20 July 2023
EMA/380123/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Degarelix Accord

International non-proprietary name: degarelix

Procedure No. EMEA/H/C/006048/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active Substance
ASM	Active substance manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics classification system
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical quality attribute
CRS	Chemical reference substance
CVMP	Committee for Medicinal Products for Veterinary Use
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File, ASMF
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration
FID	Flame ionisation detection
FMEA	Failure mode effects analysis
FPM	Finished product manufacturer
FT-IR	Fourier transmission infra-red (spectroscopy)
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GMP	Good Manufacturing Practice
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IC	Ion chromatography
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control test
IR	Infra-red
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than

MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MS	Mass spectroscopy
ND	Not detected
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal operating range
OOS	Out Of Specification
PAR	Proven Acceptable Range
PCTFE	Polychlorotrifluoroethylene
PDA	Photo diode array
PDE	Permitted daily exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PP	Polypropylene
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality Control
QL	Quantitation limit
QOS	Quality Overall Summary
QP	Qualified person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
RMS	Reference member state
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
Rt	Retention time
Rt	Room temperature
SD	Standard deviation
SmPC	Summary of Product Characteristics
SWFI	Sterile water for injections
TAMC	Total Aerobic Microbial Count
tmax	Time to achieve Cmax
TGA	Thermo-Gravimetric Analysis
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	ultra-high performance liquid chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 23 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Degarelix Accord, 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 16 December 2021.

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 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:

Degarelix Accord is a gonadotrophin releasing hormone (GnRH) antagonist indicated:

- for treatment of adult male patients with advanced hormone-dependent prostate cancer.
- for treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.
- as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer.

1.2. Legal basis

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, complete quality data and non-clinical and clinical overview instead of non-clinical and clinical data.

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: Firmagon, 80 mg and 120 mg, powder and solvent for solution for injection
- Marketing authorisation holder: Ferring Pharmaceuticals A/S, Denmark
- Date of authorisation: 17.02.2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/504/001-003

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

- Product name, strength, pharmaceutical form: Firmagon, 80 mg and 120 mg, powder and solvent for solution for injection
- Marketing authorisation holder: Ferring Pharmaceuticals A/S, Denmark
- Date of authorisation: 17.02.2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/504/001-003

1.3. Information on paediatric requirements

Not applicable

1.3.1. 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.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. 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	23 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 October 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 February 2023
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	3 April 2023

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 April 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 April 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	20 June 2023
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	5 July 2023
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 Degarelix Accord on	20 July 2023

2. Scientific discussion

2.1. Introduction

Degarelix is a selective gonadotrophin releasing-hormone (GnRH) antagonist that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of the gonadotrophins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and thereby reducing the secretion of testosterone (T) by the testes. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that removes the source of androgen. Unlike GnRH agonists, GnRH antagonists do not induce a LH surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

A single dose of 240 mg degarelix, followed by a monthly maintenance dose of 80 mg, rapidly causes a decrease in the concentrations of LH, FSH and subsequently testosterone. The serum concentration of dihydrotestosterone (DHT) decreases in a similar manner to testosterone.

Degarelix is effective in achieving and maintaining testosterone suppression well below medical castration level of 0.5 ng/ml. Maintenance monthly dosing of 80 mg resulted in sustained testosterone suppression in 97% of patients for at least one year. No testosterone microsurges were observed after re-injection during degarelix treatment. Median testosterone levels after one year of treatment were 0.087 ng/ml (interquartile range 0.06-0.15) N=167.

The first maintenance dose should be given one month after the starting dose. Degarelix Accord may be used as neo-adjuvant or adjuvant therapy in combination with radiotherapy in high-risk localised and locally advanced prostate cancer.

The therapeutic effect of degarelix should be monitored by clinical parameters and prostate specific antigen (PSA) serum levels. Clinical studies have shown that testosterone (T) suppression occurs immediately after administration of the starting dose with 96% of the patients having serum testosterone levels corresponding to medical castration (T≤0.5 ng/ml) after three days and 100% after one month. Long term treatment with the

maintenance dose up to 1 year shows that 97% of the patients have sustained suppressed testosterone levels (T≤0.5 ng/ml).

