29 May 2019
EMA/354180/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Posaconazole AHCL

International non-proprietary name: posaconazole

Procedure No. EMEA/H/C/005028/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
AS	Active substance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CVMP	Committee for Medicinal Products for Veterinary use
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
EP	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
FT-IR	Fourrier Transform Infrared 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 of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LOD	Loss on drying
LDPE	Low Density Polyethylene
LOA	Letter of Access
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 Spectrometry
ND	Not detected
NIR	Near Infrared Spectroscopy

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
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
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
SmPC	Summary of Product Characteristics
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
UPLC/uHPLC	ultra-high performance liquid chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	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 2 June 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Posaconazole AHCL, 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 March 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 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.*
- *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.

Posaconazole AHCL 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 a bioequivalence study 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 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 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 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
- Bioavailability study number: ZPS-635

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	2 June 2018
The procedure started on	21 June 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	11 September 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 September 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 October 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2019

The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 March 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	28 March 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 AHCL on	29 May 2019
The CHMP adopted a report on similarity of Posaconazole AHCL with Cresemba	29 May 2019

2. Scientific discussion

2.1. Introduction

The active substance posaconazole has been in medicinal use for more than 10 years in the Community. The reference medicinal product is Noxafil 40 mg/ml (Marketing authorisation holder: Merck Sharp & Dohme Ltd.; date of the first authorisation: 2005-10-25). The applicant's product Posaconazole AHCL 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 AHCL are, in summary, for refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy and prophylaxis of invasive fungal infections. The recommended dose is 200 mg (5 ml) four times a day. Alternatively, patients who can tolerate food or a nutritional supplement may take 400 mg (10 ml) twice a day during or immediately following a meal or nutritional supplement. 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 oral suspension containing 40 mg/ml of posaconazole as active substance.

Other ingredients are: macrogolglycerol hydroxystearate, sodium citrate dehydrate, citric acid monohydrate, simeticone emulsion (containing polydimethylsiloxane, polyethylene glycol sorbitan tristearate, methylcellulose, silica gel, polyethylene glycol stearate, sorbic acid (E200), benzoic acid

(E210) and sulfuric acid (E513)), xanthan gum, sodium benzoate (E211), liquid glucose, glycerol, titanium dioxide (E171), strawberry flavour (containing propylene glycol), and purified water

The product is available in amber glass bottle (Type III) closed with a child-resistant and tamper evident polypropylene cap and a measuring spoon (polystyrene) with 2 graduations: 2.5 ml and 5 ml 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-3H-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:

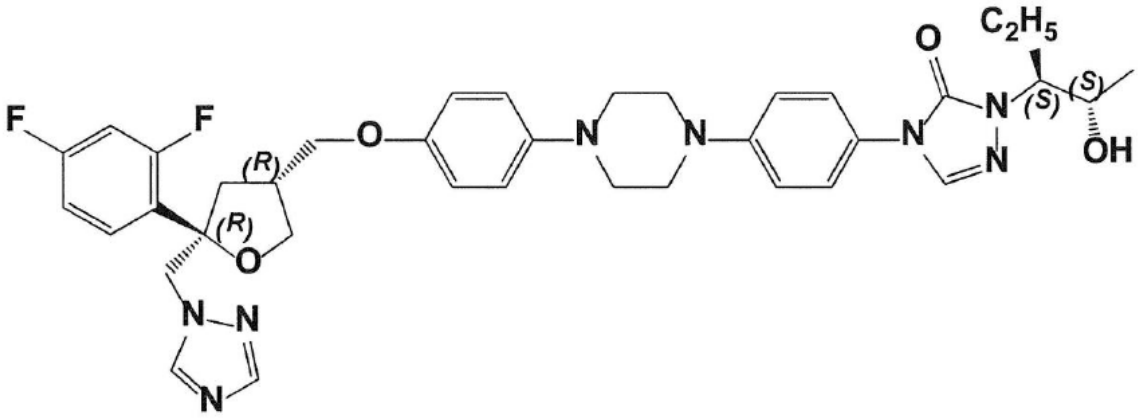

Figure 1: active substance structure.

The chemical structure of posaconazole was elucidated by a combination of ^{1}H and ^{13}C NMR (1D and 2D experiments), MS, IR, UV, DSC and elemental analysis. The obtained spectra were in agreement with the assigned structure.

Additionally, investigations on the polymorphic form were conducted by XRD and IR. Posaconazole displays polymorphism. Results demonstrate that the manufacturing process established consistently results in polymorphic Form I. The polymorphic form remains stable during storage of the active substance. Micronization has no effect on the stability of the polymorphic form I manufactured by the ASMF holder.

