Public Assessment Report

REKOVELLE

INFORMASI PRODUK

Nama obat	:	Rekovelle
Bentuk sediaan	:	Larutan injeksi
Zat aktif	:	Tiap pen mengandung: - Follitropin delta 12 mcg; - Follitropin delta 36 mcg; - Follitropin delta 72 mcg
Kemasan	:	- Box, 12 micrograms/0.36 ml solution for injection in a pre-filled pen + 3 injection needles - Box, 36 micrograms/1.08 ml solution for injection in a pre-filled pen + 9 injection needles - Box, 72 micrograms/2.16 ml solution for injection in a pre-filled pen + 15 injection needles
Pendaftar	:	PT Ferring Pharmaceuticals Industry
Produsen	:	Vetter Pharma-Fertigung Gmbh & Co. Kg, Ravensburg, Federal Republic Of Germany Dirilis Oleh Ferring Gmbh, Kiel, Federal Republic Of Germany
Kategori Registrasi	:	Registrasi perubahan indikasi dan posologi
Indikasi yang diajukan	:	*Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle*
Posologi yang diajukan	:	*Treatment should be initiated under the supervision of a physician experienced in the treatment of fertility problems.* *<u>Posology</u>* *The posology of REKOVELLE is individualized for each patient and aims to obtain an ovarian response which is associated with a favourable safety/efficacy profile, i.e. aims to achieve an adequate number of oocytes retrieved and reduce the interventions to prevent ovarian hyperstimulation syndrome (OHSS).* *REKOVELLE is dosed in micrograms (see section Pharmacodynamic properties). The dosing regimen is specific for REKOVELLE and the microgram dose cannot be applied to other gonadotropins.* *For the first treatment cycle, the individual daily dose will be determined on the basis of the woman's serum anti-Müllerian hormone (AMH) concentration and her body weight. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured by the following diagnostic test: ELECSYS AMH Plus immunoassay from Roche (i.e. assay used in clinical development trials), or alternatively the ACCESS AMH Advanced from Beckman Coulter (see section Special warnings and precautions for use). The individual daily dose is to be maintained throughout the stimulation period. For women with AMH less than 15*

pmol/L the daily dose is 12 micrograms, irrespective of body weight. For women with AMH greater than or equal to 15 pmol/L the daily dose decreases from 0.19 to 0.10 micrograms/kg by increasing AMH concentration (Table 1). The dose is to be rounded off to the nearest 0.33 micrograms to match the dosing scale on the injection pen. The maximum daily dose for the first treatment cycle is 12 micrograms. For calculation of the REKOVELLE dose, the body weight is to be measured without shoes and overcoat just prior to start of stimulation

Table 1 Dosing regimen for first treatment cycle with REKOVELLE

AMH (pmol/L)	*less than 15*	*15-16*	*17*	*18*	*19-20*	*21-22*	*23-24*	*25-27*	*28-32*	*33-39*	*greater than or equal to 40*
Fixed daily dose of REKOVELLE	*12 mcg*	*0.19*	*0.18*	*0.17*	*0.16*	*0.15*	*0.14*	*0.13*	*0.12*	*0.11*	*0.10*
		mcg/kg									

The AMH concentration is to be expressed in pmol/L and is to be rounded off to the nearest integer. If the AMH concentration is in ng/mL, the concentration should be converted to pmol/L by multiplying with 7.14 (ng/mL x 7.14 = pmol/L) before use.
mcg: micrograms

Potential high responders (patients with AMH greater than 35 pmol/L) have not been studied in a protocol using down-regulation with GnRH agonist.

