same route of administration, the same indications and the same safety profile.
The font, font size and style of writing of the Menopur and Bravelle leaflets are the same. The layout is very similar. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Menopur 150 IE, powder and solvent for solution for injection has a proven chemical-pharmaceutical quality and is an approvable line extension to Menopur 75 IE, powder and solvent for solution for injection. Menopur is a well-known medicinal product with an established favourable efficacy and safety profile.

Cross-reference to the Menopur 75 IU dossier is justified, as the only difference between Menopur 75 IU and 150 IU is the amount of drug substance. It is not expected that the difference in concentration would have any consequences on the bioavailability. Sufficient safety and efficacy data on Menopur are available, including post-marketing data.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that a favourable benefit/risk profile has been shown, and has therefore granted a marketing authorisation. Menopur 150 IE, powder and solvent for solution for injection was authorised in the Netherlands on 15 July 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse
Change in the name and/or address of a manufacturer or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient.	IB	N	19-9-2016	Approval	--
Addition of a secondary packaging site.	IA	N	3-1-2017	Approval	--
Update of the Risk Management Plan.	Post-approval commitment	N	19-7-2017	Approval	--