Posaconazole polymorphic Form I is a white to off-white non-hygroscopic powder, soluble in dichloromethane and very slightly soluble at pH 1 and insoluble from pH 2 to 14 in aqueous solutions. It is a chiral compound and possesses four chiral centres, whose origin has been discussed. These give rise to 16 different diastereomers in total. The active substance is the (3*R*, 5*R*) (1*S*, 2*S*) diastereoisomer. The correct stereochemistry of each chiral centre is controlled during the manufacturing process. The chiral impurities are limited in the active substance specification either as specified or unspecified impurities. Enantiomeric purity is controlled routinely by specific optical rotation.

Posaconazole is an established active substance. However, it is not subject of a monograph in the Ph.Eur.

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 is considered satisfactory.

The manufacturing process of posaconazole (Form I) utilizes a convergent strategy and comprises of two branches with three and one chemical stages, respectively, before the point of conversion.

All steps of the manufacturing process are conducted by the ASMF holder. The information provided on the manufacturing process in both parts of the ASMF is deemed acceptable.

Neither recovered material nor second crop from the mother liquor is used.

Reprocessing will be performed if any batch of the intermediates and or active substance does not comply with its laid down specification using the same manufacturing steps and solvents as described in the ASMF.

Reworking is not allowed.

The proposed starting materials are acceptable. Five chemical transformation steps in the sense of ICH Q11 separate the proposed starting materials from the final active substance, which is considered sufficient to ensure that the generation, fate and control of impurities can be understood and that it will consistently lead to active substance of appropriate quality.

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.

Specifically, an extensive discussion on the organic impurities arising in the manufacturing process of posaconazole was provided. Generally, impurities are effectively eliminated in the manufacturing stage where they originate and hence the risk of a carry-over to the active substance is low. Furthermore, the relevant impurities are controlled as specified impurities in the respective intermediate specification.

In addition to the discussion of impurities arising from the GMP process, an overview of the impurities arising from the respective starting material synthesis was provided.

Inorganic salts used in the manufacturing process of posaconazole may carry forward to the final stages as inorganic impurities. However, due to high solubility of these salts in water they will get removed along with aqueous washings during the manufacturing process. These impurities are controlled by the test for sulfated ash in the final active substance specification. Palladium is the only elemental impurity intentionally introduced in the manufacturing process of the active substance.). Its carry-over was investigated A test for palladium is included in the active substance specification.

Furthermore, a screening for Class 1 and 2a metals was conducted and levels for these elemental impurities were far below 30% of the respective ICH acceptable limit for parenteral administration.

No Class 1 solvents are employed throughout the manufacturing process. In addition to the discussion of residual solvents arising from the GMP process, an overview of the solvents arising from the respective starting material synthesis has been provided. Relevant solvents are controlled in the active substance specification.

A discussion on potential mutagenic impurities in-line with the requirements of ICH M7 has also been provided. All materials introduced into or originating from the manufacturing process were included in the assessment. In-line with ICH M7, the applicant proposes to control potential mutagenic impurities with no

available safety-data according to the TTC of 1.5 µg/day and a maximum daily dose of 800 mg, resulting in an acceptable limit of 1.875 ppm. The impurities identified with structural alerts were tested in three batches and an appropriate control strategy has been defined.

The active substance is packaged in double polyethylene (PE) bags which are placed inside an aluminium foil bag under nitrogen and stored inside a carton drum. The primary packaging PE bags are in compliance with EU Regulation 10/2011, as well as Ph.Eur. 3.1.3. Satisfactory specifications for the packaging materials has been provided.

Specification

The active substance specification includes tests for description, identification (IR, UPLC), water (Ph. Eur.), specific optical rotation (Ph. Eur.), sulphated ash (Ph. Eur.), palladium (ICP-MS), assay (UPLC), related substances (UPLC), residual solvents (HS-GC/MS), and polymorphism (XRPD).

The specifications adopted by the ASMF holder for posaconazole are derived from ICH guidelines, the Ph.Eur. and actual product behaviour.

As indicated above, the active substance manufacturer assessed posaconazole for elemental impurities in accordance with ICH Q3DPalladium is controlled in the active substance specification. No other Class 1, 2A, 2B or 3 elements are intentionally added in manufacture of posaconazole and, therefore, the risk of these elements is low. Furthermore, as posaconazole is of synthetic origin, the risk of environmentally sourced Class1 and 2A elements is also considered to be low.

The control of potentially mutagenic impurities is adequately discussed and in-line with ICH M7 requirements.

The limit proposed for the specified impurity is based on the qualification thresholds described in ICH Q3A: Impurities in new drug substances.

The only solvent used in the final step of the synthesis of posaconazole is methanol. The specification for methanol has been set in accordance with ICH Q3C.

