CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gonapeptyl 0.1 mg/1 ml, solution for injection Ferring B.V., the Netherlands

triptorelin 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/1427/001/MR
Registration number in the Netherlands: RVG 33462

2 February 2010

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 first authorisation in NL:	14 February 2008
Concerned Member States:	Mutual recognition procedure with BE, EL, ES, FR, HU, IT, LU, MT, PL, PT, RO, SI
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

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 Gonapeptyl 0.1 mg/1 ml, solution for injection, from Ferring B.V. The date of authorisation was on 14 February 2008 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 Gonapeptyl 0.1 mg/1 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 analogue 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 production. After discontinuation of Gonapeptyl, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.
The Gonapeptyl-induced downregulation of the pituitary can prevent the LH surge and thereby premature ovulation and/or follicular luteinization. The use of the downregulation with GnRH agonist reduces the cycle cancellation rate and improves the pregnancy rate in ART cycles.

This mutual recognition procedure concerns a full application with a known active substance. Gonapeptyl 0.1 mg/1 ml is identical to Decapeptyl 0.1 mg/1 ml. A marketing authorization for Decapeptyl 0.1 mg/1 ml was granted in the Netherlands on 26 September 1989 (NL RVG 11778), for the indication of prostate cancer, followed in December 2000 by the indication of “In vitro fertilisation (IVF)”. With this dossier the MAH applies exclusively for the indication “downregulation and prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation for assisted reproductive technologies (ART)” and has changed the name of Decapeptyl into Gonapeptyl.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

The MAH has submitted a complete dossier for this application. The results of the performed pharmacokinetic and pharmacodynamic studies are submitted. Seven clinical studies to support the efficacy of Gonapeptyl 0.1 mg SC daily administration are performed and the results submitted (see also Tables 1 and 2). In the MRP dossier three clinical studies have been added not earlier submitted as part of the dossier for Decapeptyl 0.1 mg/1 ml (NL RVG 11778). One study conducted for the development program of Gonapeptyl 0.1 mg/1 ml for the indication of IVF (study 3) and two studies conducted for the development of MENOPUR (study 6) and (study 7). An updated chemical-pharmaceutical dossier is submitted as the basis for the MRP, including the results of the conducted photostability studies.

No scientific advice has been given to the MAH with respect to this product.

No paediatric development programme has been submitted.

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

General information
The active substance is triptorelin acetate. The chemical name is L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolyl-glycine amide, acetate salt.
The active substance, a decapeptide, 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/EMEA 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.

Manufacture
The manufacture requires 17 synthesis steps. Adequate in-process controls based on TLC and HPLC methods are applied for monitoring the progress and completion of the reactions and/or the purity of the resulting products. For the drug substance protection from light measures are applied.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 10 batches.

Stability
Stability data on the active substance have been provided for 3 full scale batches stored at 2-8ºC, < -15ºC, 25º/60%RH and 40ºC/75%RH. The drug substance is stable at the two lower temperatures. The drug substance is not stable at higher temperatures (25°C/60% RH and 40°C/75% RH) and showed hygroscopic properties. The water content increased significantly on storage at 2-8°C to ca. 8% but was nearly constant at < -15°C for 60 months. Based on the provided normal testing data, the proposed retest period of 3 years if stored below -15°C or at 2-8°C (refrigerator) in the proposed packaging (providing protection from light) for both storage conditions is acceptable.

Medicinal Product

Composition
Each syringe of Gonapeptyl 0.1 mg/1 ml contains as active substance 100 micrograms triptorelin acetate equivalent to 95.6 micrograms triptorelin free base in 1 ml of aqueous solution. It is a clear, colourless solution.

The solution for injection is packed in single use pre-filled disposable borosilicate type 1 glass syringes with integrated needle and rigid needle shield. The plunger stopper is made of chlorobutyl rubber and the plunger rod of polystyrene. The prefilled syringes are packed in polyethylene blisters covered by paper,

which are subsequently paced into paper cartons. The secondary packaging is sufficient to protect the drug product against the influence of light.

