EU/UK Risk Management Plan

for

Voriconazole Accord 50 mg film-coated tablets

Voriconazole Accord 200 mg film-coated tablets

Voriconazole Accord 200 mg powder for solution for infusion

Voriconazole Accordpharma 200 mg Powder for Solution for Infusion

(Voriconazole)

RMP version to be assessed as part of this application:

RMP Version number	7.1
Data lock point for this RMP	13-Nov-2023
Date of final sign off	18-Dec-2023

Rationale for submitting an updated RMP: This RMP has been updated in line with ES agency request and European public assessment report (EPAR) -Risk-management-plan summary of Vfend (Voriconazole) version 6.3, published on 09-Nov-2023.This is a common RMP updated for four procedures.

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part I, Part II (Module SVII and SVIII), Part III, Part V, Part VI and Part VII (Annex 4, Annex 6, 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
[redacted]	[redacted]	[redacted]
6.0	EMEA/H/C/002669 and PLGB 20075/1335-1336	17-Dec-2017
[redacted]	[redacted]	[redacted]

QPPV name: Ms. Agata Gesiewicz

QPPV signature [redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Voriconazole
Pharmacotherapeutic group(s) (ATC Code)	Antimycotics for systemic use, triazole derivatives ATC code: J02AC03
Marketing Authorisation Holder	Accord Healthcare SLU, Spain Accord Healthcare B.V., Netherlands Accord Healthcare Polska Sp. z o.o., Poland
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)/United Kingdom (UK)	Voriconazole Accord 50 mg film-coated tablets Voriconazole Accord 200 mg film-coated tablets Voriconazole Accord 200 mg powder for solution for infusion Voriconazole Accordpharma 200 mg Powder for Solution for Infusion
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/002669) [redacted]
Brief description of the product	*Chemical Class:* Antimycotics for systemic use, triazole derivatives
	Summary of mode of action: Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of

[redacted]

	voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.
	Important information about its composition: ***Voriconazole Accord 50 mg film-coated tablets*** Each tablet contains 50 mg voriconazole *Excipient with known effect* Each tablet contains 63 mg lactose (as monohydrate) ***Voriconazole Accord 200 mg film-coated tablets*** Each tablet contains 200 mg voriconazole. *Excipient with known effect* Each tablet contains 251 mg lactose (as monohydrate). ***Voriconazole Accord 200 mg powder for solution for infusion*** Each vial contains 200 mg of voriconazole ***Voriconazole Accordpharma 200 mg Powder for Solution for Infusion*** Each vial contains 200 mg of voriconazole *Excipient with known effect:* This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e., essentially 'sodium-free'.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA/UK	***Current:*** Voriconazole Accord, is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

[redacted]

<table>
<tr><td></td><td>

Treatment of invasive aspergillosis.
Treatment of candidaemia in non-neutropenic patients.
Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
Treatment of serious fungal infections caused by Scedosporium spp. And Fusarium spp.
Voriconazole Accord should be administered primarily to patients with progressive, possibly life-threatening infections.
Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

</td></tr>
<tr><td>Dosage in the EEA/UK</td><td>
Current:

<u>Posology</u>

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.

<u>Treatment</u>

Adults

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral voriconazole to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96 %), switching between intravenous and oral administration is appropriate when clinically indicated. Detailed information on dosage recommendations is provided in the following table:
<table>
<tr><td></td><td>Intravenous</td><td colspan="2">Oral</td></tr>
<tr><td></td><td></td><td>Patients 40 kg and above*</td><td>Patients less than 40 kg*</td></tr>
</table>
</td></tr>
</table>

[redacted]

<table>
<tr><td></td><td>
<table>
<tr><td>Loading dose regimen (first 24 hours)</td><td>6 mg/kg every 12 hours</td><td>400 mg every 12 hours</td><td>200 mg every 12 hours</td></tr>
<tr><td>Maintenance dose (after first 24 hours)</td><td>4 mg/kg twice daily</td><td>200 mg twice daily</td><td>100 mg twice daily</td></tr>
</table>
* This also applies to patients aged 15 years and older

See the product information for full details on posology.

