29 May 2019
EMA/354142/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Posaconazole Accord

International non-proprietary name: posaconazole

Procedure No. EMEA/H/C/005005/0000

Note

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

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List of abbreviations

ASMF	Active Substance Master File = Drug Master File
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical reference substance
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File, ASMF
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
FID	Flame ionisation detection
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
HME	Hot melt extrusionICH International conference on harmonisation
IR	Infra-red
KF	Karl Fischer titration
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
PE	Polyethylene
Ph. Eur	European Pharmacopoeia
PIL	Patient Information Leaflet
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QC	Quality Control
QL	Quantitation limit
QOS	Quality Overall Summary
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
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TLC	Thin layer chromatography
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultra violet
XRPD	X-Ray Powder Diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 27 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Posaconazole 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 22 February 2018.

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 the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

use in the treatment of the following fungal infections in adults:

- *Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;*
- *Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;*
- *Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;*
- *Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.*

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Posaconazole Accord is also indicated for prophylaxis of invasive fungal infections in the following patients:

- *Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;*
- *Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.*

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 bioequivalence studies with the reference medicinal product Noxafil.

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: Noxafil 40 mg/ml oral suspension
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 25-10-2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/05/320/001

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

- Product name, strength, pharmaceutical form: Noxafil 100 mg gastro-resistant tablets
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 28-04-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/05/320/002-003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Noxafil 100 mg gastro-resistant tablets
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 28-04-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/05/320/002-003
- Bioavailability study numbers: CLCD-023-16; CLCD-024-16

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Kolbeinn Gudmundsson

The application was received by the EMA on	27 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 December 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 February 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 February 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 May 2019
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 Posaconazole Accord on	29 May 2019
The CHMP adopted a report on similarity of Posaconazole Accord with Cresemba (Appendix 1)	29 May 2019
The Applicant for the above mentioned medicinal product was changed to Accord Healthcare S.L.U. on	22 January 2019

2. Scientific discussion

2.1. Introduction

This centralised procedure application is based on Article 10(1) for a generic product as defined in Article 10(2)(b) referring to a so-called reference medicinal product with a marketing authorisation granted in a Member State or in the Community. The active substance posaconazole has been in medicinal use for more than 10 years in the Community. The reference medicinal product is Noxafil 100 mg gastro-resistant tablets.

The product Posaconazole Accord is of the same indication, strength and route of administration as that of the reference medicinal product, having the same qualitative and quantitative composition in terms of active substance and is of the same pharmaceutical form as the comparator product.

The proposed indications for Posaconazole Accord are for refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy and prophylaxis of invasive fungal infections. The recommended loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

The active substance posaconazole is a member of the antimycotics for systemic use, triazole derivatives therapeutic class. The mode of action of posaconazole is by inhibiting the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gastro-resistant tablet containing 100 mg of posaconazole as active substance.

Other ingredients are:

Tablet core: methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate (E1505), xylitol (E967), hydroxypropyl cellulose (E463), propyl gallate (E310), microcrystalline cellulose (E460), colloidal anhydrous silica, croscarmellose sodium, sodium stearyl fumarate.

Tablet coating: polyvinyl alcohol-part hydrolyzed, titanium dioxide (E171), macrogol, talc (E553b), iron oxide yellow (E172).

The product is available in triplex (PVC/PE/PVdC) white opaque-aluminium blister or perforated unit dose blister in cartons of 24 or 96 tablets as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of posaconazole is 4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one corresponding to the molecular formula $C_{37}H_{42}F_2N_8O_4$. It has a relative molecular mass of 700.8 g/mol and the following structure:

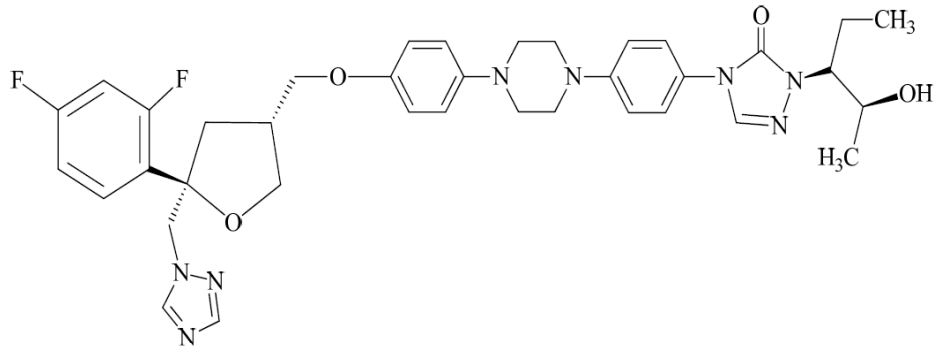

Figure 1: active substance structure.

The chemical structure of posaconazole was elucidated by a combination of spectroscopic techniques such as elemental analysis, ultraviolet, FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry, specific optical rotation

and differential scanning calorimetry (DSC). The solid state properties of the active substance were measured by powder X-Ray diffraction (PXRD).

Posaconazole is a white to off-white colour non-hygroscopic powder, soluble in dichloromethane and insoluble in water and aqueous media ranging from pH 1.2-8.0. It is a chiral compound and possesses four asymmetric carbons. The active form is the (3*R*, 5*R*) (1*S*, 2*S*) isomer. The stereogenic centers originate from the starting materials (2*S* from VPOS3, 3*R*,5*R* from PSZ5). Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.