In case the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed. Since degarelix does not induce a testosterone surge it is not necessary to add an anti-androgen as surge protection at initiation of therapy.

The Pharmacotherapeutic group of degarelix is endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX02.

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Degarelix Accord 80 mg and 120 mg powder and solvent for solution for injection, indicated for the identical therapeutic indications at the same dosage as the reference medicinal product. The applicant is Accord Healthcare S.L.U.

The originator product is Firmagon 80 mg and 120 mg powder and solvent for solution for injection (EU/1/08/504/001-003). No bioequivalence (BE) study was carried out, instead a clinical overview on the clinical pharmacology, efficacy and safety has been provided, and refers to the publications up to year 2021, and thus considered up to date.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder and solvent for solution for injection. The product is available in two strengths, containing 80 mg or 120 mg of degarelix (equal to 84 mg or 126 mg of degarelix acetate, respectively) per vial, and solvent pre-filled in a syringe barrel. After reconstitution of each product strength, each ml of the reconstituted solution contains 20 mg or 40 mg of degarelix, respectively.

The other ingredient of the powder is: mannitol.

The solvent is: water for injections.

As described in section 6.5 of the SmPC, the product is available in:
A glass (type I) vial with bromobutyl rubber stopper and aluminium-plastic cap containing the powder.
A glass (type I) pre-filled syringe barrel with luer tip and tip cap, fluoropolymer coated bromobutyl rubber containing the solvent.
The product is considered a drug-device combination product. Besides the medicinal product (vial with powder), and the syringe barrel pre-filled with solvent, the following CE-marked medical devices are co-packaged in the same tray: vial adapter and sterile hypodermic needle for single use (25 G 0.50 x 25 mm). The tray also contains a plunger rod, which is to be attached to the syringe barrel prior to use. The presentations for the 80-mg strength consist of one or three trays in a cardboard box, the presentation for the 120-mg strength consists of two trays in a cardboard box.

2.2.2. Active Substance

2.2.2.1. General Information

The chemical name of degarelix acetate is *N*-Acetyl-3-(naphthalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-({[(4*S*)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl}amino)-L-phenylalanyl-4-ureido-D-phenylalanyl-L-leucyl-*N*^{6}-(1-methylethyl)-L-lysyl-L-prolyl-D-alaninamide acetate corresponding to the molecular formula $C_{82}H_{103}ClN_{18}O_{16}\cdot xC_2H_4O_2$.

The amino acid - three letter code sequence is:

Ac-D-2Nal^1-D-4Cpa^2-D-3Pal^3-Ser^4-4Aph(L-Hor)^5-D-4Aph(Cbm)^6-Leu^7-Lys(iPr)^8-Pro^9-D-Ala^{10}-NH2

Where: 2Nal is 2-Naphthylalanine, 4Cpa is 4-Chlorophenylalanine, 3Pal is 3-Pyridylalanine, Hor is hydroorotyl, Lys(iPr) is *N*6-Isopropyllysine, 4Aph is 4-Aminophenylalanine, and Cbm is the carbamoyl group.
The active substance has a relative molecular mass of 1632.26 g/mol (as free base) and the following structure:

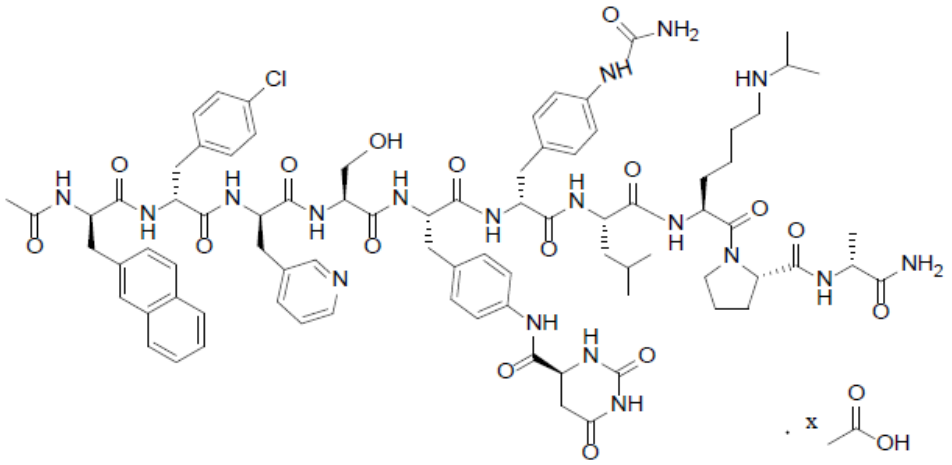

Figure 1: Active substance structure

The elucidation of the chemical structure of degarelix and the measurement of its solid-state properties were performed by amino acid analysis and the following tests: UV, IR, MS, NMR (^{1}H, ^{13}C, DEPT, COSY, HSQC and HMBC), XRPD, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), circular dichroism spectrum, amino acid complete sequence test, amino acid composition and configuration analysis, FTIR, amino acid ratio, and elemental analysis.

The active substance is a white or off-white hygroscopic and amorphous powder, very slightly soluble in N,N-dimethylformamide, soluble in water and 1% acetic acid, and slightly soluble in methanol and ethanol.

Degarelix is a synthetic linear decapeptide composed of 10 amino acids in the backbone, each of which has a chiral center, plus 1 chiral center (L-Hor) on the side chain of 5 L-Aph, resulting in 11 chiral centers in total. Seven of the amino acids are unnatural, five of which are D-amino acids. Enantiomeric purity is controlled routinely by control of chirality of individual protected amino acid starting materials, and by the active substance specification.

Polymorphism is not critical due to the administration of the product as a solution.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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

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, the control is in line with relevant ICH and EU guidelines.

The active substance is not provided sterile.

2.2.2.3. Specification(s)

The active substance specification includes tests for: appearance (visual), optical rotation (Ph.Eur.), identity (IR, HPLC, MS), acidity (pH by Ph.Eur.), related substances (three HPLC methods), isomer XI (GC-MS), oligomers (HPLC-SEC), amino acid ratio (HPLC), acetic acid (HPLC) and trifluoroacetic acid content (HPLC),residual solvents (GC), water content (Ph.Eur.), sulfated ash (Ph. Eur.), nickel (ICP-MS), bacterial endotoxin (Ph.Eur),microbiological quality (Ph.Eur) and assay (HPLC).

ICH Q3A is not strictly applicable to synthetic peptides, Ph. Eur. substances for pharmaceutical use (general monograph 2034) thresholds for synthetic peptides apply. The proposed limits for individual impurities are compliant with Ph.Eur. monograph 2034.

Residual solvent specification limits are based on ICH Q3C or based on observed data.

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 for three commercial scale batches of active substance are provided. The results are within specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in packaging representative for the proposed commercial packaging for up to 24 months under long term conditions (5°C ±3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions were also provided as part of analytical method validation.

The following parameters were tested in the long term and accelerated studies: appearance, optical rotation, identification, pH (acidity), related substances (HPLC methods 1, 2, 3), isomer XI, oligomers, assay, acetic acid, water, microbial quality, and bacterial endotoxins. Both at accelerated conditions and at long-term

conditions, all tested parameters remained within the specification limits; total impurities increased in parallel to the increase of degradation impurities. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed re-test period and storage condition

2.2.3. Finished medicinal product

2.2.3.1. Vial with powder

Description of the product and Pharmaceutical development

The finished product is Degarelix Accord, powder and solvent for solution for injection, is presented in two strengths: 80 mg and 120 mg. The finished product is provided as a vial with white or off-white powder, and a pre-filled syringe barrel with the solvent (sterile water for injections).

There is an overfill to assure the withdrawal of 80 mg or 120 mg of degarelix from the vial. The overfill was adequately justified.

The finished product was developed as a generic to the reference medicinal product Firmagon®.