<u>Method of administration</u>

For Oral film-coated tablets

Voriconazole Accord film-coated tablets are to be taken at least one hour before, or one hour following, a meal

For Powder for Solution for Infusion

Voriconazole requires reconstitution and dilution prior to administration as an intravenous infusion. Not for bolus injection.
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:

Film-coated tablets (50 mg and 200 mg)

Powder for Solution for Infusion (200 mg)</td></tr>
<tr><td>Is the product subject to additional monitoring in the EU/UK?</td><td>No</td></tr>
</table>

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

Not applicable.

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

[redacted]

Module SVII – Identified and potential risks

The safety concerns updated in this voriconazole RMP are in line with European public assessment report (EPAR) - Risk-management-plan summary of Vfend (Voriconazole) version 6.3, published on 09-Nov-2023. Hence, this section remains "Not applicable" for 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

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

SVII.3.2 Presentation of the missing information

Not applicable

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Phototoxicity • Squamous cell carcinoma (SCC)
Important potential risks	• None
Missing information	• None

[redacted]

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 to minimise the risks of the product in the proposed indication.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

Table 3: Important identified risk:

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Phototoxicity	*Routine risk communication:* • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • It is recommended that all patients, including children, avoid exposure to direct sunlight during Voriconazole Accord treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF), details are included in SmPC section 4.4. • In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation, details are included in SmPC section 4.4. • If phototoxic reactions occur, the patient should be referred to a dermatologist and voriconazole discontinuation should be considered, details are included in SmPC section 4.4. • If voriconazole is continued despite the occurrence of phototoxicity-related lesions, dermatologic evaluation should be performed on a systematic and regular basis to allow early

Safety concern	Routine risk minimisation activities
	detection and management of premalignant lesions, details are included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* • Prescription only status of the product.
Squamous cell carcinoma (SCC)	*Routine risk communication:* • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, Voriconazole Accord discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist, details are included in SmPC section 4.4. • Voriconazole Accord should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified details are included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* • Prescription only status of the product.

V.2 Additional Risk Minimisation Measures

Additional risk minimisation measures (aRMMs) have been distributed for the risks 'Phototoxicity' and 'Squamous cell carcinoma (SCC)'

[redacted]

Additional risk minimisation measures are listed below, and key elements are summarised in Annex 6 of this RMP.

Additional risk minimisation 1

Educational material for patient: Patient Alert Card for Phototoxicity and Squamous cell carcinoma (SCC)

Objectives:

To increase an awareness of patient regarding the risk of occurrence of phototoxicity and SCC with voriconazole use.

Rationale for the additional risk minimisation activity:

To minimize the risk of occurrence of phototoxicity and SCC by increasing patient awareness of these safety concerns.

Target audience and planned distribution path:

Patients whom voriconazole is prescribed.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including analysis of ADR reports to assess compliance with summary of product characteristic (SmPC) and patient information leaflet/package leaflet (PL) recommendations will allow assessing and judging the success of the risk minimisation measure during routine signal management activity.

Removal of additional risk minimisation activities

Rationale for the removal: In line with reference product Vfend RMP, version 6.3 dated 29-Jun-2023, published by EMA, additional risk minimisation measures of HCP Checklist and HCP Question & Answer Brochure have been removed.

V.3 Summary of risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Phototoxicity	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4. • It is recommended that all Patients, including paediatric patients, should avoid exposure to direct sunlight during voriconazole accord treatment and should use measures such as protective clothing and sunscreen with high sun protection factor (SPF), details are included in SmPC section 4.4. • If phototoxic reactions occur, the patient should be referred to a dermatologist and voriconazole discontinuation should be considered, details are included in SmPC section 4.4. • If voriconazole is continued despite the occurrence of phototoxicity-related lesions, dermatologic	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
	evaluation should be performed on a systematic and regular basis to allow early detection and management of premalignant lesions, details are included in SmPC section 4.4. • In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation, details are included in SmPC section 4.4. • Prescription only status of the product <u>Additional risk minimisation measures:</u> • Patient alert card	
Squamous cell carcinoma (SCC)	<u>Routine risk minimisation measures:</u> • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4. • Squamous cell carcinoma of the skin has been reported in	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
	patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, Voriconazole Accord discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist, details are included in SmPC section 4.4. • Voriconazole Accord should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified, details are included in SmPC section 4.4. • Prescription only status of the product <u>Additional risk minimisation measures:</u> • Patient alert card	<u>Additional pharmacovigilance activities:</u> None