The excipients are: sodium chloride, glacial acetic acid, water for injections. The excipients are usual for this type of dosage form. The excipients comply with the Ph. Eur.

Pharmaceutical development
The proposed formulation is identical to the Decapeptyl 0.1 mg/1 ml formulation registered in the Netherlands, RVG 11778, for the indication prostate cancer since 1989.

Manufacturing process
The manufacturing process consists of standard methods for solutions for injection. Sterile filtration is necessary as sterilization method due to the heat sensitive nature of the peptide drug substance. Process validation has been performed with four validation batches in accordance with the relevant European guidelines. Triptorelin acetate is freely soluble in aqueous solution with low pH. The stability studies show that the drug substance is compatible with the proposed excipients. The chosen pH of 4-5 is favourable for the stability of the drug substance. The solution is made isotonic by the addition of the sodium chloride. The syringe is sterilised with ethylene oxide in accordance with Ph. Eur. requirements. The plunger stopper is sterilised using a validated gamma-irradiation procedure in accordance with current Ph. Eur. requirements. Sterile filtration and filling of the syringes are performed under aseptic conditions. It is specifically stated in the description of the manufacturing process that the product is protected from light during manufacture.

Quality control of drug product
The product specification includes tests for appearance, identification of the active and sodium, pH, extractable volume, particulate matter, assay, related substances, sterility and bacterial endotoxins. The release and shelf life specifications are considered to be sufficient. The analytical methods have been adequately described and validated. Batch analytical data from 3 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product has been provided for three full scale batches stored during 48 months at 2-8ºC, 25º/60%RH and 40ºC/75%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the pre-filled 1 ml glass syringes.
The stability results show that the finished product amply meets the set requirements during the claimed shelf life period of 3 years at 2-8°C. At 25°C/60% RH after 6 months out-of-specification results arise, at 40°C/75% RH already after 2 months. At 2-8°C total impurities levels increased from 0.4-0.7% to 1.4-1.8% after 48 months. All 36 months results including particulate matter, extractable volume and sterility were in accordance with the specification. One assay result after 48 months of one batch was slightly below its specification. A photostability study has been conducted showing that the product is sensitive to light and also that the product is protected from light by the secondary packaging, i.e. polyethylene blisters covered by paper in cartons.
Based on the stability data a shelf life was granted of 3 years. The labelled storage conditions are *"Store in a refrigerator (2℃ – 8℃). Do not freeze. Store in the original package, to protect from light."*

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 contains triptorelin, which is a synthetic decapeptide and an analog of the natural hypothalamus hormone GnRH. Triptorelin is an active ingredient with well known pharmacological and toxicological characteristics in animal species and in humans. It has a well established medical use with acceptable efficacy and safety. The preclinical pharmacodynamic, pharmacokinetic, and toxicological data revealed the hormonal effects of triptorelin as its pharmacological activity.

The preclinical data have already been submitted for Decapeptyl (approved in the Netherlands in September 1989) and are considered adequate. Gonapeptyl is a copy of the dossier of Decapeptyl. No new preclinical data were submitted.
In the non-clinical overview, the pharmacological, toxicological and pharmacokinetic properties of triptorelin have been adequately described. This overview gives a good review of the data published in the open literature.

Environmental risk assessment
The active ingredient of Gonapeptyl, triptorelin, is not expected to have any ecotoxicological effects. Besides triptorelin, the Gonapeptyl formulation contains sodium chloride and glacial acetic acid. These are standard compounds and are not considered to cause environmental problems. It is concluded that the product is unlikely to present a risk for the environment following the prescribed usage in patients.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The MAH stated that according to the trial reports, all trials conducted in the clinical development programme (1992-2002) complied with the existing Declaration of Helsinki at the time of conduct. Some deficiencies have been detected in some of these studies, related to the design and conduct of the studies in comparison to current standards. However, these deficiencies do not interfere with a reliable assessment of the studies.

Table 1: Summary of the studies done for the development program of DECAPEPTYL.