The two excipients present in the formulation (mannitol and water for injections) 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 excipients are included in section 6.1 of the SmPC.

The quality target product profile (QTPP) was defined as a sterile lyophilised powder for subcutaneous injection (after reconstitution), in two strengths (80 mg and 120 mg), enabling administration of a starting dose of 240 mg via two separate subcutaneous injections of 40 mg/mL, and a maintenance dose of 80 mg in a single subcutaneous injection of 20 mg/mL, containing the same active substance salt (degarelix acetate) and the same excipient (mannitol) as the reference medicinal product and bioequivalent and with quality attributes, container closure system and in-use conditions after reconstitution with water for injections equivalent to the reference medicinal product.

The following CQAs were identified: appearance, identity, pH, related substances, water content, optical density, viscosity, assay, sterility, and bacterial endotoxins.

Considering that the reference medicinal product contains the same active substance and excipient (mannitol) in the same quantities, and the stability data package from the applicant, compatibility between active substance and the excipient was sufficiently demonstrated.

The applicant has utilised quality by design principles in the formulation development and manufacturing process development. The formulation and manufacturing process development have been evaluated through the use of risk assessment to identify the product CQAs, critical process steps and critical process parameters that may have an influence on the finished product quality attributes. The critical process parameters have been adequately identified.

The key aspects of the development were to optimize formulation variables that could potentially negatively impact finished product CQAs.

The nature of the active substance (a heat-sensitive peptide), and the need for a sterile formulation, justify the choice of sterile filtration with aseptic processing as manufacturing method. Compatibility of the product with manufacturing materials was adequately demonstrated.

Medial fill studies and process validation were adequately performed.

Suitable holding times and conditions were defined for the manufacturing process. Degarelix has a self-aggregation property and a tendency to gelatinize. The product forms a gel depot when injected subcutaneously, which results in gradual release of the peptide. According to the literature, plasma/tissue proteins are essential for the degarelix depot formation. To characterize gelling kinetics, in-vitro studies were performed.

To simulate the slow release of the drug from this depot, an in-vitro drug release method was developed.

The applicant demonstrated essential similarity to the reference medicinal product Firmagon® based on in-vitro studies following FDA´s draft product specific guidance on degarelix acetate, comparing test attributes related to primary and secondary structure, purity, physicochemical properties, gelling kinetics, in vitro drug release, and biological activity.

The results of immunogenicity testing showed no strong immune response.

The container closure system of Degarelix Accord 80 mg and 120 mg consists of a 10 mL glass (Type I) vial, with bromobutyl rubber stopper and aluminium-plastic cap.

The primary packaging material complies with Ph.Eur. and EC requirements. 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

Responding to a Major Objection (MO) raised during the procedure, the applicant provided suitable clarification on the extension of validity of GMP certificate (in the context of the Covid-19 pandemic) covering the applicable areas, workshops and activities of the manufacturing site.

Several holding times and conditions are established, which were acceptably justified.

Major steps of the manufacturing process have been validated by a number of studies.

Process validation (with three commercial scale batches per product strength) demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (UV, HPLC), pH (Ph.Eur.), reconstitution time (in-house), related substances (two HPLC methods), oligomers (SEC), acetic acid (HPLC), water content (Ph.Eur.), optical density (Ph.Eur.), viscosity (Ph.Eur.), visible particles (Ph.Eur.), sub-visible particles (Ph.Eur.), bacterial endotoxins (Ph.Eur), sterility (Ph.Eur), uniformity of dosage units (Ph.Eur.) and assay (HPLC).

During the evaluation procedure, two MOs were raised on the specifications of the finished product: one on the proposed impurity limits which were consequently tightened in line with the qualification threshold set in

Ph. Eur. 2034 and the available batch data; and one on the proposed viscosity range, which was consequently tightened in line with the available batch data. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 commercial scale batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Overall, 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 commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of each strength of finished product, stored for up to 24 months under long term conditions (25°C / 60% RH), 12 months under intermediate conditions (30°C / 65% RH), and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided, with vials placed in both upright and inverted positions. The product is in a single use packaging and batches used for stability were identical to those proposed for marketing and were packaged in the primary packaging proposed for marketing.