Posaconazole exhibits polymorphism. As described in literature, it exists in different crystalline forms. The active substance manufacturing process established by the proposed active substance manufacturer,which consistently produces the same form . This has been confirmed by XRD analysis. The polymorphic form has been shown to remain stable during storage of the active substance.

Posaconazole is an established drug substance; however, it is not subject of a monograph in the Ph.Eur.

Manufacture, characterisation and process controls

The manufacturing process of posaconazole (form I) utilizes a convergent strategy and comprises of two branches (Stage 1 and Stages 2/3) with two chemical steps, respectively, before the point of conversion (stage 4).

Two further chemical steps are performed after the point of conversion: Stage-5 followed by Stage-6.

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

The information provided on the manufacturing process in both parts of the ASMF was deemed acceptable. The proposed starting materials are acceptable. A sufficient number of true chemical transformation steps (as per ICH Q11 glossary) separate the proposed starting materials from the final active substance. This is considered adequate to ensure that the generation, fate and control of impurities can be understood and that active substance of appropriate quality is consistently obtained.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
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 ASMF holder provided a discussion and risk assessment on mutagenic impurities, and batch data for potential genotoxic impurities as per the ICH M7 guideline. Absence of carry-over for these impurities has been reported.

A risk assessment for the Class 1 elements , Class 2A elements , Class 3 elementsand Other elements used in the manufacturing process of Posaconazolewas also presented. The absences of carryover these elements was demonstrated in three commercial scale batches of active substance with suitable ICP-MS method.

The active substance is packaged in a clear low-density polyethylene (LDPE) bag tied with a strip and placed inside a black colour LDPE bag and also tied with a stripThe PE coming in direct contact with the active substance meets the requirements of the EMEA Note for guidance on plastic materials. A declaration together with vendor certificate of analysis regarding the suitability of the polyethylene bags for use with food and pharmaceuticals has been provided in line with Ph.Eur. monograph 3.1.3 for Polyolefins and the packaging components in line with Commission regulation (EU) No 10/2011.

Specification

The active substance specification includes tests for description (visual), identification (IR, HPLC), specific optical rotation (Ph. Eur.), water content (KF), sulphated ash (Ph. Eur.), related substances (Ph. Eur.), chiral purity (HPLC), assay (HPLC), residual solvents (GC) and polymorphic identification (PXRD).

The respective limits have been defined in accordance with the requirements described in the Ph. Eur. general chapters and the manufacturer's in-house specifications follow EU and ICH Guidelines. All specified impurities are limited tighter than generally acceptable by ICH Q3A.

Since posaconazole is not a sterile active substance and it is being used to manufacture a solid oral dosage form, microbial quality is not included in the active substance. Microbial quality is addressed in the finished product specification (see relevant section).

A justification for the omission of a particle size specification has been provided and deemed acceptable as not impacting the quality of the finished product.

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 from 5 commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from four commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the marketfor up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, specific optical rotation, water content, related substances, chiral purity, assay and polymorphic identification. The analytical methods used were the same as for release.

All tested parameters were within the specifications. No trends were observed at long term or accelerated conditions.

A forced degradation study was conducted to confirm the stability indicating nature of the assay method. Posaconazole was exposed to elevated temperature, high humidity, sunlight, photodegradation, oxidation, and water, acid and base hydrolysis. The study indicated that posaconazole is slightly sensitive to sunlight exposure and LUX direct, sensitive to thermal and acid exposure, and very sensitive to hydrolysis and peroxide degradation. It is relatively stable to high humidity, UV direct, UV indirect, LUX indirect and water hydrolysis.

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 in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The product is presented as gastro-resistant tablets containing 100 mg of posaconazole.

The tablets are 17.5 x 6.7 mm yellow coated, capsule shaped, debossed with "100P" on one side and plain on the other side.

The pharmaceutical development was focused on developing a product to be identical to Noxafil 100 mg gastro-resistant tablets (EMEA/H/C/000610) manufactured by Merck Sharp & Dohme Ltd. from the European market. Emphasis was given to the preparation of amorphous molecular dispersion by HME which is necessary to produce similar dissolution profiles and to stabilise the composition with regard to impurities.

Due to patent constraints, a qualitatively different composition has been selected for the test formulation when compared to the reference product.

As indicated in the active substance section, a specific posaconazole form is used for the manufacture of the finished product. Posaconazole is a crystalline, white to off-white coloured powder, insoluble in water and aqueous media and practically insoluble at physiological pH (BCS Class 4), and non-hygroscopic. No significant difference in the solubility of diverse posaconazole formsin acidic or in near neutral environment was observed. Thus, it is required to convert the active substance into an amorphous solid dispersion (molecular solution) using similar technology to that of innovator in order to increase active substance solubility at physiological pH and obtain similar dissolution profiles to the reference medicinal product. The properties of the active substance consideredas having a potential effect on the finished product were studied and discussed

The excipients used in Posaconazole Accord 100 mg gastro-resistant tablets were selected based on the excipients used in the reference medicinal product, excipient compatibility studies, prior knowledge on the formulation and experience gained through the preliminary development. A summary of the excipient-drug substance compatibility studies and the selection of each excipient grade has been provided.