A justification for omitting microbial quality from the specification was provided. It was based on the fact that posaconazole is manufactured by chemical synthesis and the final crystallisation processing steps utilise organic solvents. Any resulting water content in the active substance, as measured by loss on drying, is very low. Posaconazole is also an antifungal agent and, therefore, a potent inhibitor of yeasts and moulds. Therefore, the risk for microbial contamination in the active substance was considered extremely low. In addition, three commercial scale batches of posaconazole were analysed by the active substance manufacturer to show that the bioburden is very low and well in compliance with the acceptance criteria for substances for pharmaceutical use (Ph. Eur. 5.1.4). Furthermore, the applicant controls the microbial quality of the finished product during release and shelf life testing. Batch analyses results on the finished product (release and stability) showed that the microbiological quality of the finished product is good, with results well below the specification, indicating no microbiological growth.

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 impurity testinghas been presented.

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

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 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*:* appearance, identification (IR and HPLC), water content (KF), specific optical rotation, sulfated ash, heavy metals, Pd (long term conditions only), related substances (HPLC), chiral impurities (HPLC), assay (HPLC), residual solvents and polymorphism (XRD). The analytical methods used were generally the same as for release and were stability indicating. The specification and test method for chiral impurities and residual solvents were revised. The new methods are equal to the proposed routine test methods.Posaconazole was shown to be generally very stable at long-term and accelerated conditions and no specific degradational trends were observed. No conversion of the polymorphic form was observed under both storage conditions.

Photostability was investigated in-line with ICH Q1B on one batch. The active substance did not show signs of degradation after exposure to light without the protection of the primary packaging material. The active substance was hence considered to be photostable.

Stress testing on one batch exposed to the following conditions: acid, alkaline, oxidation, high temperature, photolysis and high humidity was also discussed. The report showed that posaconazole polymorphic form I is stable when exposed to high temperature, photolysis and high humidity. Slight unknown impurities were produced when exposed to acid or alkaline. The highest degradation occurred under oxidizing conditions. Thus, posaconazole polymorphic form I should be protected by nitrogen gas during storage and transportation. Results from mass balance and peak purity demonstrate that the methods for assay and related substances are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container with no special storage condition.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as a 40 mg/mL white to off-white free flowing oral suspension, containing the active substance posaconazole, together with the excipients macrogolglycerol hydroxystearate (wetting agent), sodium citrate dihydrate (buffering agent), citric acid monohydrate (buffering agent), simethicone emulsion 30 % (antifoaming agent), xanthan gum (suspending agent), sodium benzoate (preservative), liquid glucose (sweetener), glycerol (wetting agent),), titanium dioxide (opacifier), strawberry flavour (flavouring agent) and water purified (diluent). Only one solution strength, i.e. 40 mg/mL is proposed. The oral suspension is distributed in 125 mL amber glass bottles (Type III, filled with not less than 105 mL). The bottles are closed with white polypropylene child-resistant and tamper evident caps. The bottles are packed into cartons, along with a polystyrene spoon with 2 graduations (2.5 mL and 5 mL) for administration.

The excipients and container closure systems are common for this type of dosage form. All excipients comply with their respective monographs in the Ph.Eur., except simethicone emulsion 30 % and strawberry-flavour. Simethicone emulsion 30% is of USP quality and its full specification has been included in the dossier. The non-compendial flavouring agent is controlled by in-house specifications, ensuring adequate quality of this excipient. Additional functionality related characteristics of excipients have been discussed. The excipients are well known excipients used in pharmaceuticals and are within the

limits usually recommended for oral suspensions. The function of each excipient has been explained. 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 strawberry flavour used in posaconazole 40 mg/mL suspension was chosen based on experience with other oral suspension manufactured at the same manufacturing site. During the bioequivalence study conducted, test and reference products were randomly given to 31 subjects. No negative observations were reported for the strawberry flavoured test product compared to the cherry flavoured reference product. Therefore, palatability of the test product is considered comparable to that of the reference product.

Based on a daily maximum dosage of 20 mL of Posaconazole Suspension (= 800 mg of posaconazole), the maximum amount of sodium consumed would be 15.6 mg/day. Therefore the following statement has been included in the SmPC: <This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'>.

The finished product Posaconazole AHCL 40 mg/mL oral suspension was developed as a generic product equivalent to Noxafil 40 mg/mL oral suspension (EMEA/H/C/000610) from Merck Sharp & Dohme from the European market. The product is intended as an immediate release product.

The qualitative composition of the finished product is similar to the reference product except for the wetting agent (macrogolglycerol hydroxystearate was replaced by polysorbate 80). Nevertheless, both surfactants have comparable wetting abilities.

The formulation contains the active pharmaceutical ingredient Posaconazole Form-1, which is a non-hygroscopic white to off-white crystalline powder, practically insoluble in water and aqueous media (pH 2-14) and very slightly soluble at pH 1, freely soluble in DCM; slightly soluble in ACN; sparingly soluble in methanol and acetone; very slightly soluble in ethanol and isopropanol.