No	Study ID	Design	Treatments	No. of subjects	Primary Endpoint
1	DECA 93/12/NL Dose-response (ART)	Randomised, double-blind Stimulation with 225 IU hMG	DECAPEPTYL 0.05 mg, 0.1 mg, 0.2 mg SC	18 (6 subjects / dose group)	Hormonal response (LH, FSH, E2 and progesterone) including suppression of premature LH surges
2	DECA 93/11/NL Dose-finding (ART)	Randomised, double-blind Stimulation with 225 IU FSH	DECAPEPTYL 0.015 mg, 0.05 mg, 0.1 mg SC, placebo	240 (60 subjects / dose group)	Rate of occurrence of premature LH surges
3	DECA 98/01/NL Dose-duration (ART)	Randomised, double-blind, early cessation, mid-cessation and no cessation (standard long) protocol Stimulation with hMG (dose at the discretion of the investigator)	DECAPEPTYL 0.1 mg SC	196 subjects started DECAPEPTYL 0.1 mg; 178 were randomised to the three regimens of different GnRH agonist duration	Rate of occurrence of premature LH surges
4	DECA 95/1.1/NL Efficacy (ART)	Open, uncontrolled Stimulation with 225 IU FSH	DECAPEPTYL 0.1 mg SC	50	Hormonal response (LH)
5	DECA 95/02/NL Efficacy (ART)	Open, uncontrolled Stimulation with 225 IU hMG	DECAPEPTYL 0.1 mg SC	141	Hormonal response (LH)

Table 2: Summary of the studies done for the development program of MENOPUR.

No	Study ID	Design	Concomitant medication	No. of subjects	Population
6	MFK/IVF/0399 E Efficacy (ART)	Randomised (HP-hMG vs. rFSH), open Stimulation with HP-hMG or rFSH (225 IU for the first 5 days, then individual adjustment)	DECAPEPTYL 0.1 mg SC DECAPEPTYL Depot 3.75 mg (single injection) Other GnRH agonists	GnRH agonist. 781, COH: 727 DECAPEPTYL 0.1 mg SC: 117 started down-regulation, 113 started downregulation with DECAPEPTYL 0.1 mg and underwent COH	Ongoing pregnancy rate
7	FE999906 CS003 Efficacy (ART)	Randomised (HP-hMG vs. rFSH), open, assessor-blind Stimulation with HP-hMG or rFSH (225 IU for the first 5 days, then individual adjustment)	DECAPEPTYL 0.1 mg SC	DECAPEPTYL 0.1 mg SC: 781 Randomised to HP-hMG or FSH for COH: 731	Ongoing pregnancy rate

Pharmacokinetics

The systemic bioavailability of triptorelin after subcutaneous administration is estimated close to 100% compared to intravenous administration. Protein binding has not been investigated. Human metabolism after administration of triptorelin was not studied. After intravenous administration the mean half-life for terminal elimination was 5.1 hours (range: 2.5-13.81 hours). Triptorelin is predominantly excreted in urine. Renal clearance over 24 hours was on average 25.3 mL/min. The mean percentage of the dose recovered in urine over the 24 hours was 17%. The pharmacokinetics of triptorelin seem dose-proportional. There are no formal drug-drug interaction studies with triptorelin 0.1 mg. No major differences in concentrations of triptorelin prior to or during concomitant gonadotrophin administration were observed. The pharmacokinetics of triptorelin has been evaluated in male subjects with varying degrees of renal dysfunction and in male subjects with hepatic insufficiency, after administration of 0.5 mg triptorelin IV. According to the MAH the study showed that the elimination half-lives were similarly prolonged in subjects with mild to moderate renal insufficiency (6.6 hours), severe renal insufficiency (7.7 hours) and hepatic insufficiency (7.6 hours) compared to healthy subjects (2.8 hours). Total clearance decreased with increasing renal dysfunction. The risk of accumulation of triptorelin in patients with severe liver and renal impairment is small; the impact of these profiles on LH levels and the magnitude of downregulation have not been evaluated. Additionally, due to the short half-life on the day of embryo transfer 2-3 days after oocyte retrieval there will be no triptorelin, or very low levels, in circulation. In general, pharmacokinetic properties are sufficiently evaluated.