Excipient-active substance compatibility was assessed by analysing mixtures of excipient and posaconazole in the solid state. Common excipients functioning as polymer, filler, plasticizer, disintegrant, binder, glidant, lubricant and the film forming material were evaluated. The physical mixtures were stored at 40°C/75 % RH in both open and closed containers. No change in the impurities trend was observed. Subsequent assurance of compatibility of selected excipients was provided by accelerated stability data of development batches and ongoing stability studies using the formulation proposed for commercialization. From the results of ICH stability testing, it is concluded that the active substance is compatible with the excipients of the present formulations and that the formulation is stable.

The excipients in posaconazole Accord gastro-resistant tablets 100 mg are methacrylic acid-ethyl Acrylate Copolymer (1:1) (Type-B) as enteric polymer, xylitol (E967)as processing aid, triethyl citrate (E1505) as plasticiser, hydroxypropylcellulose (E463) as binder, propyl gallate (E310)as antioxidant, microcrystalline cellulose (E460) as diluent, colloidal anhydrous silica as glidant, sodium stearyl fumarate as lubricant and the coating agent (polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc (E553b), iron oxide yellow (E172)) . All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the film coating agent which is not listed in the Ph. Eur, but its single ingredients either comply with it, or were mentioned in the list of approved drug colours to those listed in Commission directive 2008/128/EC and Commission Regulation (EU) No 231/2012 which regulates food and colours. 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 level of excipients used in the formulation was studied conducting an initial risk assessment to investigate the effect of formulation variables that may affect product critical quality attributes (CQAs), followed by subsequent formulation development studies.

Initial development trials were executed based on available literature, patent review, earlier experience on similar molecules and preliminary experimentation to evaluate process feasibility, dissolution and the stability.

The reference manufacturer uses a HME process to convert the active substance to an amorphous molecular dispersion to improve the dissolution and the bio-availability of posaconazole. Hence, as indicated above. emphasis was given to the preparation of an amorphous molecular dispersion for this product using HME, to produce similar dissolution profiles. The polymorphic conversion was confirmed by PXRD analysis. In parallel, work was done to stabilise the composition with respect to impurities.

In this regard, an initial prototype formulation was prepared and subjected to stability studies at accelerated condition to check the suitability of the formulation with respect to the related substances. An unspecified impurity was found at relatively high level in the initial sample and outside the specification limits at 6 months. The forced degradation studies indicated that the impurity is formed under peroxide and thermal degradation, and the addition of an anti-oxidant will reduce the formation of this impurity.

Given the need of a high processing temperaturefor the HME process, and based on earlier experience, it was decided to use propyl gallate in the test formulation to reduce the degradation since this anti-oxidant is relatively stable to temperature that prevails during the manufacturing process. The inclusion of the antioxidant was not sufficiently justified in the dossier, and in line with the guideline on inclusion of antioxidants and antimicrobial preservatives in medicinal products (CPMP/CVMP/QWP/115/95) a Major Objection was raised during the review. The applicant justified the choice of the manufacturing process and further explained that various formulations which different amounts of propyl gallate were manufactured to evaluate the effectiveness on control of impurity by exposing the tablets to accelerated conditions. These were used to perform shelf-life predictions for the product. The predictive value was demonstrated by comparison to real time data. The unspecified impurity was significantly reduced when adding propyl gallate, but lower (and always below the specific limit) when using the highest amount ofantioxidant. Based on these results, it was decided how much propyl gallate shall be used to ensure stability of the formulation throughout shelf life, and to reduce the total weight of the tablet to make the size of generic formulation almost equivalent to the reference product. Considering the posology of the product, the maximum consumption of propyl gallate from the test formulation is negligible when compared to the ADI recommended by either EFSA (30 mg/day) or FAO/WHO Expert committee (84 mg/day) for an average body weight of 60 kg. Therefore, the inclusion of propyl gallate as an antioxidant to prevent posaconazole oxidation in the hot-melt extrusion process is considered acceptable.

The revised test formulation and reference products showed similar dissolution profiles and after exposure of the test product for 6 months at accelerated condition the unspecified individual impurity was well within the specification limits. The content uniformity of posaconazole and propyl gallate was also well within the limits. There was no reduction in the content of propyl gallate upon exposure to the accelerated condition. No form conversion was observed in the finished product.

Subsequently, it was decided to evaluate the impact of specific functional excipients on the dissolution, polymorphism and manufacturability of the generic formulation. Composition of the formulation in the further studies was similar to the revised test formulation, except the amount of the excipient under study, namely methacrylic acid-ethyl acrylate copolymer, triethyl citrate, xylitol, hydroxypropylcellulose, colloidal anhydrous silica, croscarmellose sodium and sodium stearyl fumarate. Constant weight of the tablet was obtained by changing the quantity of diluent microcrystalline cellulose. The composition of generic posaconazole 100 mg gastro-resistant tablets was finalized based on these formulation development trials.

Following these studies, the risk assessment of the formulation variables was updated, resulting in low level of risk for all.The composition of the test product used in the bioequivalence study is same as that proposed for marketing.