The following properties of the active substance were considered for having a potential effect on the finished product: isomerism and polymorphism, particle size distribution and stability (studied in the stress study described in the stability section).

Particle size specifications are not being proposed for the active substance. This is acceptable, since the active substance is milled to achieve a desired particle size during the manufacture of the finished product.

The compatibility of the active substance with the proposed excipients was verified by a dedicated compatibility study conducted with tertiary mixtures of the active substance and the excipients as well as sufficient water to make a paste (the finish product is formulated as an aqueous liquid), and through a stability study for scale-up batches under accelerated conditions (6 months, 40ºC/75%RH). From the results it was concluded that the active substance is compatible with the excipients of the proposed formulation and that the formulation is stable.

The finished product manufacturer performed a number of comparative studies to demonstrate that the test product is comparable to Noxafil 40 mg/mL oral suspension. This included assay and impurity profile as well as testing of additional quality attributes: pH; viscosity; density; particle size distribution; sodium benzoate, titanium dioxide and glycerol content; and polymorphic form.

Experiments on initially micronized and non-micronized active substance demonstrated that the required particle size reduction in the finished product is achieved by the proposed manufacturing equipment and parameters. An IPC for particle size reduction was included.

Sodium benzoate is used as an antimicrobial preservative, similar to the reference product. The content of sodium benzoate was investigated at levels well below the WHO limits. Preservative efficacy testing

was conducted for Posaconazole 40 mg/mL oral suspension as well as for placebo product in accordance with the Ph.Eur. The testing demonstrated that chosen level of sodium benzoate is sufficient to preserve the suspension. This level is further supported by stability results under accelerated condition for a scale-up batch. In accordance with CPMP/CVMP/QWP/115/95, a reason for inclusion, a proof of efficacy, safety information and a method of identification/control in the medicinal product have provided for the antimicrobial preservative sodium benzoate. The parameter "Assay of Sodium benzoate" was controlled in an in-use stability study and is part of the stability testing.

The dissolution method for posaconazole oral suspension is based on solubility studies. Posaconazole is insoluble (10 mg/100 mL) over a pH range from 1.2-8. A study was conducted to establish sink conditions From the results it was concluded that a surfactant is required During the marketing authorisation assessment it was noticed that a lower concentration of surfactant that the one originally proposed by the applicant gave a similar, only slightly lower, dissolution profile and therefore, the applicant was requested by the CHMP to further justify the level of surfactant chosen. This led to additional investigation of the sink conditions. Dissolution profiles generated in a medium of 0.1 M HCl without surfactant showed dissolution results comparable to those generated with the originally proposed concentration of surfactant. The re-investigation contradicted the original result and confirmed that sink conditions can be achieved in the selected medium without the addition of surfactant. Therefore, the selected medium with no surfactant was selected as the quality control (QC) dissolution medium.The applicant is using a stirring speed for the QC dissolution test whichis not covered by Ph.Eur. 5.17.1. However, taking into consideration that the finished product is an oral suspension and not a solid oral dosage form (no disintegration phase) and the observed general low variability of results at all tested time points, the employed stirring speed is considered adequately justified and suitable for the intended use.

The discriminatory power of the proposed on method was investigated by comparing unmilled batches with different particle size and batches with different concentrations of the suspending agent xanthan gum. The unmilled batch displayed significant retardation of release. Differences in the xanthan gum level were also observable in the dissolution profiles. Furthermore, the viscosity of the two suspensions are also different and viscosity is part of the finished product specification. Based on these results, the discriminatory power of the dissolution method is considered demonstrated.

The dissolution characteristics of the 40 mg/mL test product (commercial scale) were compared to the innovator Noxafil 40 mg/mL from the European market using the originally proposed QC method (with surfactant) as well as additional media to cover pH 1.2, pH 4.5 (acetate buffer +surfactant) and at pH 6.8 (phosphate buffer + surfactant).

At pH 1.2, the dissolution profiles are different within the first 20 minutes of the dissolution; however, after 30 minutes, the test and reference products showed similar release of the active substance ($f2<50$). No release of the active was observed at pHs 4.5 and 6.8 for both products. To note, all employed dissolution media contained a surfactant contrary to the required dissolution settings as stated in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). This is normally not considered acceptable. However, taking into account the general poor solubility of the active substance in aqueous systems, as well as the non-release of posaconazole under pHs 4.5 and 6.8 even with the addition of the surfactant, the repetition of dissolution experiments without including a surfactant was not be considered of additional value. In addition, since the conducted bioequivalence study demonstrated similarity of test and reference products (see non-clinical/clinical sections), the discrepancies observed *in vitro* did not raise a concern. Dissolution profiles generated in a medium of 0.1 M HCl following the revision of the QC method conditions showed dissolution results comparable to those generated with the originally proposed QC method.

