VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

One in six couples worldwide experience some form of infertility problem at least once during their reproductive lifetime. The current prevalence of infertility lasting for at least 12 months is estimated to be around 9% worldwide for women aged 20-44.

Not all infertile couples seek help. However, advances in assisted reproductive technologies (ART) have led to a steady increase in percentage of females seeking treatment for infertility. Based on data from 31 European countries, approximately 565,000 treatment cycles, in form of in-vitro fertilisation (IVF) and other ART treatment, are performed per year, mainly in 30-39 year-old women.

Progesterone is a hormone produced by the ovaries and a requirement for the uterus in order to optimise chances of achieving pregnancy. Patients undergoing IVF and other types of assisted reproduction therapy often require progesterone administration as their normal progesterone production is impaired due to treatment.

VI.2.2 Summary of treatment benefits

A clinical trial was conducted in 1,211 patients in US with the purpose of comparing and evaluating the effects of administration of different doses of ENDOMETRIN (either 200 mg or 300 mg per day) versus another progesterone product during controlled ovarian stimulation in regard to achieving pregnancy with a living foetus. The results showed that irrespective of dose administered, almost 40 % of the patients were pregnant with a living foetus five weeks after start of treatment, and the effect was at least as good as the one achieved with a similar progesterone product on the market.

VI.2.3 Unknowns relating to treatment benefits

The effects of progesterone treatment have not been studied in women >42 years.

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks	What is known	Preventability
None	-	-

Important potential risks

Important potential risks	What is known (Including reason why it is considered a potential risk)
Birth defects	There is limited and inconclusive data on the risk of birth defects after

Important potential risks	What is known (Including reason why it is considered a potential risk)
	progesterone exposure to foetus during pregnancy. During the clinical study with Ferring progesterone (ENDOMETRIN) seven cases of birth defects in 154 live births were reported in ENDOMETRIN (300 mg daily) group, as against three cases in 153 live births in other progesterone product. No noticeable trend of similar birth defects was identified in ENDOMETRIN group. The published literature regarding large studies suggests that assisted reproduction itself is associated with higher incidence of birth defects compared to naturally conceived pregnancies. Keeping in view the rates of birth defects reported in general population (up to 4.3%) and with assisted reproduction (up to 9%) the rate of birth defects seen with ENDOMETRIN (300 mg daily) (4.5%) is comparable to the rate expected in the general population, and consequently substantially lower than would be expected after assisted fertilisation. However, due to the quantitative difference seen between ENDOMETRIN group (4.5%) compared to other progesterone product (2.0%), birth defects is considered as a potential risk. In a limited patient population, the observed difference in rate of birth defects (between ENDOMETRIN and other progesterone product) might be a chance finding. Moreover, during the post-marketing period no case of foetal anomaly or birth defect has been reported after the use of Ferring progesterone.

Missing information

Missing information	What is known
None	-

VI.2.5 Summary of risk minimisation measures by safety concern

The information about the rate (incidence) of birth defects seen with Ferring progesterone during clinical studies has been included in the prescription text and patient leaflet for the respective Ferring progesterone products.

During the post-marketing period no case of any birth defect associated with the use of Ferring progesterone products has been reported.

No additional risk minimisation measures have been proposed.

VI.2.6 Planned post authorisation development plan

None.

Studies which are a condition of the marketing authorisation

None.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	17 December 2007 (Submitted with MAA)	Identified Risks: None Potential Risks: Birth defects Missing information: None	-
2.0	03 November 2009 (At time of EU authorisation)	Identified Risks: None Potential Risks: Birth defects Missing information: None	No change in safety concerns.
New template version 1.0*	February 2014	Identified Risks: None Potential Risks: Birth defects Missing information: None	No change in safety concerns. RMP updated to new EU template.

**supersedes version 2.0 03 Nov 2009, old format*