As indicated above, posaconazole is insoluble in physiological pH range. Since the selected manufacturing process involves the conversionof posaconazole form to an amorphous molecular dispersion using HME, it was decided to generate the solubility data of the molecular dispersion to have good correlation during selection of medium for *in-vitro* dissolution. The saturation solubility of the molecular dispersion of posaconazole over physiological pH range with and without surfactant indicated that the solubility of posaconazole in phosphate buffer solution pH 6.8 is significantly low when compared to the solubility in presence ofPolysorbate. Hence, phosphate buffer pH 6.8 containing polysorbate was selected as the buffer medium for the dissolution.

Considering the drug release in acid stage, the dissolution was evaluated using 0.01N hydrochloric acid followed by phosphate buffer pH 6.8 containing polysorbate simulating the conditions obtained from the literature search. The test and reference products showed similar dissolution profiles, exhibiting a delayed-release in acid stage followed by a rapid complete release in buffer stage.

To estimate the discriminatory power of the dissolution method used as a routine quality control (QC) test, quantitative changes were made to the final tablet composition and varying the temperature during HME.

Based on the results presented, it can be concluded that the proposed QC dissolution method has adequate discriminatory power to differentiate the bad batches from the good batches at both the specification points. Since the polymorphic form of the API is considered to be a critical process parameter, it was demonstrated that the QC dissolution method is able to detect the presence of crystalline material.

Multimedia dissolution studies on the test and reference product biobatches were also conductedacetate buffer pH 4.5 followed by of phosphate buffer pH 6.8 containing polysorbate. No release after 120 min at pH 4.5 and complete release after 60 min at pH 6.8 buffer stage were observed for both formulations. In both cases, more than 85% of drug was released within 15 min in pH 6.8 buffer stage. This similarity ($f2>50$) was also observed using tight sampling schedule in the buffer stageboth with the QC medium and the multimedia at pH 4.5.

In addition, *in vitro* studies of the release in different concentrations of alcoholic solution were performed to evaluate dose dumping from the formulation of test and reference product. The conditions for dissolution were selected based on the recommendations from the guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and need for in-vitro dissolution studies with alcohol for modified-release oral products as per the EMA Quality of medicines questions and answers: Part 2. In line to these requirements, the release medium was substituted with different concentrations of alcohol. Dissolution of the test product was more or less similar to the reference product and no dose dumping from the test product was observed.

Posaconazole 100 mg gastro-resistant tablets were further compared with the reference product Noxafil® 100 mg with regard to the impurity profile, showing similar related substances in both products.

As discussed earlier in the process selection, the development strategy was to design and develop a stable and bioequivalent generic product of posaconazole gastro-resistant tablets using commonly used excipients and similar to the reference product. HME was selected to prepare a molecular dispersion of posaconazole. The process development was specifically aimed at conversion of posaconazole form to an amorphous molecular dispersion which is the prime requirement to meet the required dissolution profiles because posaconazole is practically insoluble in physiological pH range since it belongs to BCS class-4. An initial risk assessment of the overall manufacturing process and justifications were provided. Earlier experience on similar product with these process steps was used to determine the degree of risk associated with each process step and its potential to impact the CQAs of the finished finished product.

The critical quality attributes (CQAs) of the delayed-release Posaconazole Accord tablets are: impurities and degradants, assay, dose uniformity, water content, dissolution, and polymorphism. It was demonstrated that the particle size distribution of the extrudate has no impact on dissolution and does not constitute a CQA.

Process parameters identified as having high or medium impact where further evaluated at lab scale to define the process parameter settings. Specifically, complete conversion of posaconazole formto amorphous form which ensures the required dissolution profile has been achieved. Hence, testing to ensure complete conversion to amorphous state, i.e. PXRD analysis as the in-process test after completion of the HME process has been defined to ensure desired quality of finished product. A larger batch at commercial scale was subsequently manufactured to verify the lack of impact of scale up on finished product CQAs. The risk assessment of the manufacturing process was updated based on the results of the formulation development studies, and concluded there is no risk in any process step.

According to the guideline EMA/CHMP/QWP/245074/2015, holding time data is not necessary, if the maximum processing time (time from dispensing of the ingredients to the final coating) should normally not exceed 30 days. However, given the criticality of extrudes and that an excess quantity of (left over from previous batch) extrudes can be used in subsequent commercial batches a hold time study for extrudes was performed on one batch stored at room temperature. The data demonstrates that posaconazole extrudes packed in bulk pack and stored at room temperature are stable for the period tested. The bags comply with EU regulation (EU) No. 10/2011, the Directive 2002/72/EC as well as Ph.Eur. chapters 3.1.3 and 3.2.2. Based on these data the proposed shelf life for posaconazole milled extrudes when stored in bulk pack at room temperature is acceptable.

A bulk stability study was performed to evaluate the stability of the product stored or shipped in bulk containers. Two batch samples were stored. The data demonstrates that the tablets stored in bulk are stable for the studied period. Based on these data the shelf lifefor posaconazole 100 mg gastro-resistant tablets when stored in bulk pack has been defined.

