Risk Management Plan for

Posaconazole AHCL 40 mg/mL oral suspension

Posaconazole Accord 100 mg gastro-resistant tablets

(Posaconazole)

RMP version to be assessed as part of this application:

RMP Version number	2.1
Data lock point for this RMP	29-Jun-2022
Date of final sign off	29-Jun-2022

Rationale for submitting an updated RMP: RMP has been updated in line with Request for Supplementary Information (RfSI) of Posaconazole Type IB variation (EMEA/H/C/005028/IB/0007/G), dated 31-May-2022.

Summary of significant changes in this RMP:

Significant changes have been done in followings sections of RMP: Part II (Module Module SVII, and Module SVIII), Part VI and Part VII (Annex 7 and Annex 8)

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

Version	Approved with procedure	Date of approval (opinion date)
1.1	Centralised Procedure (EMEA/H/C/005028): [redacted] Centralised Procedure (EMEA/H/C/005005) [redacted]	29-May-2019

QPPV name: Agata Gesiewicz

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Posaconazole
Pharmacotherapeutic group(s)(ATC Code)	Antimycotics for systemic use, triazole derivatives (J02AC04)
Marketing Authorisation Holder	Accord Healthcare SLU, Spain
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Posaconazole AHCL 40 mg/mL oral suspension Posaconazole Accord 100 mg gastro-resistant tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/005028); [redacted] Centralised Procedure (EMEA/H/C/005005); [redacted]
Brief description of the product	Chemical class: Triazole derivatives
	Summary of mode of action: Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.
	<u>Important information about its composition</u> Each mL of oral suspension contains 40 mg of posaconazole. <u>Excipient(s) with known effect:</u> This medicinal product contains approximately 1.75 g of glucose per 5 mL of suspension.

[redacted]

	List of excipients: Macrogolglycerol hydroxystearate Sodium citrate dihydrate 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 (E415) Sodium benzoate (E211) Liquid glucose Glycerol (E422) Titanium dioxide (E171) Strawberry flavour, (containing propylene glycol) Purified water <u>Important information about its composition</u> Each gastro-resistant tablet contains 100 mg of posaconazole. **List of excipients** <u>Tablet core</u> Methacrylic acid-Ethyl acrylate copolymer (1:1) Triethyl citrate (E1505) Xylitol (E967) Hydroxypropyl cellulose (E463) Propyl gallate (E310) Cellulose, microcrystalline (E460) Silica, colloidal anhydrous Croscarmellose sodium Sodium stearyl fumarate <u>Tablet coating</u>

[redacted]

	Polyvinyl alcohol-part hydrolyzed Titanium dioxide (E171) Macrogol Talc (E553b) Iron oxide yellow (E172)
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA Proposed	Posaconazole AHCL 40 mg/mL oral suspension: Posaconazole AHCL oral suspension 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.

[redacted]

	Posaconazole AHCL oral suspension 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. Posaconazole Accord 100 mg gastro-resistant tablets: Posaconazole Accord is indicated for use in the treatment of the following fungal infections in adults • Invasive aspergillosis • 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.

[redacted]

<table>
<tr><td></td><td>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.</td></tr>
<tr><td>Dosage in the EEA
Proposed</td><td>Posaconazole is also available as 100 mg gastro-resistant tablet. Posaconazole tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than Posaconazole oral suspension.

Recommended dose according to indication is shown in below Table:<table><tr><th>Indication</th><th>Dose and duration of therapy</th></tr><tr><td>Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy</td><td>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</td></tr></table></td></tr>
</table>

[redacted]

		immunosuppression, and clinical response.
	Oropharyngeal candidiasis	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. Each dose of Posaconazole AHCL should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure
	Prophylaxis of invasive fungal infections	200 mg (5 mL) three times a day. Each dose of Posaconazole AHCL should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Posaconazole AHCL should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.
	Posaconazole is also available as 40 mg/mL oral suspension and 300 mg concentrate for solution for infusion. Posaconazole	

[redacted]

tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than posaconazole oral suspension.

Recommended dose according to indication

Indication	**Dose and duration of therapy**
Treatment of invasive aspergillosis	Loading dose of 300 mg (three 100 mg tablets or 300 mg concentrate for solution for infusion) twice a day on the first day, then 300 mg (three 100 mg tablets or 300 mg concentrate for solution for infusion) once a day thereafter. Each tablet dose may be taken without regard to food intake. Recommended total duration of therapy is 6-12 weeks. Switching between intravenous and oral administration is appropriate when clinically indicated.
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	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.