Time of initiating treatment with REKOVELLE depends on the type of protocol
- in a protocol using a gonadotropin-releasing hormone (GnRH) antagonist, the treatment with REKOVELLE should be initiated on day 2 or 3 after start of menstrual bleeding:
- in a protocol using down-regulation with a GnRH agonist, the treatment with REKOVELLE should be initiated approximately 2 weeks after the start of agonist treatment

Treatment should continue until adequate follicular development (greater than or equal to 3 follicles greater than or equal to 17 mm) has been achieved, which on average is by the ninth or tenth day of treatment (range 5 to 20 days). With pituitary desensitisation caused by a GnRH agonist, a longer duration of stimulation and therefore a higher total dose of REKOVELLE may be necessary to achieve adequate follicular response. A single injection of 250 micrograms recombinant human chorionic gonadotropin (hCG) or 5,000 IU hCG is administered to induce final follicular maturation. in patients with excessive follicular development (of greater than or equal to 25 follicles greater than or equal to 12mm), treatment with REKOVELLE should be stopped and triggering of final follicular maturation with hCG should not be performed.

For subsequent treatment cycles, the daily dose of REKOVELLE should be maintained or modified according to the patient's ovarian response in the previous cycle. If the patient had adequate ovarian response in the previous cycle without developing OHSS, the same daily dose should be used. In case of ovarian hypo-response in the previous cycle, the daily dose in the subsequent cycle should be increased by 25% or 50%, according to the extent of response observed. In case of ovarian hyperresponse in the previous cycle, the daily dose in the subsequent cycle should be decreased by 20% or 33%, according to the extent of response observed. In patients who developed OHSS or were at risk of OHSS in a previous cycle, the daily dose for the subsequent cycle is 33% lower than the dose used in the cycle where OHSS or risk of OHSS occurred. The maximum daily dose is 24 micrograms.

Patients with renal and hepatic impairment
Safety, efficacy and pharmacokinetics of REKOVELLE in patients with renal or hepatic impairment have not been specifically studied in clinical trials. Although limited, data did not indicate a need for a different dosing regimen of REKOVELLE in this patient population (see section Special warnings and precautions for use).

Polycystic ovarian syndrome patients with anovulatory disorders
Anovulatory patients with polycystic ovarian syndrome have not been studied. Ovulatory patients with polycystic ovaries have been included in clinical trials (see section Pharmacodynamic properties).

Elderly
There is no relevant use of REKOVELLE in the elderly population.

Paediatric population
There is no relevant use of REKOVELLE in the paediatric population.

Method of administration
REKOVELLE is intended for subcutaneous use, preferably in the abdominal wall. The first injection should be performed under direct medical supervision. Patients must be educated on how to use the REKOVELLE injection pen and to perform injections. Self-administration should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

For instructions on the administration with the pre-filled pen, see the "Instructions for Use"

PENGANTAR

Rekovelle mengandung zat aktif follitropin delta, yang merupakan rekombinan folliclestimulating Hormone (FSH) manusia, telah memiliki izin edar di Indonesia dengan indikasi untuk stimulasi ovarium pada wanita yang menjalani assisted reproductive technologies (ART) seperti fertilisasi in-vitro (IVF) atau intracytoplasmic sperm injection (ICSI) cycle.

Saat ini pendaftar mengajukan indikasi dan posologi baru, yaitu penggunaan protokol long GnRH agonist sebagai alternatif dari protokol GnRH antagonist yang telah disetujui sebelumnya pada indikasi Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. Efek yang paling penting yang dihasilkan dari pemberian parenteral FSH adalah perkembangan beberapa folikel yang matang.
Follitropin delta adalah FSH manusia rekombinan. Urutan asam amino dari dua subunit FSH dalam follitropin delta identik dengan urutan FSH manusia endogen. Karena follitropin delta diproduksi dalam sel manusia PER.C6, profil glikosilasi berbeda antara follitropin alfa dan follitropin beta.

ASPEK MUTU
Tidak ada evaluasi aspek mutu dalam pengajuan ini.

ASPEK KHASIAT KEAMANAN
STUDI NON KLINIK
Tidak ada evaluasi aspek non klinik dalam pengajuan ini.