The tablets are packed in triplex (PVC/PE/PVdC) white opaque-aluminium blister packs or perforated unit dose blister in cartons of 24 or 96 tablets. The materials comply with relevant Ph. Eur. requirements and/or with the EU regulation No. 10/2011 as amended. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the excipients methacrylic acid-ethyl acrylate copolymer (1:1) (Type-B), triethyl citrate, xylitol, hydroxypropyl cellulose, propyl gallate, cellulose microcrystalline, silica colloidal anhydrous, croscarmellose sodium, sodium stearyl fumarate, the film-coated agent used for manufacture of Posaconazole Accord 100 mg gastro-resistant tablets are not made from and does not come in contact with products of human or animal origin and complies with the requirements of EMA/410/01 Rev. 3. Relevant TSE/BSE certifications have been provided.

The active substance posaconazole is not made from and does not come in contact with the products of human or animal origin.

Manufacture of the product and process controls

The manufacturing process of Posaconazole Accord 100 mg gastro-resistant tablets comprises eleven stages: sifting, granulation, blending, hot melt extrusion, sizing (milling), blending, lubrication, compression, film-coating and packaging.

The process is considered to be a non-standard manufacturing process. The presented in-process controls are considered sufficient

The manufacturing process for was validated at the proposed manufacturing site. Results from process validation on three commercial scale batches have been provided. A process optimisation batch was further improved and the resulting optimised parameter confirmed by two validation batches. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. Overall, the process is considered to be satisfactorily validated. The critical phases were evaluated and the process found to be well controlled producing consistent quality of the medicinal product that complies with the acceptance criteria and finished product specifications.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV, PDA, titanium dioxide, propyl gallate), water (KF), dissolution-acid and buffer stage (HPLC), assay of posaconazole (HPLC), assay of propyl gallate (HPLC), uniformity of dosage units by content uniformity for posaconazole (Ph. Eur.), uniformity of dosage units by content uniformity for propyl gallate (Ph. Eur.), related substances (HPLC) and microbial quality (TAMC, TYMC and *E. coli*) (Ph. Eur.).

As indicated above, posaconazole is optically active (four chiral centres). Each isomer (*SSSS*, *RRRR*, *SSRR*) are controlled as impurity in the active substance Specifications are in line with ICH and/or Ph.Eur. requirements.

Three tests for identification by UV, PDA and HPLC are included in the specification, the specification for the *in vitro* dissolution to be used for quality control is in accordance with EMA/CHMP/QWP/428693/2013 for the acid stage of delayed release dosage forms.

The analyses of inorganic impurities in final product were performed according to the ICH Q3D guideline on elemental impurities. Elements included were Class 1 and Class 2A elements, which should be taken into consideration for oral route of administration as well as a further element, which is not part ICH Guideline Q3D, but intentionally added during the manufacture of the active substance. The control of this element in the finished product specification was considered as unnecessary based on the demonstrated absence of carry-over by a validated ICP-MS method. Among the excipients, microcrystalline cellulose and hydroxypropylcellulose possess the highest potential for introduction for elemental impurities based on their plant origin. Overall, the contribution of excipients was considered low relative to the relevant safety thresholds in the finished product. The manufacturing process and equipment can be discounted as source of elemental impurities based on the process knowledge, equipment design/qualification, equipment cleaning and visual inspection procedures in accordance with GMP. The risk of elemental impurities leaching from the packaging material into a solid dosage form is negligible in accordance with ICH Q3D.

Based on the risk assessment 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. Microbiological quality of the finished product is monitored according to the requirements of Ph. Eur. An accelerated stability study of the exhibit batch demonstrated that the finished product is not capable of supporting microbial growth. Routine microbiological testing of Posaconazole Accord 100 mg gastro-resistant tablets is not necessary. However, for the reason of data collection, skip/periodic microbiological testing will be performed in the course of routine production. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Forced degradation studies are part of the validations of the methods for assay and related substances. Stress conditions such as acid, base, water, humidity, heat, H_20_2 and light (UV/visible) were investigated. The degraded samples were analysed to determine the posaconazole peak purity. The mass balance was also determined. Batch analysis results are provided for three commercial 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 for up to 18 months under long term conditions (25 ºC / 60% RH) and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Posaconazole Accord 100 mg gastro-resistant tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (white opaque PVC/PE/PVdC-Alu blisters), as well as Alu-Alu blisters, white opaque PVC/PCTFE-Alu blisters and HDPE bottles.

Samples were tested for description, identification by HPLC, water content, dissolution, assay of posaconazole, assay of propyl gallate, related substances and microbial quality (TAMC, TYMC and E. Coli). The analytical procedures used are stability indicating.

The finished product is generally very stable. No out of specification results and no degradational trends were observed over time. According to the ICH Q1E guideline and based on the results from accelerated and long term stability studies a shelf-life of 24 months is proposed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant degradation was observed.

Based on available stability data, the proposed shelf-life of 24 months with no storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.2.4. 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. Following the major objection raised during the review, the applicant presented development data to justify the inclusion of the antioxidant propyl gallate (and its level) in the generic formulation in line with the guideline on inclusion of antioxidants and antimicrobial preservatives in medicinal products (CPMP/CVMP/QWP/115/95). 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.

2.2.5. 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. Recommendations for future quality development

n/a

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.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Posaconazole Accord is considered unlikely to result in any significant increase in the combined sales volumes for all posaconazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology for Posaconazole Accord has been provided. The pharmacology, pharmacokinetics and toxicology data are well known for posaconazole and thus new non-clinical data are not required. 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.

