VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Infertility is a disease of the reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.[88]

The World Health Organization considers infertility as a disability (an impairment of function) being classified as the fifth highest serious global disability in populations under 60 years old.[89]

The most common risks of infertility are: sperm abnormalities, ovulation dysfunction and tubal pathology.
Many lifestyle factors (age, nutrition, weight, exercise, psychological stress, environmental and occupational exposures, smoking, illicit drug use, alcohol and caffeine consumption) can have substantial effects on fertility.[90]

Infertility affects between 8 and 12% of reproductive-aged couples worldwide with 9% cited as the probable global average. A global examination of infertility trends based on analysis of 277 reproductive and health surveys available from 190 countries and territories during the period 1990–2010 estimated that 48.5 million couples were affected by infertility in 2010.[91]

VI.2.2 Summary of treatment benefits

Two studies were conducted in order to analyse the efficacy and tolerability of two progesterone containing products, pessary and gel, used in the context of assisted reproduction technology (ART) as luteal phase support (LPS) (term used to describe the administration of medications with the aim to support the process of implantation. The implantation refers to the very early stage of pregnancy at which the embryo adheres to the wall of the uterus). ART is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in-vitro fertilization.

In total a number of 438 female were treated with progesterone pessary 400 mg, taken twice daily.

The first study demonstrated a dose-dependent transformation of the endometrium for progesterone pessary. (The endometrium is the mucous membrane lining the uterus which thickens during the menstrual cycle – in the secretory phase - in preparation for

possible implantation of an embryo). Progesterone pessary was non-inferior to progesterone gel and led to an optimized condition for successful embryo implantation.

The second study compared the success rate for getting pregnant (after 18, 38 or 70 days) of vaginally applied progesterone pessary and progesterone gel, after in-vitro fertilization. Progesterone pessary was non-inferior to progesterone gel.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
None	NA	NA

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Birth defects	The risks of congenital (conditions present at birth) anomalies, including genital abnormalities in male or female infants, from exposure to exogenous progesterone during pregnancy have not been fully established.

Missing information

Risk	What is known
Long term effects in children exposed in utero	The risks of congenital (conditions present at birth) anomalies, including genital abnormalities in male or female infants, from exposure to progesterone ingested by the mother during pregnancy, have not been fully established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for progesterone.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	14-01-2016	Important identified risks None Important potential risks None Missing informationLong term effects in children exposed in utero	First version - new MA application for Progesterone 400 mg pessaries (DCP No. UK/H/6113/001)
2.0	06-07-2016	Important identified risks None identified Important potential risks Birth defects Missing information Long term effects in children exposed in utero	Update in relation to Day 70 RMP Final Assessment Report Addition of one important potential risk: Birth defects