Pharmacodynamics

Healthy female volunteers

In pharmacodynamic study DECA 92/11/NL in healthy female volunteers in which the effect of once daily doses of 0.025 mg, 0.05 mg, 0.1 mg, and 0.2 mg of Gonapeptyl (subcutaneously administrated) on the degree of pituitary desensitization has been studied, demonstrated adequate pituitary suppression after 17 days of treatment. Suppression of LH, but not of FSH appeared to be dose-dependent, with no difference in degree of suppression between the 0.05 mg and 0.1 mg dose. After cessation of Gonapeptyl therapy both LH and FSH values initially decreased further to values below treatment values. Six days after cessation of Gonapeptyl treatment, LH-levels were still comparable with those at the end of the treatment, but FSH levels were increasing. No data beyond six days after cessation of treatment are available.

Healthy women undergoing IVF/ICSI

Additionally, LH-measurements showed adequate pituitary suppression in women undergoing IVF/ICSI during down-regulation and/or ovarian stimulation with either Menotrophin (FSH+LH preparation) or an

FSH preparation.
Overall, the results suggest that even a dose as low as Gonapeptyl 0.015 mg is able to substantially blunt pituitary response to endogenous GnRH when there is no concomitant administration of gonadotrophins.

Clinical efficacy

Dose selection

GnRH agonists have initially been introduced in the field of reproductive medicine on an 'off label use' basis without preceding proper dose finding studies. The doses used in IVF were derived from treatment schedules used in disseminated prostate cancer, which aim at complete gonadal suppression under all circumstances. This raises the question whether these schemes would not lead to LH levels that were too low for the maintenance of proper follicle growth in some patients. During the period of follicle stimulation with hMG (FSH + LH) this aspect might stay unnoticed as there will always be a sufficient exogenous administration to sustain follicle growth, but this may change for some patients since the wide scale use of recombinant FSH devoid of any LH activity (Jansen and Tucker, 2003). It was shown in 2 clinical studies that a daily dose of 0.05 mg triptorelin creates a state of pituitary desensitization comparable with the 'standard' dose of 0.1 mg (Janssens et al., 1998) and that daily doses of 0.05 mg are capable of preventing an LH surge, but with a lower grade of pituitary desensitization, as shown by the higher LH secretion in the stimulatory phase (Janssens et al., 2000). In terms of implantation rate, pregnancy rate and baby take-home rate, the results of the higher dose groups appeared to be better, although the differences were not significant. Therefore, on the basis of these observations the investigators concluded that using the 0.05 mg dose is possible, without negatively affecting the success rate. Although the 0.05 mg dose was shown to be effective, there are no comparative data with 0.05 mg in large clinical trials. Only 66 women undergoing IVF/ICSI in clinical trials have been exposed to 0.05 mg, of whom nine women obtained an ongoing pregnancy and live birth.

Data from large clinical trials (MFK/IVF/0399E, FE999906 CS003) with almost 900 patients indicate that 95% of the patients initiating treatment achieve adequate downregulation with the dose of 0.1 mg. The 0.1 mg dose has been administered to 1,351 women undergoing IVF/ICSI in clinical trials, of whom 283 had an ongoing pregnancy. A clinically relevant difference in treatment outcome (e.g. 5% of ongoing pregnancy rates) between Gonapeptyl 0.1 mg and 0.05 mg is difficult to document statistically, as it would require at least 2,000 patients.

Furthermore, the available safety and efficacy data do not suggest that the 0.1 mg dose is associated with a poorer benefit/risk profile compared to the 0.05 mg dose, although the total exposure will be higher for the relatively short treatment period.

In addition, it should be noted that the triptorelin acetate 0.1 mg dose is currently marketed and in clinical use for the intended indication in the concerned member states proposed for an MRP subsequent to this national procedure.

Clinical endpoints

The main new submitted study, which was solely conducted for the clinical development program of Gonapeptyl (study 3), addresses the question of the most adequate duration of Gonapeptyl use (early/mid/no cessation).

