19 May 2022
EMA/588110/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ganirelix Gedeon Richter

International non-proprietary name: ganirelix

Procedure No. EMEA/H/C/005641/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ganirelix Gedeon Richter
Applicant:	Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) Gyömrői út 19-21 1103 Budapest HUNGARY
Active substance:	ganirelix acetate
International Nonproprietary Name/Common Name:	ganirelix
Pharmaco-therapeutic group (ATC Code):	Pituitary and hypothalamic hormones and analogues, Anti-gonadotropin-releasing hormones (H01CC01)
Therapeutic indication(s):	Prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART). In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.
Pharmaceutical form(s):	Solution for injection in pre-filled syringe
Strength(s):	0.25mg/ 0.5 mL
Route(s) of administration:	Subcutaneous use
Packaging:	pre-filled syringe (glass)
Package size(s):	1 pre-filled syringe and 6 pre-filled syringes

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List of abbreviations

ASM	Active substance manufacturer
ASMF	Active Substance Master File = Drug Master File
BDL	Below the limit of detection
CMS	Concerned Member State
CoA	Certificate of Analysis
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File, ASMF
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
FT-IR	Fourier transmission infra-red (spectroscopy)
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IPCs	In-process controls
IR	Infra-red
LDPE	Low density polyethylene
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection
LoQ	Limit of Quantitation
MAH	Marketing Authorisation holder
MS	Mass spectroscopy
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PDA	Photo diode array
PDE	Permitted daily exposure
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
QbD	Quality by Design
QL	Quantitation limit
QOS	Quality Overall Summary
QTTP	Quality target product profile
RH	Relative Humidity
RMS	Reference member state
RSD	Relative standard deviation
Rrt	Relative retention time
Rt	Retention time
Rt	Room temperature
SD	Standard deviation
SmPC	Summary of product characteristics
SWFI	Sterile water for injections
TTC	Threshold of toxicological concern
TGA	Thermo-Gravimetric Analysis
(U)HPLC	(Ultra) High performance liquid chromatography
USP	United States Pharmacopeia
UV	Ultra violet
XRD	X-Ray Diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) submitted on 4 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ganirelix Gedeon Richter, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Ganirelix Gedeon Richter is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART).

In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. According to the Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), bioequivalence studies are not required if the test product is to be administered as a subcutaneous solution containing the same active substance in the same concentration as the reference product and the same excipients in similar amounts as the reference product. As this is the case with Ganirelix Gedeon Richter, bioequivalence study is not required.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Orgalutran, 0.25mg/0.5mL, solution for injection
- Marketing authorisation holder: N.V. Organon
- Date of authorisation: 17/05/2000
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/00/130/001, EU/1/00/130/002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Orgalutran, 0.25mg/0.5mL, solution for injection

- Marketing authorisation holder: N.V. Organon
- Date of authorisation: 17/05/2000
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/00/130/001, EU/1/00/130/002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	4 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 January 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	28 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	13 April 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ganirelix Gedeon Richter on	19 May 2022

2. Scientific discussion

2.1. Introduction

Ganirelix Gedeon Richter 0.25 mg/0.5 mL solution for injection in pre-filled syringe MAA has been submitted according to the Article 10.1 of Directive 2001/83/EC, as amended (i.e. generic application) containing the same active substance in the same pharmaceutical form and strength as the reference product. The reference product is Orgalutran solution for injection 0.25mg/0.5mL, marketed by N.V. Organon, that was first approved in the European Union on 17/05/2000 via centralised procedure (EU/1/00/130/001-002).

Ganirelix is an anti-gonadotropin-releasing hormone which blocks the receptors for the natural hormone gonadotrophin-releasing hormone and therefore prevents premature ovulation.

The indication applied for Ganirelix Gedeon Richter is the same as that for the reference product.

Ganirelix Gedeon Richter is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART).

In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing ganirelix acetate (hydrate) equivalent to 0.25 mg of ganirelix in 0.5 mL aqueous solution.