Further, a study was performed to ensure that the suspension can be re-dispersed once settled. Bottles of suspension were centrifuged and each bottle was then vigorously shaken followed by a resting period of up to 25 hours. Uniformity of dosage units was analysed (on doses of 2.5 mL, equivalent to the minimum prescribing dose) after the initial shake and again following the resting period. The results demonstrated that, bottles showing any visible settling should be vigorously shaken for a minimum of 10 seconds to ensure the active substance is well dispersed in the matrix. This is reflected in section 4.2. of the SmPC.

Mass of delivered dose in accordance with Ph. Eur. 2.9.7 was also investigated for both spoon administration volumes (2.5 mL and 5 mL) on the three registration batches. The results presented, demonstrate that the proposed spoon is suitable for use with posaconazole 40 mg/mL suspension.The primary packaging is an amber glass bottle (Type III) closed with a child-resistant and tamper evident polypropylene cap. The filled and sealed bottle is packed into a carton along with a graduated polystyrene spoon (2.5 mL and 5 mL) for dispensing and administration of the suspension. The glass vials are compliant with the Ph.Eur. monograph 3.2.1, "Glass containers for pharmaceutical use". The polypropylene child-resistant and tamper-evident cap comply with ISO 8317:2015 and with EC regulation 10/2011 and its amendments.

The measuring device meets the demand of the medical Directive 93/42/EEC and is CE certified. A certificate from Notified Body 0373 is provided. The uniformity of mass of delivered doses as per Ph. Eur. 2.9.27 is tested upon batch release of the finished product (see specifications section). 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

No excipients of human or animal origin are used in the manufacturing Posaconazole AHCL 40 mg/ml oral suspension.

Manufacture of the product and process controls

Posaconazole 40 mg/mL oral suspension is manufactured using a simple process of combining and mixing the ingredients in a step-wise manner. The formulation is then passed through a mill to reduce the particle size of the entire batch. The resulting suspension is then de-aerated, filtered and filled into the glass bottles. The process is considered to be a standard manufacturing process.

The proposed critical quality attributes (CQAs) and the critical steps in the manufacturing process of the posaconazole 40 mg/ml oral suspension have been thoroughly discussed. The order of addition of the individual premixes, mixer type and its capacity, mixing times and speeds for compounding (IPC) were evaluated during manufacturing process development. The implemented IPC are sufficient for this type of pharmaceutical form.

The bulk hold time of the suspension was initially investigated during development. Analyses of the critical parameters confirmed that the scale-up batch was stable after the studied holding period. Subsequent process validation of commercial scale registration batches established a maximum bulk hold time.

The manufacturing process was validated on three production scale batches. A summary of the in-process information during manufacture has been provided to confirm that the proposed Posaconazole AHCL 40 mg/ml oral suspension can be manufactured according to the proposals in the dossier. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. Appropriate reference to the analytical methods applied during process validation was provided. It has been

demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description, density (Ph. Eur.), pH (Ph. Eur.), viscosity (Ph. Eur.), identification of posaconazole (UV-PDA and UPLC), identification of sodium benzoate (UPLC), identification of titanium dioxide (colour reaction), redispersibility/homogeneity (UPLC), assay of posaconazole (UPLC), assay of sodium benzoate (UPLC), uniformity of mass of delivered dose (Ph. Eur.), related substances (UPLC), dissolution (UV), and microbiological quality (TAMC, TYMC, *E. coli*).

The proposed finished product specification is considered acceptable.

No specified impurities are controlled in the finished product.

Posaconazole is optically active (four chiral centres). Each isomer (SSSS, RRRR, SSRR) is controlled as impurity in the active substance with the limit NMT 0.10%. The isomers are not degradation products, therefore it is acceptable to control their content only in the active substance.

As indicated above, the proposed suspension formulation contains sodium benzoate as an antimicrobial preservative. Microbiological testing has been incorporated as an additional test into the proposed finished product specification. Stability studies also include microbial limits testing.

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. The analyses of inorganic impurities included Class 1 elements and Class 2A elements, which should be taken into consideration for oral route of administration as well as the element Pd, which is not part ICH Guideline Q3D, but intentionally added during the manufacture of active substance. Further class 2b elements and class 3 elements were investigated. The incoming active substance, excipients, manufacturing equipment and utilities, as well as packaging components were evaluated as part of the risk assessment. The limit was calculated by Option 2a of ICH Q3D based on the expected concentration limits of elemental impurities across the finished product components and the maximum daily dose of 0.800 g/day the finished product. The risk assessment concluded that none of the elemental impurities considered is expected to exceed the 30 % oral PDE control threshold. Therefore, there is no need to specify any elemental impurities in final active substance or finished product specification. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Forced degradation studies were performed in connection with the UHPLC methods for assay and related substances (acidic, base, oxidative, heat and light degradation). The highest degradation occurred under oxidative conditions. Peak purity was investigated. Both methods are considered as stability indicating.