The following parameters were tested: appearance, pH, reconstitution time, related substances 1 and 2, acetic acid, water, oligomers, optical density, viscosity, visible and sub-visible particles, bacterial endotoxins, sterility and assay. The analytical methods used were the same as for release and were stability indicating. In the accelerated stability study, after 6 months storage, some individual impurities as well as total impurities were out of specification, both in product stored in upright and inverted position, and for both product strengths. There was no trend visible for the other tested attributes. In the intermediate stability study, after 12 months storage, one individual impurity increased to the stability limit with an upward trend for other individual impurities and for total impurities (but still within specifications), both in product stored in upright and inverted positions, and for both strengths. There was no trend visible for the other tested attributes.

In the long-term stability study, after 24 months storage, an upward trend was visible for some individual impurities and total impurities, but less pronounced than under the accelerated and intermediate studies, with all results well within specification limits, both in product stored in upright and inverted positions, and for both strengths. There was no trend visible for the other tested attributes.

One commercial scale batch of each strength was tested for photostability (ICH Q1B); this study demonstrated that the product is stable to light exposure.

An in-use study was performed for both product strengths, with fresh product and product close to expiry. The powder was reconstituted with water for injections as per the instructions in the package insert, and then drawn up and stored in the syringe for 0, 1, 2, and 4 hours at room temperature to simulate pre-administration storage. Then the solution was tested for appearance, pH, osmolality, related substances 1 and 2, assay, optical density, viscosity, oligomers, and visible and sub-visible particles. Test results demonstrated chemical and physical in-use stability for 4 hours at 25°C, as stated in the SmPC (section 6.3).

Based on available stability data, the proposed shelf-life of 24 months and storage condition `Store below 25°C, as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

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

2.2.3.2. Solvent – water for injections in pre-filled syringe barrel

Since the solvent (WFI) is an excipient of the medicinal product (and included in section 6.1 of the SmPC) and the syringe barrel serves both as primary container closure system, and as administration device (after mounting of the plunger), the applicant provided both a 'drug product' section and evidence of compliance with the GSPRs from the Medical Devices Regulation for the WFI-pre-filled syringe barrels.

The syringe barrels pre-filled with 3 mL of WFI are to be used with the 120 mg strength vials; the syringe barrels pre-filled with 4.2 mL of WFI are to be used with the 80 mg strength vials.

The reference medicinal product Firmagon has the same solvent (water for injections).

The primary packaging is a Glass (type I) syringe barrel with luer tip and tip cap and a fluoropolymer coated bromobutyl rubber plunger. The material complies with Ph.Eur. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Compatibility of the manufacturing materials, including extractables and leachables testing, was adequately demonstrated.

The syringe barrels filled with WFI are terminally sterilised.

Manufacture of the product and process controls

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 WFI-pre-filled syringe barrels of intended quality in a reproducible manner.

Container closure integrity post-sterilisation was validated and demonstrated that the container closure system of the WFI-filled barrels ensure adequate product integrity. The in-process controls are adequate for this filling/stoppering and terminal sterilisation process for the WFI-pre-filled syringe barrels.

Product specification(s)

The release specifications for the WFI-pre-filled syringe barrels include appropriate tests for this kind of dosage form: appearance (visual), conductivity (Ph.Eur.), oxidisable substances (Ph.Eur.), residue on evaporation (Ph.Eur.), visible particles (Ph.Eur.), sub-visible particles (Ph.Eur.), bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.), container content (Ph.Eur.), stopper sliding force (in-house), tightness of syringe body (in-house).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. No reference standards are used.

Batch analysis results are provided for three commercial scale batches of each fill volume, 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 WFI-pre-filled syringe barrels of each fill volume, stored for up to 18 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of WFI-pre-filled syringe barrels are identical to those proposed for marketing.