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

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects are considered adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Gastro-resistant tablet containing posaconazole. To support the marketing authorisation application, the applicant conducted two bioequivalence studies with cross-over design, under fasting and fed conditions. These studies were pivotal for the assessment.

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

For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), the draft "Posaconazole gastro-resistant tablet 100 mg product specific bioequivalence guidance" (EMA/CHMP/800785/2017), the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and Clinical pharmacology and pharmacokinetics: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000179.jsp&mid=WC0b01ac0580aff2ec) in their current version, are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Not applicable

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies, CLDC-023-16 and CLDC-024-16, in a fasting and in a fed state, respectively.

Table 1 - Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Date of report	BE relevance
Pivotal	CLCD-023-16 (Fed-High fat)	-To demonstrate the bioequivalence of POSACONAZOLE 100 mg GASTRO-RESISTANT TABLETS, with Noxafil® 100 mg Gastro-Resistant Tablets) of Merck Sharp & Dohme Ltd, United Kingdom in healthy adult human male subjects under fed (high-fat) condition. -To monitor the adverse events and to ensure the safety of the study subjects.	The current study was randomized, open label, two treatment, three period, three sequence, single oral dose, crossover, partial replicate, pivotal, bioequivalence study under fed condition.	Test product (T): POSACONAZOLE 100 mg GASTRO-RESISTANT TABLETS Batch number: EC020 Oral administration Reference product (R): NOXAFIL ® 100mg MAGENSAFTRESISTENTE TABLETTEN Batch number: 6N0XA01H00 Oral administration	28.02.2018	Relevant for BE assessment (positive outcome
Pivotal	CLCD-024-16 (Fasting)	-To demonstrate the bioequivalence of POSACONAZOLE 100 mg GASTRO-RESISTANT TABLETS with Noxafil® 100 mg Gastro-Resistant Tablets of Merck Sharp & Dohme Ltd, United Kingdom in healthy adult human male subjects under fasting condition. -To monitor the adverse events and to ensure the safety of the study subjects	The current study was randomized, open label, two treatment, three period, three sequence, single oral dose, crossover, partial replicate, pivotal, bioequivalence study under fasting condition.	Test product (T): POSACONAZOLE 100 mg GASTRO-RESISTANT TABLETS Batch number: EC020 Oral administration Reference product (R): NOXAFIL ® 100mg MAGENSAFTRESISTENTE TABLETTEN Batch number: 6N0XA01H00 Oral administration	01.03.2018	Relevant for BE assessment (positive outcome)

2.4.2. Pharmacokinetics

- **Study CLDC-024-16 – FASTING STUDY**

Methods

Study design

The study was a randomized, open label, two treatment, three period, three sequence, single oral dose, crossover, partial replicate, pivotal, bioequivalence study of Posaconazole Accord 100 mg gastro-resistant tablets, Test (T) with Noxafil® 100 mg magensaftresistente Tabletten, of Merck Sharp & DohmeUnited Kingdom Reference (R) in healthy adult human subjects under fasting condition.

Test and reference products

Posaconazole Accord 100 mg gastro-resistant tablets has been compared to Noxafil 100 mg gastro-resistant tablets, manufactured by Merck Sharp & Dohme United Kingdom.

Population(s) studied

Sixty-six (66) healthy adult male subjects (18 - 42 years old, BMI 18.73 – 29.76 kg/m2) of Asian origin were enrolled and randomized. Seven (7) subjects dropped out or were withdrawn. Fifty-nine (59) subjects completed all three periods. Fifty-nine (59) subjects were used for T/R ratio calculation and 61 subjects were used for Intra-Subject %CV of Reference calculation.

Analytical methods

A LC-MS/MS method by liquid-liquid extraction method for the determination of posaconazole concentrations in K_2EDTA human plasma was successfully validated pre-study and within study. A total of 5253 samples were analysed. A total of 97.18% of samples were found to be within a variation of 20% from the mean value. Long term stability at -70°C nominal was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

Pharmacokinetic variables

The primary pharmacokinetic parameters for this study were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and the secondary pharmacokinetic parameters were T_{max}, K_{el}, $t_{1/2}$, t_{lag} and AUC%_Extrapolated. The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach.

Statistical methods

A parametric ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The ANOVA model included sequence, period, treatment and subject nested within sequence as fixed effects. The test to reference ratio of geometric LS means and the corresponding 90% confidence interval based on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ data were calculated.

Criteria for conclusion of bioequivalence:

For AUC_{0-t} and $AUC_{0-\infty}$:

The test product should be considered bioequivalent to the reference product, if 90% confidence interval for AUC_{0-t} and $AUC_{0-\infty}$ of the transformed natural log ratios of posaconazole between the test and reference formulation is in the range of 80.00% to 125.00%.

For Cmax:

If within-reference intra-subject CV of ln-transformed $C_{max} \leq 30\%$ then the test product should be considered bioequivalent to the reference product, if 90% confidence interval for C_{max} of the transformed natural log ratios of posaconazole between the test and reference formulation is in the range of 80.00% to 125.00%.

