Summary of the Risk Management Plan (RMP)

REKOVELLE (follitropin delta)

Product concerned (brand name)               REKOVELLE

Active substance                             Follitropin delta

Pharmaco-therapeutic group (ATC Code)         Sex hormones and modulators of the genital system, gonadotropins (G03GA10)

Pharmaceutical form and strength              Solution for injection in cartridge with reusable pen
12 micrograms/0.36 mL, 36 micrograms/1.08 mL and 72 micrograms/2.16 mL

Marketing Authorisation Holder                Ferring AG, Baarermatte, 6340 Baar

Data lock point for this RMP                 02 July 2015

Version number of this RMP                   3.0
First and current version of RMP approved in CH

Date of final sign off                       06 September 2016

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of REKOVELLE is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of REKOVELLE in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorised by Swissmedic. Ferring Pharmaceuticals A/S is fully responsible for the accuracy and correctness of the content of the published summary RMP of REKOVELLE.
Table of Contents

Elements for a Public Summary .................................................................................................................... 3
  VI.2.1 Overview of disease epidemiology ................................................................................................. 3
  VI.2.2 Summary of treatment benefits .................................................................................................... 3
  VI.2.3 Unknowns relating to treatment benefits ..................................................................................... 3
  VI.2.4 Summary of safety concerns ....................................................................................................... 3
  VI.2.5 Summary of risk minimisation measures by safety concern ....................................................... 4
  VI.2.6 Planned post authorisation development plan ............................................................................. 5
  VI.2.7 Summary of changes to the Risk Management Plan over time .................................................. 5
Elements for a Public Summary

VI.2.1 Overview of disease epidemiology
One in six couples worldwide experience some form of infertility (problem conceiving) at least once during their reproductive lifetime. The major causes of infertility are tubal infertility, male infertility, endometriosis (womb lining cells outside the womb), and unexplained infertility. During the last decade, advances in assisted reproductive technologies (ART) have led to a steady increase in percentage of couples undergoing infertility treatment.

VI.2.2 Summary of treatment benefits
REKOVELLE is used in women undergoing controlled ovarian stimulation in an assisted reproductive technology (ART) programme such as an in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) cycle. REKOVELLE is a recombinant follicle-stimulating hormone (FSH) that stimulates the ovaries to grow and develop many egg sacs / follicles, from which eggs are collected and fertilised in the laboratory (in vitro). When the fertilised eggs have reached an appropriate development and quality stage, one or several fertilised eggs are put back in the woman’s womb. The aim is for the woman to become pregnant.

REKOVELLE has been evaluated in clinical trials and has been used in more than 1,000 controlled ovarian stimulation cycles. When compared in clinical trials, REKOVELLE provided pregnancy rates at least as good as another recombinant FSH product.

VI.2.3 Unknowns relating to treatment benefits
In the main and supporting trials nearly all women were white Caucasians, so the impact of race on the efficacy of REKOVELLE could not be evaluated.

VI.2.4 Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels of activity in the ovaries (Ovarian hyperstimulation syndrome (OHSS))</td>
<td>OHSS occurs when the ovaries overreact to treatment, especially when a medicine called human chorionic gonadotropin (hCG) for final development of the eggs has been used. Symptoms may include pain, discomfort or swelling of the abdomen, nausea, vomiting, diarrhoea, weight gain, difficulty breathing. Known risk factors are low body weight, young age, high estradiol levels, many follicles during stimulation, polycystic ovaries and previous episodes of OHSS. In rare cases OHSS might be complicated by twisting of an ovary or blood clot formation inside the blood vessels (veins or arteries), especially in patients with known blood clotting disease (thrombophilia).</td>
<td>If the ovaries are overreacting, hCG for final development of the eggs should not be used.</td>
</tr>
</tbody>
</table>

Ferring Pharmaceuticals A/S
### Important potential risk

**Hypersensitivity / Immunogenicity**

- No cases of severe allergic reactions (anaphylactic reactions) have been reported during clinical trials.

- Immunogenicity in terms of development of anti-FSH antibodies is a potential risk of gonadotropin therapy. Rare cases observed in clinical trials were not associated with decreased ovarian response, and did not induce immune-related adverse events.

- Available data do not suggest a specific safety concern in terms of hypersensitivity / immunogenicity.

### Missing information

| Experience in patients with kidney or liver impairment | Women seeking fertility treatment are generally healthy. REKOVELLE is mainly removed from the body by the kidneys. |
| Experience in anovulatory patients with polycystic ovarian syndrome | Women with polycystic ovaries or polycystic ovarian syndrome often have high AMH, and these patients are expected to benefit from the AMH-based dosing regimen of REKOVELLE. Anovulatory patients with polycystic ovarian syndrome have not been studied in clinical trials, but ovulatory patients with polycystic ovaries have been studied and found to have a significant reduction in OHSS-related events when following the REKOVELLE dosing regimen. |
| Experience with REKOVELLE in the long GnRH agonist protocol | There is no clinical trial experience with FE 999049 in the long GnRH agonist protocol. |
| Limited experience in women >40 years | The maximum age of women included in the main clinical trial ESTHER-1 was up to and including 40 years. However, there is experience from some women who continued in another trial and at that time were more than 40 years. |

### 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

List of studies in post-authorisation development plan

<table>
<thead>
<tr>
<th>Study/activity (including study number)</th>
<th>Objectives</th>
<th>Safety concerns /efficacy issue addressed</th>
<th>Status</th>
<th>Planned date for submission of (interim and) final results</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Version (Compiled)</th>
<th>Sign off date</th>
<th>Safety Concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 (First and current version of RMP approved in CH)</td>
<td>06 Sep 2016</td>
<td>Identified Risk</td>
<td>Ovarian hyperstimulation syndrome -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential Risk</td>
<td>Hypersensitivity / Immunogenicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing information</td>
<td>Experience in patients with renal or hepatic impairment Experience in anovulatory patients with polycystic ovarian syndrome Experience with REKOVELLE in the long GnRH agonist protocol Limited experience in women &gt;40 years</td>
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</tbody>
</table>