Other ingredients are: glacial acetic acid, mannitol (E 421), water for injections, sodium hydroxide (for pH adjustment)

The product is available in a pre-filled glass syringe with staked stainless steel needle, closed with a plunger stopper and supplied with a plunger rod. The injection needle is provided with a rigid needle shield, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of ganirelix acetate is N-acetyl-3-(2-napthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^9 ,N^{10}-diethyl-D-homoarginyl-L-leucyl-N^9,N^{10}-diethyl-L-homoarginyl- L-prolyl-D-alanylamide acetate corresponding to the molecular formula $C_{80}H_{113}ClN_{18}O_{13}\cdot xC_2H_4O_2$ y H_2O ($2<x<3$, $y\leq10$), with the number of acetates being between 2 and 3. It is supplied in the hydrated form, with less than 10 molecules of water per molecule of active substance. The acetic acid-free anhydrous active substance has a relative molecular mass of 1570.42.

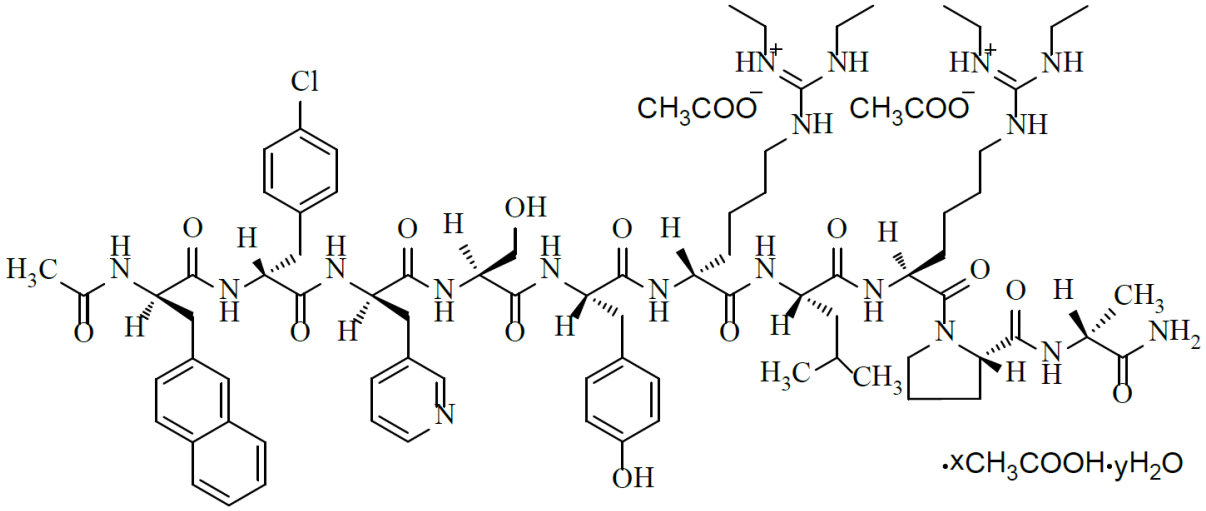

Figure 1: active substance structure

The chemical structure and solid state properties of ganirelix was elucidated by a combination of tests: amino acids analysis UV, IR, RP-HPLC, MS, NMR, XRD, CD and elemental analysis.

An appropriate comparison to the reference product, Orgalutran, for primary, secondary and tertiary structure has been provided.

Ganirelix is a white or off-white powder and loose lumps substance. It is amorphous and highly soluble under aqueous physiological pH. Additionally, polymorphism is not relevant as the active substance is present in solution in the finished product.

Ganirelix exhibits stereoisomerism due to the presence of 10 chiral centres, associated with chiral centres of individual amino acids. Chirality is ensured at the level of the starting materials (i.e. modified amino-acids) and controlled at the level of the active substance specifications by specific optical rotation.

Polymorphism has not been observed for ganirelix.

Manufacture, characterisation and process controls

One active substance manufacturer (ASM) is proposed. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. During the procedure starting materials, solvents and reagents have been included in the description of the manufacturing method in the applicant's part of the ASMF.