If within-reference intra-subject CV of ln-transformed $C_{max} > 30\%$ then C_{max} bioequivalence limit should be widen using scaled-average-bioequivalence.

The test product was considered bioequivalent to the reference product for C_{max}, if both of the following conditions were satisfied:

• The 90% confidence interval for ln-transformed data of C_{max} falls within the newly widen range [U, L] = exp [±k·SWR], which was based upon the within-reference intra-subject CV observed for C_{max}.

• The geometric least square mean ratio (GMR) of test to reference for C_{max} falls within the acceptance range of 80.00–125.00%

Results

Table 2 - Pharmacokinetic parameters for posaconazole (non-transformed values)

Pharmacokinetic parameter (Units)	Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (ng.hr/mL)	10686.563 ± 3035.0335	11003.962 ± 3321.7982
AUC_{0-inf} (ng.hr/mL)	11279.627 ± 3257.7810	11654.570 ± 3735.5790
C_{max}(ng/mL)	338.092 ± 149.4853	367.183 ± 143.0240
T_{max}*(hr)	4.33 (2.00 , 12.00)	5.00 (2.00 , 10.00)

*Median and Range values reported for Tmax

Table 3 - Statistical analysis for posaconazole (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90% Confidence Limits(T vs. R)	Intra Subject CV %
Ln(C_{max})(ng/mL)	92.44	(85.23 , 100.25)	31.33
Ln(AUC_{0-t})(ng.hr/mL)	97.43	(91.85 , 103.34)	22.51
Ln(AUC_{0-inf})(ng.hr/mL)	97.29	(91.69 , 103.23)	22.64

The test to reference ratio of geometric LS means and corresponding 90% confidence interval for the Cmax, AUC0-∞ and AUC0-t were all within the acceptance range of 80.00 to 125.00%.

Safety data

A total of 2 post-dose adverse events were reported by 2 of the 66 subjects included in the study. Two subjects (3.03%) reported 2 adverse events after the single dose administration of the reference product. The reported adverse events were fever and vomiting. The severity of adverse events was mild. The subjects were withdrawn from the study. No severe adverse events were observed during the study. No serious adverse events or deaths were reported during this study. No subject was withdrawn from the study for safety reasons. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

- **Study CLDC-023-16 – FED STUDY**

Study design

The study was an open label, randomised, single dose, 3-period, 3-sequence, crossover bioequivalence study comparing two 100 mg posaconazole gastro-resistant tablets formulations in 66 healthy adult male subjects under fed conditions.

Test and reference products

Posaconazole Accord 100 mg gastro-resistant tablets has been compared to Noxafil 100 mg gastro-resistant tablets, manufactured by Merck Sharp & Dohme United Kingdom.

Population studied

Sixty-six (66) healthy adult male subjects (19 – 44 years, BMI 18.59 – 29.07 kg/m^2) of Asian origin were enrolled and randomized. Fifty-seven (57) subjects completed all three periods and 59 subjects completed two periods (with one Test and one reference) of the study. Samples from 61 subjects (59 subjects were used for T/R ratio calculation and 61 subjects were used for Intra-Subject %CV of Reference calculation) were included in PK and statistical analysis.

Analytical methods

A LC-MS/MS method by liquid-liquid extraction method for the determination of posaconazole concentrations in K_2EDTA human plasma was successfully validated pre-study and within study. A total of 5140 samples were analysed. A total of 99.06% of samples were found to be within a variation of 20% from the mean value. Long term stability at 20±10°C and -70±10°C was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

Pharmacokinetic Variables

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and the secondary pharmacokinetic parameters were T_{max}, K_{el}, $t_{1/2}$, t_{lag} and AUC%_Extrapolated. The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach.

Statistical methods

A parametric ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The ANOVA model included sequence, period, treatment and subject nested within sequence as fixed effects. The test to reference ratio of geometric LS means and the corresponding 90% confidence interval based on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ data were calculated.

Criteria for conclusion of bioequivalence:

For AUC_{0-t} and $AUC_{0-\infty}$:

The test product should be considered bioequivalent to the reference product, if 90% confidence interval for AUC_{0-t} and $AUC_{0-\infty}$ of the transformed natural log ratios of posaconazole between the test and reference formulation is in the range of 80.00% to 125.00%.

For C_{max}:

If within-reference intra-subject CV of ln-transformed $C_{max} \leq 30\%$ then the test product should be considered bioequivalent to the reference product, if 90% confidence interval for C_{max} of the transformed natural log ratios of posaconazole between the test and reference formulation in the range of 80.00% to 125.00%.

If within-reference intra-subject CV of ln-transformed $C_{max} > 30\%$ then C_{max} bioequivalence limit should be widen using scaled-average-bioequivalence.

The test product was considered bioequivalent to the reference product for C_{max}, if both of the following conditions were satisfied:

• The 90% confidence interval for ln-transformed data of C_{max} falls within the newly widen range [U, L] = exp [±k·SWR], which was based upon the within-reference intra-subject CV observed for C_{max}.