Only 1 (1.8%) patient in the mid-cessation protocol group experienced an LH surge during the stimulation phase, leading to an upper limit of the one-sided 95% confidence interval of 8.1%. None of the patients in the 'early cessation' and 'no cessation' groups had an LH surge, and the corresponding upper limits of the one-sided 95% confidence intervals were 5.8% and 5.5%, respectively. According to the MAH, this outcome is a consequence of a lower actual sample size than planned (the planned sample size was chosen such that, if the actually observed number of unwanted LH surges in a group turned out to be zero, it could be concluded that the true incidence is smaller than 5%). By combining the mid-cessation group with the early cessation group, the upper limit of the one-sided 95% CI is below the 5% cut-off (0.9% point estimate with upper limit 4.4% 95%CI).

In 2 studies, the adequacy of down-regulation with Gonapeptyl 0.1 mg by means of LH-measurements was established in women undergoing IVF/ICSI programs that were primarily performed in the indication of IVF/ICSI (studies 4 and 5).

Supporting evidence of adequate pituitary suppression is provided by two IVF/ICSI studies (studies 6 & 7), for results see table 3. Inclusion of the data in this submission is considered acceptable as in both studies Gonapeptyl 0.1 mg was used for down-regulation. These were the most recently conducted studies (1999-2000 and 2004, respectively). The large number of patients recruited and using Gonapeptyl 0.1 mg add credibility to the results (117 and 781 respectively).

Table 3: Efficacy summary in studies 4, 5, 6, and 7

	Study 4 (n =50)	Study 5 (n =141)	Study 6 (n =117)	Study 7 (n =781)
Serum LH (IU/L)				
Down-regulation	2.5 ± 1.4	1.3 ± 0.6	-	2.28 ± 1.35
Stimulation day 6	-	-	2.1 ± 1.2	1.44 ± 0.81
Stimulation day 7	1.6 ± 0.8	1.1 ± 0.3	-	-
Day of hCG	1.3 ± 0.6	1.2 ± 0.4	1.4 ± 0.8	1.71 ± 0.90
Serum P4 (nmol/L)				
Day of hCG	8.3 ± 24.8	2.8 ± 1.2	-	3.1 ± 2.8
Serum E2 (pmol/L)				
Day of hCG	7567 ± 4218	6135 ± 3960	6510 ± 4571	6900 ± 4200
Total number of follicles	14	19	12.0 ± 4.7	15.3 ± 7.3
Treatment efficiency				
Total gonadotrophin dose (IU)	-	-	2543 ± 713	2446 ± 679
Duration of gonatrophins (d)	-	-	11.0 ± 2.1	10.3 ± 1.8
Total duration of DECA + gona (d)	26	20.4	23.4	25.1
Patients with oocyte retrieval	37	120	108	691
Number of oocytes retrieved	9.3	11.7±7.9	12.7 ± 7.9	10.9 ± 5.6
Fertilisation rate (%)	81.4 ± 31.9	54.2	53.9 ± 29.3	52.1 ± 28.7
Patients with embryo transfer	32	118	97	601
Embryos transferred	1.6	1.81 ± 0.9	2.1 ± 0.6	1.7 ± 0.5
Positive βhCG rate	8 (16%)	26 (19%)	37 (33%)	251 (34%)
Clinical pregnancy rate	-	-	30 (27%)	187 (26%)
Ongoing pregnancy rate	8 (16%)	22 (16%)	27 (24%)	179 (24%)
Live birth rate	8 (16%)	21 (16%)	26 (23%)	-

A general remark can be made on the choice of the primary endpoint, which in study 1-5 has not been adapted to current standards. In the original submission for this indication in 2000, the choice of LH measurement during the treatment was accepted as in line with the current knowledge of that time. However, in 2006 the current public literature recommends that down-regulation is to be verified by serum estradiol measurement of less than 30 pg/mL. The estradiol levels were commented upon in the submitted studies but none was powered to address that issue.
In the other two studies (studies 6 & 7) most recently conducted (1999-2000 and 2004, respectively), the primary endpoint chosen was the ongoing pregnancy rate (defined as at least one viable foetus at 10-11 weeks after embryo transfer) after one cycle.