STUDI KLINIK
1. Diserahkan assessment report dari EMA (untuk mendukung registrasi penambahan indikasi dan posologi baru Rekovelle melalui jalur 120 Hari Kerja, 1 studi klinik fase III (Studi Beyond 000304), data keamanan pasca-pemasaran dan dokumen Perencanaan Manajemen Risiko (RMP).
2. Studi Beyond (studi 000304, n=435) yang mengevaluasi efikasi dan keamanan folitropin delta pada wanita infertile usia 18 tahun ke atas, yang menjalani controlled ovarian stimulation dengan protokol long GnRH agonist dibandingkan protokol GnRH antagonist, menunjukkan:
   a. Efikasi sebanding antara kedua protokol:
      - Parameter efikasi primer, yaitu jumlah rata-rata oosit yang diambil (FAS), adalah 10,82 pada protokol long GnRH agonist dan 9,51 pada protokol GnRH antagonist, dengan perbedaan antara protokol long GnRH agonist dan protokol GnRH antagonist sebesar 1.31 (95% CI: 0.22; 2.40, p = 0.0185).
      - Jumlah rata-rata oosit yang diambil, berdasarkan analisis terhadap subjek yang memulai Controlled ovarian stimulation dengan folitropin delta, adalah 11,1 vs 9,6.
      - Ongoing pregnancy rates 36,85% pada protokol long GnRH agonist dan 29,11% pada protokol GnRH antagonist dengan nilai Difference 7,74 (95% CI: -1.49; 16.97, Pvalue=0.1002).
      - Live Birth Rates 35,81% pada protokol long GnRH agonist dan 28,67% pada protokol GnRH antagonist dengan nilai Difference 7,15 (95% CI: -2.02; 16.31, P-value=0.1295).
      - Parameter efikasi sekunder lain seperti perkembangan folikel (Number of Follicles by Minimum Size at End-of-stimulation), perkembangan blastosit, profil endokrin (serum FSH), dosis total gonadotropin dan jumlah hari stimulasi juga menunjukkan hasil sebanding secara statistik.
   b. Perbedaan jumlah oosit yang diambil dipengaruhi oleh usia dan konsentrasi anti mullerian hormone (AMH) dalam serum:
      - Jumlah oosit yang diambil lebih banyak pada pasien dengan usia yang lebih muda (usia <35 tahun), dibanding usia >35 tahun.
      - Pada pasien dengan usia <35 tahun, jumlah oosit yang diambil lebih banyak pada protokol long GnRH agonist dibandingkan dengan protokol GnRH antagonist, yaitu 11,7 vs 10,18 (perbedaan 1,52; 95%CI 0,05;2,99, p=0,0431). Sedangkan untuk pasien dengan usia >35 tahun, jumlah oosit yang diambil adalah sebanding antara kedua kelompok.

- Jumlah oosit yang diambil lebih banyak pada pasien dengan cadangan ovarium yang lebih tinggi (AMH >15 pmol/L) dibanding pasien dengan kadar AMH<15 pmol/L.
- Pada pasien dengan AMH >15 pmol/L, jumlah oosit yang diambil adalah lebih banyak pada protokol long GnRH agonist dibandingkan dengan protokol GnRH antagonist, yaitu 12,74 vs 11,01 (perbedaan 1,73; 95%CI 0,09;3,36, p=0,0383). Sedangkan pada pasien dengan kadar AMH< 15 pmol/L, jumlah oosit yang diambil adalah sebanding antara kedua protokol.

3. Data keamanan:

   Hasil studi Beyond menunjukkan profil keamanan follitropin delta dengan dosis individual adalah serupa pada kedua protokol analog GnRH. Tidak ada masalah keamanan yang berkaitan dengan kesehatan neonatal setelah controlled ovarian stimulation dengan follitropin delta dalam protokol analog GnRH, baik GnRH antagonist maupun GnRH agonist. Berdasarkan data keamanan pasca-pemasaran Rekovelle secara global (periode 01 December 2020 – 30 November 2023 dan 01 December 2022 – 30 Desember 2023), sebagian besar efek samping yang dilaporkan adalah Ovarian Hyperstimulation Syndrome (OHSS).