• The geometric least square mean ratio (GMR) of test to reference for C_{max} falls within the acceptance range of 80.00–125.00%

Results

Table 4 - Pharmacokinetic parameters for posaconazole (non-transformed values)

Pharmacokinetic parameter (Units)	Arithmetic Means (±SD)	
	Testproduct	ReferenceProduct
$AUC_{(0-t)}$ (ng.hr/mL)	16722.684 ± 4062.1790	16838.426 ± 3945.4968
AUC_{0-inf} (ng.hr/mL)	17870.742 ± 4520.6222	18153.169 ± 4749.1525
C_{max}(ng/mL)	518.009 ± 109.2765	537.304 ± 124.6827
T_{max}*(hr)	6.33 (3.00 , 12.02)	6.33 (2.00 , 12.00)

*Median and Range values reported for Tmax

Table 5 - Statistical analysis for posaconazole (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90%Confidence Intervals	Intra-Subject %CV
$Ln(C_{max})$(ng/mL)	96.60	(93.50 , 99.81)	12.34
$Ln(AUC_{0-t})$(ng.hr/mL)	99.19	(96.80 , 101.63)	9.19
$Ln(AUC_{0-inf})$(ng.hr/mL)	98.64	(96.41 , 100.92)	8.63

The test to reference ratio of geometric LS means and corresponding 90% confidence interval for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptance range of 80.00 to 125.00%.

Safety data

A total of 2 post-dose adverse events were reported by one of the 66 subjects included in the study. One subject (1.52%) reported 2 adverse events after the single dose administration of the test product. The adverse events were fever and perianal abscess. The severity of adverse events was mild. The subject was withdrawn from the study. No severe adverse events were observed during the study. No serious adverse events or deaths were reported during this study. No subject was withdrawn from the study for safety reasons. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Pharmacokinetic Conclusions

Based on the presented bioequivalence studies Posaconazole Accord is considered bioequivalent with Noxafil.

2.4.3. Additional data

No additional data is available. Dissolution studies have been presented to support the dosage form and these are assessed in the quality section.

2.4.4. Pharmacodynamics

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

2.4.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

Based on the presented bioequivalence studies Posaconazole Accord is considered bioequivalent with Noxafil.

2.4.7. Conclusions on clinical aspects

The application contains an adequate review of published clinical data. The bioequivalence has been shown appropriately under fasting and fed conditions between Posaconazole Accord 100 mg gastro-resistant tablets and reference product Noxafil 100 mg gastro-resistant tablets.

The treatment was well tolerated by the subjects enrolled in the study. Posaconazole Accord 100 mg gastro-resistant tablets and Noxafil 100 mg gastro-resistant tablets have similar safety profiles.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Elevated liver enzymes; Hepatotoxicity; Hepatic failure; Hepatitis • Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome • Torsades de pointes • Drug interaction • Injury, Poisoning, and Procedural Complications – Medication Error – Related to potential substitution between different formulations (tablet and oral suspension)
Important potential risks	• Agranulocytosis; Aplastic Anemia • QTc prolongation; Heart Failure; Myocardial infarction • Depression; Suicide • Adrenal Insufficiency • Convulsion; Cerebral ischemia; Cerebral haemorrhage • Pulmonary haemorrhage • Hypertension; Venous thrombosis; Arterial thrombosis • Hypokalemia • Occurrence of any neoplasm/malignancy, especially: Hepatic adenoma; Hepatic neoplasm; Adrenal adenoma; Adrenal neoplasm; Phaeochromocytoma • Fungal infections • Photopsia; Visual brightness; Visual disturbances
Missing information	• Experience in children

The safety concerns listed are in line with the reference Medicinal Product.

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns.

Targeted questionnaires (see RMP Annex) are proposed for the following risks:

- Elevated liver enzymes; Hepatotoxicity; Hepatic failure; Hepatitis (identified risks)
- Torsades de pointes (identified risk)
- Drug interaction (identified risk)
- Agranulocytosis; Aplastic Anemia (potential risk)
- QTc prolongation; Heart Failure; Myocardial infarction (potential risk)
- Adrenal Insufficiency; (potential risk)
- Convulsion; Cerebral ischemia; Cerebral haemorrhage (potential risk)
- Venous thrombosis; Arterial thrombosis (potential risk)

Risk minimisation measures

In line with the reference product, routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

A warning about non-interchangeability of tablets and oral solution is reflected on the outer carton.

Conclusion

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

2.6. Pharmacovigilance

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.

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 Noxafil 100 mg gastro-resistant tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Posaconazole 100 mg gastro-resistant tablets.

The reference product, Noxafil 100 mg gastro-resistant tablets, is indicated for use in the treatment of the following fungal infections in adults:

- *Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;*
- *Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;*
- *Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;*
- *Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;*
- *Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.*

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil gastro-resistant tablets are also indicated for prophylaxis of invasive fungal infections in the following patients:

- *Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;*
- *Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.*

No non-clinical 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 was considered sufficient.

The bioequivalence studies form the pivotal basis, both with a randomized, open label, single dose, three period, crossover design.

The design of the studies was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The basis of the bioequivalence studies under fasting and fed conditions is justified. Choice of dose, sampling points, overall sampling time and wash-out periods were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of posaconazole 100 mg gastro-resistant tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Noxafil (100 mg gastro-resistant tablets). The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

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. Recommendation

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

use in the treatment of the following fungal infections in adults:

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Posaconazole Accord is also indicated for prophylaxis of invasive fungal infections in the following patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

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 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.