Part VI: Summary of risk management plan

Summary of risk management plan for Progedex 25mg Injektionslösung (progesterone)

This is a summary of the risk management plan (RMP) for Progedex 25mg Injektionslösung.The RMP details important risks, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).

Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Progedex 25mg Injektionslösung should be used.

Important new concerns or changes to the current ones will be included in updates of Progedex 25mg Injektionslösung's RMP.

I. The medicine and what it is used for

Progedex 25mg Injektionslösung is authorized for luteal phase support in assistive reproductive technology treatment (ART) in infertile women, who cannot use or are unable to tolerate vaginal preparations. It contains progesterone as the active substance and it is given subcutaneously in dosage of 25 mg.

II. Risks associated with the medicine and activities to minimize or further characterise the risks

Important risks of Progedex 25mg Injektionslösung, together with measures to minimize such risks and the proposed studies for learning more about Progedex 25mg Injektionslösung' risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Progedex 25mg Injektionslösung are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Progedex 25mg Injektionslösung. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important Identified Risks	None
Important Potential Risks	- Conditions affected by fluid retention (such as for instance) epilepsy, cardiac or renal dysfunctions - Arterial or venous thromboembolism including cerebrovascular disorders, myocardial infarction, thrombophlebitis, retinal thrombosis - Depression - Diabetes and reduced glucose tolerance
Missing information	None

II.B Summary of important risks

Important potential risks

Conditions affected by fluid retention (such as for instance) epilepsy, cardiac or renal dysfunctions	
Evidence for linking the risk to the medicine	There is sufficient evidence from literature that progesterone can affect fluid homeostasis.
Risk factors and risk groups	Women with underlying cardiac and renal disorders as well as any other disorders sensitive to fluid alterations, not adequately addressed or unstable or with congenital deficit which may affect fluid balance.
Risk minimization measures	Routine risk minimization measures: *SPC section 4.4* *PL section 2* Additional risk minimization measures: *None*

Arterial or venous thromboembolism including cerebrovascular disorders, myocardial infarction, thrombophlebitis, retinal thrombosis	
Evidence for linking the risk to the medicine	Moderate evidence, multiple publications on oral contraceptives, including progestin with or without oestrogen are independent risk factors for incident veno-thromboembolism - VTE - or pulmonary embolism – PE. However, Progedex 25mg Injektionslösung is not intended to be a contraceptive, therefore evidence for ART program remains linked to the overall hormonal stimulation. Blood clot formation and alteration of coagulation process may importantly impact all the organic functions, primarily cardiac, cerebral, respiratory functions which are crucial for life.
Risk factors and risk groups	Women with familiarity for VTE or PE, coagulation disorders acquired or congenital, cardiac deficit, vascular abnormalities.

Risk minimization measures	Routine risk minimization measures: *SPC section 4.3 – 4.4* *PL section 2* Additional risk minimization measures: *None*
Depression	
Evidence for linking the risk to the medicine	Clinical studies in have found higher rates of depression exacerbation as compared to controls. However, these studies were carried out in non-pregnant women. The studies with progesterone in pregnant women did not show an increase of depression or mood changes. However, there is no evidence from post-marketing use of However there is no evidence from post-marketing use of depression in patients without medical history of depression.
Risk factors and risk groups	Patients with a medical history of depression. Also, the abrupt discontinuation of progesterone has been found to be a risk factor.
Risk minimization measures	Routine risk minimization measures: *SPC section 4.4 – 4.8* *PL section 2 -4* Additional risk minimization measures:

	None
Diabetes and reduced glucose tolerance	
Evidence for linking the risk to the medicine	The studies with progesterone in pregnant women did not show an increase of glucose impaired metabolism. In this context, patients with type 2 diabetes should be closely monitored. There is no evidence from post-marketing data of effects of progesterone on impaired glucose metabolism effects. Diabetes and altered blood glucose may affect importantly the woman's and baby's health with potentially deleterious effects. Overall hormonal treatment during ART program may impact on the anti-diabetic therapies.
Risk factors and risk groups	Pregnant women which maybe more prone to measure abnormal level of blood glucose due to the altered metabolism during pregnancy. This risk may be higher in patients at risk for developing type 2 diabetes mellitus (familiarity, obese, overweight etc).
Risk minimization measures	Routine risk minimization measures: *SPC section 4.4 – 4.5* *PL section 2* Additional risk minimization measures: *None*

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of Progedex 25mg Injektionslösung.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Progedex 25mg Injektionslösung.