Samples were tested for appearance, conductivity, visible particles, sub-visible particles, bacterial endotoxins, sterility, container content, stopper sliding performance and tightness of syringe body. No significant changes have been observed. In addition, one batch of each fill volume was exposed to light as per ICH Q1B guideline. The study demonstrated that light exposure did not cause any change to the WFI-pre-filled barrels.

Based on the available stability data, the proposed shelf-life of 24 months, without any special storage condition is acceptable. The SmPC (section 6.3) however mentions `Store below 25°C` in view of the vials with powder containing the active substance which are co-packaged with a pre-filled syringe barrel, a vial adapter, a needle and a plunger in a tray in a cardboard box.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. During the procedure, 3 MOs were raised to which the applicant responded adequately by 1) clarifying the validity of GMP certificate covering the applicable areas, workshops and activities of the finished product manufacturing site; 2) tightening the acceptance criteria for two impurities (Qualification threshold Ph. Eur. 2034); and 3) tightening the acceptance criteria for viscosity based on batch results, both on the finished product specification (powder vial). 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.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. The QbD approach was used to define the QTPP and identify the CQAs, but no design spaces were claimed for the manufacturing process of the finished product.

2.2.5. 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.

2.2.6. Recommendation(s) 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 was considered acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of Degarelix acetate are well known. As Degarelix acetate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Degarelix Acetate manufactured by Accord Healthcare is considered unlikely to result in any significant increase in the combined sales volumes for all Degarelix 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. Conclusion on the non-clinical aspects

A summary of the literature concerning non-clinical data of Degarelix Accord was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for powder and solvent for solution for injection containing degarelix acetate. To support the marketing authorisation application the applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of degarelix acetate based on

published literature. The SmPC is in line with the SmPC of the reference medicinal product.

No formal scientific advice by the CHMP 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

No bioequivalence study or other biopharmaceutic studies have been performed. These studies are not considered necessary based on the following facts:

- The product is solution for subcutaneous administration using the same active substance in the same concentration as the reference product and the same excipients in similar amounts as the reference product.
- Since the generic version of Degarelix acetate contains the same qualitative and quantitative composition as the European reference product the efficacy and safety of the product should be assumed to be the same as that of Firmagon, which has been demonstrated by its continuous clinical use for more than 10 years.
- The essential similarity of the product has been justified by detailed comparative studies. To summarise, essential similarity was justified by performing the following comparisons:
- Compositions of the powder and solvent for solutions for injection
- Physical characterization of the originator product and applied product (appearance, reconstitution time, optical density, viscosity, pH, visible/sub-visible particulate contamination)
- Chemical attributes of the solutions for injections (assay, related substances)
- Primary and secondary sequence comparison
- Gelling kinetics
- in-vitro drug release
- Biological activity, binding studies
- Aggregation states

Degarelix Accord is considered essentially similar to the reference medicinal product Firmagon, Ferring Pharmaceuticals. The justification for not submitting an in vivo bioequivalence study is acceptable.

2.4.2. Conclusions on clinical aspects

The application contains an adequate review of published clinical data. The indications applied are the same as for the reference product, as well as the method of administration, posology, patient population and pharmaceutical form. The absence of bioequivalence studies is acceptable.

Approval is recommended from a clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

None

2.5.2. Pharmacovigilance plan

There are no on-going or planned additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Firmagon (EMEA/H/C/0986). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of the reference medicinal product Firmagon 80 mg powder and solvent for solution for injection and Firmagon 120 mg powder and solvent for solution for injection. The reference product Firmagon is a gonadotrophin releasing hormone (GnRH) antagonist indicated:

- for treatment of adult male patients with advanced hormone-dependent prostate cancer.

- for treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

- as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and 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.

From quality perspective, all issues have been resolved.

3.1. Conclusions

The overall benefit /risk balance of Degarelix Accord is positive.

4. Recommendations

Outcome

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

Degarelix Accord is a gonadotrophin releasing hormone (GnRH) antagonist indicated:

- for treatment of adult male patients with advanced hormone-dependent prostate cancer.
- for treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.
- as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer

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.

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.