Satisfactory information regarding the reference standards used for assay and sodium benzoate testing has been presented.

Batch analysis results for three batches of finished product are presented. All parameters are within the specified limits. Impurities are very well controlled and pH is stable. Therefore, it can be concluded that the process is well controlled and the proposed manufacturer is capable of manufacturing a product within tight quality margins and a consistent impurity profile.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to eighteen months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Bottles were stored in the upright and

inverted position (three batches and one batch, respectively). The batches of Posaconazole AHCL 40 mg/ml oral suspension are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, density, viscosity, pH, redispersibility/homogeneity. assay of posaconazole, assay of sodium benzoate, related substances, dissolution, and microbiological quality (TAMC, TYMC, *E. coli*). The analytical procedures used are stability indicating.

The finished product was generally very stable and no degradation trends were observable over time. Assay remained constant for posaconazole as well as for the preservative sodium benzoate. Overall, a slight decrease in viscosity and a slight increase in related substances were observed for the three batches of posaconazole suspension (upright and inverted) at both storage conditions for the time points tested to date. However, all results remained well within specification. Density, pH, dissolution and microbial quality also remained constant over time. No difference was seen in samples stored in upright or inverted position.

A photostability study was also performed on one batch of posaconazole 40 mg/ml oral suspension as per ICH Q1B. No significant differences in the stressed sample were observed when compared to the unstressed sample and the dark control. All results were well within the proposed specification. Therefore, the finished product is considered to be photostable.

To ensure that the proposed product is stable once opened, an in-use stability study was performed in-line with the requirements of the Note for Guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99), but only on one batch. Bottles were stored in the upright position and in the inverted position. Each bottle was opened each day for 30 days in both the upright and inverted positions.The results showed no significant difference in results when compared to the time zero testing results confirming that the suspension can be used for up to 30 days after opening. To simulate an approximately two-year shelf-life, the same batch was tested for in-use stability after storage at 40 ºC/75 % RH for 6 months (upright and inverted position). All results were well within the proposed specifications, indicating that the product is stable "in-use" over a 24 months shelf-life. In addition, the CHMP recommended to submit in-use stability data on the same batch after storage for 18 months under long term conditions by mid-May 2019 and from a different batch stored for 24 months under long term conditions by November 2019.

Further, a temperature cycling investigation (freeze/thaw) was performed on posaconazole 40 mg/mL suspension in the proposed commercial container closure system. The product is frozen and then exposed to high temperature. In this study bottles of posaconazole suspension were subjected to several cycles of storage between -20 °C and 40 °C. Following the cycling periods the bottles of suspension were visually inspected for any deformations and the suspension was microscopically inspected for any crystallisation. The samples were also analysed and compared to acceptance criteria.

No damage, physical defects, discolouration or leakage of contents was observed over the studied cycle periods for each of the bottles when compared to time zero. No significant differences were observed in the container closure system after completion of the temperature excursion study.Microscopic analysis showed a slight increase in the size of the flakes after the last cycle when compared to time zero , however, this is not considered to be significant. Analytical testing according to the acceptance criteria confirmed that results are well within specification after completion of the temperature excursion study with no changes in particle size distribution. Thus, posaconazole 40 mg/mL Suspension has demonstrated to be stable when subjected to excursions of -20 °C to 40 °C.

Based on available stability data, the proposed shelf-life of 30 months with no special storage conditions as stated in the SmPC (section 6.3) and the in-use shelf life of 30 days (after first opening of the container) are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The proposed product is a generic of Noxafil 40 mg/ml oral suspension (EMEA/H/C/000610). Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. 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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To submit additional supportive in-use stability data from the same batch after storage for 18 months under long term conditions and from a different batch stored for 24 months under long term conditions by November 2019.

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 AHCL manufactured by Accord Healthcare S.L.U. 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 AHCL 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 Oral Suspension containing posaconazole. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fed conditions. This study was the pivotal study 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) are of particular relevance.

GCP

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

The applicant has 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 submitted one bioequivalence study: ZPS-635.