Part VI: Summary of the risk management plan

Summary of risk management plan for Voriconazole Accord 50 mg film-coated tablets, Voriconazole Accord 200 mg film-coated tablets, Voriconazole Accord 200 mg powder for solution for infusion, Voriconazole Accordpharma 200 mg Powder for Solution for Infusion (Voriconazole)

This is a summary of the risk management plan (RMP) for Voriconazole Accord 50 mg film-coated tablets, Voriconazole Accord 200 mg film-coated tablets, Voriconazole Accord 200 mg powder for solution for infusion Voriconazole Accordpharma 200 mg Powder for Solution for Infusion. Throughout this summary product name to refer as Voriconazole Accord. The RMP details important risks of Voriconazole Accord, how these risks can be minimised, and how more information will be obtained about Voriconazole Accord's risks and uncertainties (missing information).

Voriconazole Accord's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Voriconazole Accord should be used.

This summary of the RMP for Voriconazole Accord 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 Voriconazole's RMP.

I. The medicine and what it is used for

Voriconazole Accord is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
- Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.

Voriconazole Accord should be administered primarily to patients with progressive, possibly life-threatening infections.

[redacted]

Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

It contains voriconazole as the active substance and it is given by oral and intravenous route.

Further information about the evaluation of Voriconazole Accord's benefits can be found in Voriconazole Accord's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/voriconazole-accord.

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

Important risks of Voriconazole Accord together with measures to minimise such risks and the proposed studies for learning more about Voriconazole 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 SmPC 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;
- 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 the case of Voriconazole Accord, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Voriconazole Accord are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Voriconazole Accord. 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	• Phototoxicity • Squamous cell carcinoma (SCC)
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified Risk: **Phototoxicity**	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4. • It is recommended that all patients, including paediatric patients, should avoid exposure to direct sunlight during voriconazole treatment and should use measures such as protective clothing and sunscreen with high sun protection factor (SPF), details are included in SmPC section 4.4. • If phototoxic reactions occur, the patient should be referred to a dermatologist and voriconazole discontinuation should be considered), details are included in SmPC section 4.4. • If voriconazole is continued despite the occurrence of phototoxicity-related lesions, dermatologic evaluation should be performed on a systematic and regular basis to

	allow early detection and management of premalignant lesions), details are included in SmPC section 4.4. • In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation), details are included in SmPC section 4.4. • Prescription only status of the product Additional risk minimisation measures: • Patient alert card
Important Identified Risk: **Squamous cell carcinoma (SCC)**	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8 • PIL Sections: 4. • Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, Voriconazole Accord discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist), details are included in SmPC section 4.4. • Voriconazole Accord should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified), details are included in SmPC section 4.4. • Prescription only status of the product Additional risk minimisation measures: • Patient alert card

[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 Voriconazole Accord.

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

There are no other studies in post-authorisation development plan for Voriconazole Accord.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable

Annex 5– Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6 – Details of proposed additional risk minimisation activities

Prior to the use of Voriconazole 50 mg/200 mg film-coated tablets and Voriconazole 200 mg powder for solution for infusion in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to minimise the risk of occurrence of Phototoxicity and Squamous cell carcinoma (SCC) by increasing awareness of patients for these risks.

The MAH shall ensure that in each Member State where Voriconazole 50 mg/200 mg film-coated tablets and Voriconazole 200 mg powder for solution for infusion is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense, or use Voriconazole 50 mg/200 mg film-coated tablets and Voriconazole 200 mg powder for solution for infusion have access to/are provided with the following educational package:

- Patient Alert Card

Patient Alert Card for Phototoxicity and SCC

- Reminds patients of the risk of phototoxicity and skin SCC during voriconazole treatment.
- Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.
- Reminds patients to take steps to minimise the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) during voriconazole treatment and inform HCPs if they experience relevant skin abnormalities.