   Berdasarkan data RMP Follitropin delta Version 8.0 (Data lock point for RMP : 14 December 2022 yang telah disetujui di EMA, tidak terdapat risiko keamanan yang diklasifikasikan sebagai risiko penting yang teridentifikasi, risiko potensial yang penting dan missing information.

EVALUASI

Penilaian Manfaat-Risiko

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, produk Rekovelle memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan pada registrasi variasi penambahan indikasi baru untuk *Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle*, sebagai berikut:

a. Aspek yang menguntungkan:
   Berdasarkan data studi klinik menunjukkan efikasi primer memberikan hasil yang lebih baik pada subyek yang mendapatkan terapi dengan Rekovelle yaitu perbedaan antara protokol long GnRH agonist dan protokol GnRH antagonist sebesar 1.31 (95% CI: 0.22; 2.40, p = 0.0185). Parameter efikasi sekunder lain seperti perkembangan folikel (Number of Follicles by Minimum Size at End-of-stimulation), perkembangan blastosit, profil endokrin (serum FSH), dosis total gonadotropin dan jumlah hari stimulasi juga menunjukkan hasil sebanding secara statistik.
b. Aspek yang tidak menguntungkan :
   - Tidak ada masalah keamanan yang berkaitan dengan kesehatan neonatal setelah controlled ovarian stimulation dengan follitropin delta dalam protokol analog GnRH, baik GnRH antagonist maupun GnRH agonist.
   - Sebagian besar efek samping yang dilaporkan adalah Ovarian Hyperstimulation Syndrome (OHSS).
c. Ketidakpastian dan keterbatasan :
   Belum ada data efikasi dan keamanan pada usia < 18 tahun.
d. Kesimpulan evaluasi manfaat-risiko:
   Secara keseluruhan Obat ini menunjukkan kemanfaatan dalam Pengobatan dengan indikasi yang diterima sebagai berikut:

Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle

Indikasi yang diajukan

Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle

Posologi yang diajukan

Treatment should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

Posology

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REKOVELLE is dosed in micrograms (see section Pharmacodynamic properties). The dosing regimen is specific for REKOVELLE and the microgram dose cannot be applied to other gonadotropins.

For the first treatment cycle, the individual daily dose will be determined on the basis of the woman's serum anti-Müllerian hormone (AMH) concentration and her body weight. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured by the following diagnostic test: ELECSYS AMH Plus immunoassay from Roche (i.e. assay used in clinical development trials), or alternatively the ACCESS AMH Advanced from Beckman Coulter (see section Special warnings and precautions for use). The individual daily dose is to be maintained throughout the stimulation period. For women with AMH less than 15 pmol/L the daily dose is 12 micrograms, irrespective of body weight. For women with AMH greater than or equal to 15 pmol/L the daily dose decreases from 0.19 o 0.10 micrograms/kg by increasing AMH concentration (Table 1). The dose is to be rounded off to the nearest 0.33 micrograms to match the dosing scale on the injection pen. The maximum daily dose for the first treatment cycle is 12 micrograms. For calculation of the REKOVELLE dose, the body weight is to be measure without shoes and overcoat just prior to start of stimulation

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For subsequent treatment cycles, the daily dose of REKOVELLE should be maintained or modified according to the patient's ovarian response in the previous cycle. If the patient had adequate ovarian response in the previous cycle without developing OHSS, the same daily dose should be used. In case of ovarian hypo-response in the previous cycle, the daily dose in the subsequent cycle should be increased by 25% or 50%, according to the extent of response observed. In case of ovarian hyperresponse in the previous cycle, the daily dose in the subsequent cycle should be decreased by 20% or 33%, according to the extent of response observed. In patients who developed OHSS or were at risk of OHSS in a previous cycle, the daily dose for the subsequent cycle is 33% lower than the dose used in the cycle where OHSS or risk of OHSS occurred. The maximum daily dose is 24 micrograms.
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