Table 1 - Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
BE	*Hung 2017* [Study Code: ZPS-635 (C17-021.LBB)]	Module 5.3	to evaluate the bioequivalence of the test formulation, 40 mg/ml Posaconazole oral suspension (Douglas), relative to that of the reference formulation, Noxafil® 40 mg/ml Oral Suspension (Merck Sharp & Dohme) following oral administration of a single oral dose of 400 mg (10 ml) in healthy, adult, subjects under fed conditions as well as to monitor the safety and tolerability of subjects	single dose, blinded, balanced, randomised, 2-treatment, 3-period, 3-sequence, single centre, partial replicate, reference scaled, cross-over, oral bioequivalence study, adult, human subjects, fed condition; treatment-controlled	• **Posaconazole 40 mg/ml suspension** • Noxafil® 40 mg/ml Oral Suspension; single oral dose of 400 mg (10 ml) posaconazole	required sample size: 30; enrolled: 37; drop-out prior to participation: 3; received at least one dose: 34; drop-out/withdrawal during study: 3; completed: 31; data set for safety analysis: 34; data set for statistical analysis: 31	healthy, adult, non-smoking, male and female volunteers, 18-55 years of age, with a body mass index greater than or equal to 18.5 and less than or equal to 30.0 kg/m^2, with normal clinical and laboratory results, with no evidence of underlying disease at screening, and who voluntarily provided written informed consent to participate	single dose; during each study period, venous blood (5 ml) was collected prior to dosing (0 hour sample) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 18, 24, 32, 48, 56 and 72 hours post-dose (i.e., 27 blood sample profile/subject); the doses in the three treatment periods were separated by a washout period of 1-week.	completed

2.4.2. Pharmacokinetics

Study ZPS-635: A single dose, blinded, balanced, randomised, two-treatment, three-period, three-sequence, partial replicate, reference scaled, crossover, bioequivalence study comparing 40 mg/ml posaconazole oral suspension (Douglas, New Zealand) with 40 mg/ml Noxafil® oral suspension (Merck Sharp & Dohme ltd, UK) in healthy volunteers under fed conditions.

The primary study objective was to evaluate the bioequivalence of posaconazole (as summarised by C_{max} and AUC) for the two formulations, the test formulation, 1 x 400 mg (10 ml) of 40 mg/ml posaconazole oral suspension, Douglas (Batch No.: A0967), relative to that of the reference 1 and 2 formulation, 1 x 400 mg (10 ml) of 40 mg/ml Noxafil® oral suspension, Merck Sharp & Dohme (Batch No.: M05001), in healthy, adult, subjects under fed conditions in a single-centre, single dose, two treatment, three period, three sequence, partial replicate, reference scaled, randomized study.

Methods

Study design

The study was a single dose, blinded, balanced, randomised, two-treatment, three-period, three-sequence, partial replicate, reference scaled, crossover, bioequivalence study comparing 40 mg/ml posaconazole oral suspension (Douglas, New Zealand) with 40 mg/ml Noxafil® oral suspension (Merck Sharp & Dohme ltd, UK) in 34 healthy volunteers under fed conditions.

Test and reference products

Posaconazole AHCL 40 mg/ml oral suspension manufactured by Accord Healthcare (batch No. A0967; exp. date 24 October 2017) has been compared to Noxafil 40 mg/ml oral suspension manufactured by Merck Sharp & Dohme ltd (Batch No: M05001, exp. date November 2018).

Product Characteristics	**Test Product**	**Reference Product**
Name	Posaconazole	Noxafil ®
Strength	40 mg/ml	40 mg/ml
Dosage Form	suspension	suspension
Manufacturer	Douglas	Merck Sharp & Dohme
Batch number	A0967	M05001
Measured content(s) (% of label claim)	100.7%	99.2%
Expiry Date (retest date)	Oct 2017	Nov 2018
Member State from where the reference product was purchased	N/a	Germany
This product was used in the following trials	ZPS-635	ZPS-635

Population studied

Thirty-seven (37) healthy adult subjects were enrolled and randomized, 34 subjects (14 females and 20 males; 18 - 55 years, BMI 18.5 - 30 kg/m^2) of European, Pacific, Asian, European/Pacific, European/Maori and African origin received at least one dose. Three (3) subjects dropped out prior to dosing. Three (3)

subjects (no. 062-37, no. 034-36 and no. 009-30) dropped out. Thirty-one (31) subjects completed both periods and were included in the pharmacokinetic and statistical analysis.

Analytical methods

A LC-MS/MS method for the determination of posaconazole concentrations in K_2EDTA human plasma was validated pre-study. The internal standard was Posaconazole D5. The calibration curve range during study sample analysis was from 8.0 ng/ml to 2048.0 ng/ml and the quality control concentrations (seeded controls) were 24.0, 220.0 and 1600.0 ng/ml).

A total of 2646 samples were analysed. A total of 48 samples (1.81%) were reanalysed due to IS peak absent. For incurred sample reanalysis 294 samples were run. A total of 90.1% of samples were found to be within a variation of 20% from the mean value. Long term stability at -60°C nominal was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

Pharmacokinetic variables

The pharmacokinetic parameters for this study were AUC_{0-72} and C_{max}, $AUC_{0-\infty}$, T_{max}, $T_{1/2}$ and K_{el}. The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach. The PK analysis software used was SAS® Package (Version 6.0).