Comparative data
There were no comparative studies versus other GnRH agonists in the development programme for Gonapeptyl. This was justified by the MAH with the argumentations that at the time the other agents were not widely registered for the proposed indication, and the efficacy of the currently used doses of other GnRH agonists for prevention of premature LH surge has not been adequately established in placebo-controlled trials. However, some comparative data can be interpreted from study 6, in which the ongoing pregnancy rate using Gonapeptyl 0.1 mg was 24% (27/113) compared to 22% (133/614) using all other GnRH agonists (buserelin, leuprolin, goserelin, nafarelin and triptorelin 3.75 mg depot).
In public literature, Gonapeptyl 0.1 mg was compared to ganirelix 0.25 mg (GnRH antagonist) in a randomised multicenter study performed in 236 patients by The European and Middle East Orgalutran Study Group. The two treatment regimens produced similar pregnancy rates; 31.0% with ganirelix 0.25 mg and 33.9% with Gonapeptyl 0.1 mg.

In conclusion, the efficacy data presented from the submitted clinical studies are open to several points of criticism e.g. minimum effective dose. However, it is acknowledged that there is very wide clinical experience with Gonapeptyl in the acclaimed dose of 0.1 mg SC. In addition, in comparison to other GnRH or antagonists, Gonapeptyl 0.1 mg has shown to be as effective, in valid clinical endpoints as ongoing pregnancy rates. Accordingly, its efficacy in the indication of IVF is considered sufficient to grant

the application.

Clinical Safety

Adverse drug reactions

Although the causality of adverse events was not always assessable due to concomitant administration of gonadotrophins, the pattern of adverse drug reactions (ADRs) observed during treatment with Gonapeptyl 0.1 mg is considered typical for a GnRH agonist and acceptable within the context of ART procedures.
There was no indication of dose-response on adverse events, serious adverse events or discontinuation due to adverse events in the dose-ranging or dose-finding studies.
Although no evaluation of the adverse event time profile was performed, study 3 showed no apparent differences in the incidence of adverse events for the different durations of treatment.
A higher frequency of adverse events was noted in the two Menopur studies, possibly explained by the fact that they were conducted more recently than the studies in the Decapeptyl development program.

Table 4: Most frequently reported adverse events in studies 6 and 7, during down regulation and after start of stimulation with Menotrophin/FSH.

Study 6		Study 7	
Prior* 57%	After** 61%	Prior* 12 %	After** 50 %
Headache (27%)	Headache (27%)	Headache (4%)	Headache (5%)
Injection site inflammation (12%)	Injection site inflammation (10%)		Spontaneous abortion (7%)
Abdominal pain (9%)	Abdominal pain (15%)		Pelvic pain (6%)
Dysmenorrhea (6%)		Dysmenorrhea (3%)	Vaginal haemorrhage (24%)
Nausea (5%)	Nausea (10%)		Nausea (3%)
Injection site pain (4%)	Injection site pain (7%)		OHSS (3%)
Dizziness (4%)	Dizziness (5%)		Post-procedural pain (4%)
Upper respiratory tract infection (4%)	Upper respiratory tract infection (4%)		
Flushing/hot flushes (4%/2%)			
Fatigue (3%)	Fatigue (4%)		
Vomiting 3%			
	Injection site bruising (3%)		

* Prior to stimulation with menotrophin (FSH+LH)/FSH only
** After stimulation with menotrophin (FSH+LH)/FSH only

OHSS (ovarian hyperstimulation syndrome)
The overall incidence of OHSS in clinical trials with Gonapeptyl 0.1 mg ranged from 0% to 3.1%, which is better than that reported with other GnRH agonists in the same studies.

Postmarketing experience
The reporting rate for the post marketing data of 14 cases of adverse events per 50,000 patient years for the Gonapeptyl 0.1 mg and 0.5 mg formulations is too low to draw any reliable conclusion.
In conclusion, the data shown do not include any signs that the safety profile of Gonapeptyl is different from other GnRH agonists in the indication requested.