Ganirelix is synthesized using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered adequate.

The reagents and solvents used in the manufacture are typical reagents and solvents (class 2 and 3) with suitable controls in place for each. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Limits are set according to ICH Q3A. Three reagents have been identified as potential mutagens/genotoxic impurities due to their reactivity. All three impurities are easily purged. This is also confirmed by batch data. All peptide related substances are controlled as specified or unspecified impurities to well below the strictest TTC.

The manufacturing process development has been adequately described in the restricted part of the ASMF. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a triple layer bag (2 LDPE, 1 composite)which is placed in a container, to protect the active substance from light. The LDPE contact material complies with the EC 10/2011 as amended.

Specification

The active substance specification includes tests for; appearance (in house-organoleptic), specific optical rotation (in-house), appearance of solution (Ph. Eur.), pH (in-house), identification (HPLC, amino acid analysis), purity (in house), bacterial endotoxin (Ph. Eur.), microbiological purity (Ph. Eur.) and assay (in-house).

The specification is set based on ICH Q3A, Q3C, Q6A, and Ph.Eur. /USP pharmacopoeial tests were relevant methods or tests are available.

Detailed impurity profile has been provided.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (3 commercial scale batches and 3 validation batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial packagefor up to 36 months under long term conditions (5°C) and for up to 6 months under accelerated conditions (25°C and 60% RH) according to the ICH guidelines were provided. 36 months data at- 20°C was also provided for the same batches.

The following parameters were tested: appearance of solution (Ph. Eur.), pH (in-house), purity (in-house) and assay (in-house).

The results obtained for the batches stored both at -20°C and 5°C are comparable: no major trends are observed.

Photostability testing following the ICH guideline Q1B was performed on one batch and provided during the procedure. The results demonstrate that ganirelix acetate is sensitive under light and that the proposed packaging is adequate to protect the active substance from light.

Results on stress conditions (acid, alkali, oxidation, high temperature, high humidity and light) were also provide on samples of the active substance as part of the validation of related substances and assay tests. As expected, the active substance is most sensitive towards hydrolysis and oxidation; a minor degree of degradation is also observed at high heat and under light/UV. The mass is acceptable; the tests are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored at 2-8°C when stored in the original container in order to protect from light. Keep the container tightly closed in order to protect from moisture.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product Ganirelix is a clear and colourless solution for injection, filled in a glass syringe with staked stainless steel needle, closed with a plunger stopper and supplied with a plunger rod. The injection needle is provided with a rigid needle shield.

The glass syringe with stacked needle is considered an integral device, which is intended exclusively for use in the given combination and not reusable, hence, no CE mark is required. The applicant claimed compliance with the MDR and in response to a Major Objection raised during the procedure a satisfactory Notified Body Opinion, confirming full compliance with the relevant GSPRs, was provided.

Each syringe contains 0.5 mL of solution. The applied product is qualitatively the same as the reference product has the same active substance strength and volume as the reference product.

The aim of the pharmaceutical development was to formulate a sterile solution for injection containing ganirelix as active substance that shows essential similarity to the reference product, Orgalutran 0.25 mg/0.5 mL solution for injection (Merck Sharp & Dohme Limited) containing Ganirelix.

Pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) is summarised in Table 1 below.

Table 1: Quality target product profile

QTTP element	Target	Justification
Dose	0.25 mg / 0.5 mL ganirelix (as acetate)	Same as the reference product
Indication	Indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART).	Same as the reference product
Route of administration	Subcutaneously	Same as the reference product
Dosage form	Solution for injection in pre-filled cartridge in single use pen	Same as the reference product
Dosing	0.25 mg ganirelix should be injected subcutaneously once daily	Same as the reference product
Shelf life	3 years	Same as the reference product

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. The development section focuses on addressing identified potential high or medium risk parameters or attributes, and understanding the impact the process could have on those.