Statistical methods

PROC GLM of SAS® software version 6.0 was employed for statistical analysis. A parametric ANOVA was performed on the ln-transformed C_{max}, AUC_{0-72} and $AUC_{0-\infty}$. The ANOVA model included sequence, period and treatment. The test to reference ratio of geometric LS means and the corresponding 90% confidence interval based on the ln-transformed C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ data were calculated. The parameter T_{max} was analyzed using a non-parametric approach.

Criteria for conclusion of bioequivalence:

Bioequivalence will be confirmed by the 90% confidence interval calculated for log normal data falling within the limits 80.00 – 125.00% for $AUC0_{-72}$, and

(iii) 80.00 – 125.00% for C_{max} if the within-subject variability for C_{max} of the reference compound in the study is 30% or less; or

(iv) (a) of a widened acceptance range calculated using scale-average-bioequivalence according to [U,L] = exp[±k.sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log transformed values of C_{max} of the reference product, and

(b) the point estimate of the Test-to-Reference (T/R) geometric mean ratio (GMR) falls within 80.00 – 125.00%.

Results

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

	Arithmetic Means (± SD) [4]		
	Test Product (Treatment B)	Reference Product (Treatment A)	Reference Product (Treatment C)
$AUC_{(0-72)}$ [1]	23298.8 (±8408.4)	22100.5 (±7172.0)	22720.8 (±7116.9)
$AUC_{(0-\infty)}$ [2]	27730.4 (±11096.7)	26287.4 (±9099.1)	26824.9 (±8980.4)
C_{max}	824.4 (±300.4)	773.3 (±262.4)	797.4 (±263.3)
t_{max} [3]	5.00 (4.07,10.00)	5.00 (4.50,31.73)	5.00 (3.50,12.02)

[1] $AUC_{(0-72h)}$ can be reported instead of $AUC_{(0-t)}$, in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

[2] $AUC_{(0-\infty)}$ does not need to be reported when $AUC_{(0-72h)}$ is reported instead of $AUC_{(0-t)}$.

[3] Median (Min, Max)

[4] Arithmetic Means (± SD) may be substituted by Geometric Mean (± CV %)

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

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	CV % [1]
$AUC^{2}_{(0-t)}$	102.79	(97.28,108.61)	14.59
C_{max}	104.27	(98.52,110.36)	16.57

[1] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV % using only the reference product data.

[2] In some cases $AUC_{(0-72)}$

The test to reference ratio of geometric LS means and corresponding 90% confidence interval for the C_{max} and AUC_{0-72} were all within the acceptance range of 80.00 to 125.00%.

Safety data

A total of 15 post-dose adverse events were reported by 11 of the 34 subjects included in the study. Three (3) subjects (8.8%) reported 4 adverse events after the single dose administration of the test product. Eight (8) subjects (25%) reported 11 adverse events after the single dose administration of the reference product. The reported adverse events were sore throat, feeling dizzy/lightheaded, breathlessness, nausea, redness at IV site, pain at IV site, nauseous, flu (head-cold), tired, drowsy, cold, skin reaction to ECG stickers, acute thrombophlebitis. The severity of adverse events was mild or moderate. No severe adverse events were observed during the study. No serious adverse events or deaths were reported during this study. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Conclusions

Based on the presented bioequivalence studies Posaconazole AHCL oral suspension is considered bioequivalent with Noxafil oral suspension.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

To support this generic application for the marketing authorisation of Posaconazole Accord 40mg/ml suspension, the applicant submitted one bioequivalence study, ZPS-635.

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

Based on the presented bioequivalence study Posaconazole AHCL oral suspension can be considered bioequivalent with Noxafil oral suspension.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Posaconazole AHCL and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were considered necessary.

The bioequivalence has been shown appropriately under fed conditions between Posaconazole AHCL 40 mg/ml oral suspension and Noxafil® 40 mg/ml oral suspension.

The treatment was well tolerated by the subjects enrolled in the study. Posaconazole AHCL 40 mg/ml oral suspension and 40 mg/ml oral suspension 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

Summary of safety concerns	
	• 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 version 1.1 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 40 mg/mL oral suspension. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Posaconazole 40 mg/ml oral suspension. The reference product Noxafil is indicated for:

- 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 study forms the pivotal basis, with a single dose, blinded, balanced, randomised, two-treatment, three-period, three-sequence, partial replicate, reference scaled, crossover design summary. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements.

The basis of the bioequivalence study under fed conditions is justified. The bioequivalence has been shown appropriately under fed conditions between Posaconazole AHCL 40 mg/ml oral suspension and Noxafil 40 mg/ml oral suspension. Choice of dose, sampling points, overall sampling time as well as

wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Posaconazole AHCL 40 mg/ml oral suspension met the protocol-defined criteria for bioequivalence when compared with the Noxafil 40 mg/ml oral suspension. 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 decision that the benefit-risk balance of Posaconazole AHCL is favourable in the following indication:

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.

Posaconazole AHCL 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.