Pharmacovigilance system
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

Risk management plan
The MAH stated that a risk management plan has not been submitted due to the following reasons:
- Triptorelin acetate is considered a well known active substance as it has been on the market for more than 15 years.
- Gonapeptyl 0.1 mg/1 ml is not considered a biosimilar product.

- No specific safety concern has been identified with the product during the up to 15 years for which a Marketing Authorisation for the in vitro fertilisation indication has been granted in several EU countries.
- There is extensive clinical experience with triptorelin acetate treatment in higher doses, other patient groups and with a longer duration of treatment than covered by this application.
- No significant changes in the Marketing Authorisation (e.g. new dosage form, new route of administration, significant change in indication) are being applied for.

The MAH's rationale can be followed. No risk management plan is deemed necessary at this time. If, in future, new data suggest differently the submission of a risk management plan and a riks minimisation plan can be necessary.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is a good translation of the approved Dutch SPC of Decapeptyl.

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 two test rounds, first a diagnostic test round and second a verification test round. There were in total 22 questions about the content, for each key safety section two questions were asked. The questionnaire contains three types of questions, relating to findability, understandability and applicability. The participants selected for this test were potential users of the medication the patient information leaflet is destined for. They were spread on age and level of education in order to create a representative statistical sample. All participants were women which is logic as the product is indicated to be used by women.

The answers to the test questions are scored and recorded using predefined answer categories: 'incorrect', 'incomplete' and 'correct'. The results of the first test round of the patient information leaflet for Gonapeptyl led to the formulation of 3 areas for attention. A total of 91% of the questions were answered correctly or incompletely in this test round. Answers categorised as 'incomplete' are those for which the respondent refers to the correct passage in the leaflet, but does not supply the complete correct answer.

A number of areas for improvement were identified during the first test round and recommendations were made for modifications. The MAH implemented modifications based on these recommendations. The second round, in which the modified patient information leaflet was tested, resulted in a readability of 93%. The second test round generated no new areas for attention.

Two general open questions were asked to obtain information about the leaflet. The positive feedback was in general that the leaflet was clear and the negative feedback that section 1 was not clear and that an advice in section 2b was missing. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Although the efficacy data presented from the submitted clinical studies are open to points of criticism e.g. choice of minimum effective dose, it is acknowledged that there is very wide clinical experience with Gonapeptyl in the dose of 0.1 mg SC. Gonapeptyl 0.1 mg/1 ml is identical to Decapeptyl 0.1 mg/1 ml registered in the Netherlands, RVG 11778, for the indication prostate cancer since 1989. In addition, in comparison to other GnRH agonists or antagonists, Gonapeptyl 0.1 mg has shown to be as effective, in valid clinical endpoints as ongoing pregnancy rates. Accordingly, its efficacy in the indication of IVF is considered sufficient to grant the application. Although comparative data included only a mixed group of other GnRH agonists and a comparison with the GnRH antagonist ganirelix in the public literature, the data shown do not include any signs that the safety profile of Gonapeptyl is different from other GnRH agonists in the indication requested.

In conclusion, the MEB, on the basis of the data submitted, considered that Gonapeptyl 0.1 mg/1 ml demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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

The Board followed the advice of the assessors. Gonapeptyl 0.1 mg/1 ml was authorised in the Netherlands on 14 February 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 20 January 2009.

A European harmonised birth date has been allocated (5 March 1986) and subsequently the first data lock point for triptorelin is March 2009. The first PSUR will cover the period from February 2008 to March 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 November 2012.

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

<u>Quality - medicinal product</u>

- The MAH committed to express the content of triptorelin free base in mg in agreement with the strength given for the product (0.1 mg/ml). This commitment has been fulfilled.

List of abbreviations

ART	Assisted Reproductive Technologies
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
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HMG	Human Menopausal Gonadotrophin
ICH	International Conference of Harmonisation
ICSI	Intracytoplasmic Sperm Injection
IVF	In Vitro Fertilisation
LH	Luteinizing Hormone
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OHSS	Ovarian Hyperstimulation Syndrome
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
SC	Subcutaneous
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
Addition of a secondary packaging site.	NL/H/1427/ 001/IA/001	IA	8-10-2009	22-10-2009	Approval	N