The manufacturing process is simple and has the following steps: compounding, sterile filtration and terminal sterilisation; no major manufacturing development took place as terminal sterilisation was possible. Compatibility with the manufacturing equipment has been supported by several studies

including an extractables study of the filling assembly used for processing. Adequate critical process parameters and IPCs have been identified.

Eventually, all identified potential risks were downgraded to low, by appropriately controlling compounding variables.

The essential similarity of Ganirelix 0.25 mg/0.5 mL solution for injection in pre-filled syringe by Gedeon Richter with the reference product Orgalutran 0.25 mg/0.5 mL solution for injection (Merck Sharp and Dohme B.V.) has been justified by performing the following comparisons: compositions, physical characterization (appearance, clarity of liquid, colour of liquid, pH, osmolality, particulate contamination), identity of active substance and chemical comparison of products (active substance, related substances and ganirelix agglomeration). The quantitative composition of the USA reference product is known and has been matched by the applicant. Mannitol is the main excipient in solution, in view of the equivalent osmolality value/range, which is a critical quality attribute, it can be further concluded that the test and reference products have the same quantitative composition of mannitol. The pH is also identical to one of the innovator product. Based on this no bioequivalence study was performed, as discussed under Section 3.3.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is a colourless borosilicate glass syringe (type I), with stainless steel hypodermic G29 needle and rigid needle shield; the plunger stopper is bromobutyl elastomer plunger stopper coated with silicone.

Both the syringes and plunger stoppers are purchased sterile, ready-to-use (RTU). The material complies with Ph.Eur. and EC requirements. Satisfactory extractable and leachables studies have been provided. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process is considered to be a standard manufacturing process.

Hold time has been included in the validation and considered acceptable.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and end of shelf-life specifications include appropriate tests for this kind of dosage form: characters (visual, in-house), clarity of liquid (Ph.Eur.), colour of liquid (Ph.Eur), extractable volume (Ph.Eur), pH (Ph.Eur), osmolality (Ph.Eur), particulate contamination (visible and sub-visible particles (Ph.Eur), identification (UHPLC and UV-diode array), related substances (UHPLC), assay (UHPLC), sterility (Ph.Eur.) and bacterial endotoxin (Ph.Eur.).

The parameters tested, methods and acceptance criteria given in the finished product specifications have been established considering pharmacopoeial and ICH requirements and are supported by batch results and stability data.

The acceptance criteria for related substances have been revised during the procedure in response to a MO raised by CHMP and are in line with ICH Q3B (R2) or based on the results found for the reference product.

At release the specification has been set in accordance with the Directive 75/318/EEC and EMA 3AQ11a guideline. For the shelf-life specification, the wider specification range has been set which allows for assay method variability and takes into consideration a limited batch history with the finished product manufacturing.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored upright and inverted position for up to 24 months under long term conditions (30ºC / 75% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the finished product specification parameters. The analytical procedures used are stability indicating.

A slight increase in total impurities is observed at accelerated conditions but results still remain within the proposed specification. No significant changes have been observed at long term and accelerated stability studies for the remaining test parameters. All parameters remained within the proposed specifications.

As part of the validation of related substance test, samples of the finished product were exposed to stress conditions: pH sensitivity (acid, alkaline), oxygen sensitivity, photostability (ICH Q1B) and heat sensitivity. The finished product is sensitive to all stress conditions and especially to acid, alkaline, and

heat. During the oxidative and photostability test some degradation products were generated in amount higher than QL.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the results of the photostability studies the finished product is not light sensitive. However, taking into consideration the stress testing results and that the storage condition of reference product, Orgalutran injection, requires that it is protected from light, the light protection is prescribed for the storage of Ganirelix 0.25 mg/0.5 mL solution for injection in pre-filled syringe. This is accepted.

Based on available stability data, the proposed shelf-life of 3 years and “Store in the original package in order to protect from light. Do not freeze.” as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Post-approval change management protocols

Two PACMPs are submitted for this procedure. Both PACMPs are considered acceptable.