	Prophylaxis of invasive fungal infections	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 is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Posaconazole Accord should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.
	Method of administration *Posaconazole AHCL 40 mg/mL oral suspension:* For oral use. The oral suspension must be shaken well before use. Bottles showing any visible settling should be vigorously shaken for a minimum of 10 seconds. *Posaconazole Accord 100 mg gastro-resistant tablets:* For oral use. Posaconazole Accord may be taken with or without food. The tablets should be swallowed whole with water and should not be crushed, chewed, or broken	
Pharmaceutical form(s) and strengths Proposed	Oral suspension (40 mg/mL) Gastro-resistant tablet (100 mg)	

[redacted]

Is the product be subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The methodology used for calculating an estimate of patient exposure for Posaconazole is:

$$\text{Patient-time Exposure in patient treatment years (PTY)} = \frac{\text{Volume sales in mg}}{\text{Defined Daily Dose (DDD) X 365}}$$

WHO - DDD for Paroxetine is 20 mg. considering the same, above mentioned calculation has been done assuming that a patient was administered Posaconazole 0.3 g (i.e 300 mg) daily.

[redacted]

SV.1.2 Exposure

The number of paroxetine tablets distributed by MAH till DLP 04-Feb-2022 along with the calculation of the total amount sold is summarised in table below.

EU-

Region	Product Name	Strength	Pack size	Quantity Sold	Count	Total mg Sold
EU	Posaconazole	100 mg	24	78,183	18,76,392	187639200
			90	4,420	3,97,800	39780000
			96	11,104	10,65,984	106598400
		40 mg	1	8,314	8,314	332560
Grand total						334350160

[redacted]

$$\text{Patient-time Exposure in patient treatment years (PTY)} = \frac{\text{Volume sales in mg}}{\text{Defined Daily Dose (DDD) X 365}} = \frac{837102360}{300 \text{ X } 365} = 7644$$

Based on the sales data and above methodology assumption, the total estimated patient exposure of posaconazole is approximately 7,644 patient treatment years (PTY).

[redacted]

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The safety concerns are updated in line with Request for Supplementary Information (RfSI) of Posaconazole Type IB variation (EMEA/H/C/005028/IB/0007/G), dated 31-May-2022. Further to this, MAH does not propose any change in these safety concerns.

As per the RfSI, the Assessor has recommended to add "Medication error – related to substitution between different formulations (oral suspension and powder for oral suspension)" as an important potential risk in the RMP. MAH has two Posaconazole formulation i.e. gastro-resistant tablets and oral suspension. Hence in line with MAH Posaconazole formulation, "Medication error – related to substitution between different formulations (**tablet and oral suspension**)" has been added as an important potential risk in this RMP.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

[redacted]

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

[redacted]

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Medication error – related to substitution between different formulations (tablet and oral suspension)
Missing information	• Safety in children below 2 years of age

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the mentioned safety concerns.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

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

V.1. Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets (Posaconazole)

This is a summary of the risk management plan (RMP) for Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets. The RMP details important risks of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets, how these risks can be minimised, and how more information will be obtained about Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets risks and uncertainties (missing information).

Posaconazole AHCL 40 mg/mL oral suspension's/ Posaconazole Accord 100 mg gastro-resistant tablets product information and its package leaflet give essential information to healthcare professionals and patients on how Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets should be used.

This summary of the RMP for Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Posaconazole AHCL 40 mg/mL oral suspension's/ Posaconazole Accord 100 mg gastro-resistant tablets RMP.

I. The medicine and what it is used for

Posaconazole Accord is indicated for use in the treatment of the following fungal infections in adults:

- Invasive aspergillosis
- 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;

[redacted]

- 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 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.

It contains posaconazole as a active substance and given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets, together with measures to minimise such risks and the proposed studies for learning more about Posaconazole AHCL 40 mg/mL oral suspension's/ Posaconazole Accord 100 mg gastro-resistant tablets risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and Product Information (PI) addressed to patients and healthcare professionals.
- Important advice on the medicine’s packaging.
- The authorised pack size -the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.

[redacted]

- The medicine's legal status- the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and signal management activity, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important identified risks	• None
Important potential risks	• Medication error – related to substitution between different formulations (tablet and oral suspension)
Missing information	• Safety in children below 2 years of age

II.B Summary of important risks

Routine risk minimisation measures are sufficient to manage the safety concerns of the medicinal product and there is no additional risk minimisation measure required for posaconazole.

[redacted]

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Posaconazole AHCL 40 mg/mL oral suspension/ Posaconazole Accord 100 mg gastro-resistant tablets.

[redacted]