2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A satisfactory NBOP for the integral device has been provided in response to a MO raised during the procedure. Another MO raised in relation to the specification limits for impurities has also been resolved by revising the concerned limits as requested. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and is considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Ganirelix Gedeon Richter manufactured by Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) is considered unlikely to result in any significant increase in the combined sales volumes for all ganirelix containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers there are no objections to approval of Ganirelix Gedeon Richter from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for solution for injection containing ganirelix.

The applicant provided a clinical overview outlining the clinical pharmacology as well as efficacy and safety of ganirelix based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

Exemption

According to Appendix II to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), there is no requirement for a bioequivalence study for solutions for

subcutaneous administration in case the generic formulation contains the same active substance in the same concentration as the reference product and the same excipients in similar amounts as the reference product.

According to the applicant, the generic version developed by Chemical Works Of Gedeon Richter PLC has the same qualitative and quantitative composition as the European Reference Product (in terms of both active substance and excipients), thus the efficacy and safety of the product should be assumed to be the same as that of Orgalutran, which has been demonstrated by its continuous clinical use for more than 20 years. Therefore, it can be concluded that the Ganirelix Gedeon Richter (generic product) and Orgalutran (reference product) are sufficiently similar.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

No bioequivalence study was submitted by the applicant as part of this application.

Ganirelix Gedeon Richter, 0.25 mg/0.5 mL, is a solution for injection in pre-filled syringe for subcutaneous use. The reference product Orgalutran 0.25 mg/0.5 mL solution for injection in pre-filled syringe, marketed by N.V. Organon, was first approved in the European Union on 17/05/2000 via centralised procedure (EU/1/00/130/001-002).

The application concerns a generic application, based on article 10(1) of Directive 2001/83/EC, claiming essential similarity with the innovator product Orgalutran 0.25 mg/0.5 mL solution for injection.

According to Appendix II to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), there is no requirement for a bioequivalence study for solutions for subcutaneous administration in case the generic formulation contains the same active substance in the same concentration as the reference product and the same excipients in similar amounts as the reference product.

Both products, the applied generic product Ganirelix Gedeon Richter and the reference product Orgalutran, contain 0.25 mg of the same active substance (ganirelix acetate). In addition, both products contain the same excipients (acetic acid and mannitol).

The essential similarity of the products has been justified by performing the following comparisons:

- Compositions of the solutions for injections

- Physical characterization of the reference product and Gedeon Richter's product (appearance, clarity of liquid, colour of liquid, pH, osmolality, particulate contamination)

- Chemical attributes of the solutions for injections (assay, related substances and ganirelix agglomeration)

Therefore, the Ganirelix Gedeon Richter is considered essentially similar to Orgalutran.

The lack of an in vivo bioequivalence study is considered acceptable.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

A clinical overview on the clinical pharmacology, efficacy and safety based on published literature has been provided and is considered adequate.

No bioequivalence study was submitted to support the application; this is in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

Ganirelix Gedeon Richter is considered essentially similar to Orgalutran (reference product).

2.4.4. Conclusions on clinical aspects

Based on the data provided, Ganirelix Gedeon Richter is considered bioequivalent with Orgalutran.

The CHMP considers that there are no objections to approval of Ganirelix Gedeon Richter from a clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity reaction Injection site reactions
Important potential risks	None
Missing information	Patients with renal or hepatic impairment Pregnant and lactating women Women with a history or current Type I hypersensitivity

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of ganirelix solution for injection. The reference product Orgalutran is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART). In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance has been presented and is considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

No bioequivalence study between Ganirelix Gedeon Richter and the reference medicinal product Orgalutran was submitted to support the application; this is in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

The CHMP considers that the relevant criteria are met for Ganirelix Gedeon Richter to support the above exemption.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ganirelix Gedeon Richter is favourable in the following indication:

Ganirelix Gedeon Richter is indicated for the prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques

(ART).

In clinical studies ganirelix was used with recombinant human follicle stimulating hormone (FSH) or corifollitropin alfa, the sustained follicle stimulant.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- *Periodic Safety Update Reports*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.