

EU Risk Management Plan for Clotrimazole**RMP version to be assessed as part of this application:**

RMP Version number: 0.1

Data lock point for this RMP: 03-OCT-2018

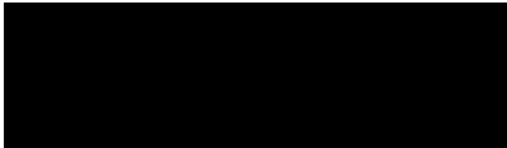
Date of final sign off: 8-NOV-2018

Rationale for submitting an updated RMP: N/A

Summary of significant changes in this RMP: N/A

QPPV name: 

QPPV signature:



QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation by Special Concept Development QPPV.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Clotrimazole
Pharmacotherapeutic group(s) (ATC Code)	G01A F02
Marketing Authorisation Applicant	Special Concept Development (UK) Limited
Medicinal products to which this RMP refers	Clotrimazole
Invented name(s) in the European Economic Area (EEA)	Clotrimazole
Marketing authorisation procedure	National - Initial Application - Article (10) a
Brief description of the product	<p>Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane.</p> <p>Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane.</p> <p>Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc.</p> <p>Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062-8.0 µg/ml substrate. The mode of action of clotrimazole is fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In-vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.</p> <p>Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.</p>
Hyperlink to the Product Information	SmPC PIL
Indication(s) in the EEA	<p>Clotrimazole vaginal tablets are indicated for the treatment of candidal vaginitis.</p> <p>Proposed (if applicable): N/A</p>

Dosage in the EEA	Adults: One 500mg tablet should be inserted at night (Clotrimazole should not be used in the treatment of children and adolescents under the age of 16 years.)
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current: 500mg Tablets
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Not Applicable

Part II: Module SI – Epidemiology of the indication (s) and target population (s)

Not Applicable

Part II: Module SII – Non-Clinical part of the safety specification

Not Applicable

Part II: Module SII – Non-Clinical trial exposure

Not Applicable

Part II: Module SIV – Populations not studied in clinical trials

Not Applicable

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 underrepresented in clinical trial development programmes

Not Applicable

Part II: Module SV – Post-authorisation experience

Not Applicable

Part II: Module SVI – Additional EU requirements for the safety specification

Not Applicable

Part II: Module SVII - Identified and potential risks

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease. • More than two infections of candidal vaginitis in the last 6 months. • Pregnancy or suspected pregnancy. • Known hypersensitivity to imidazoles or other vaginal antifungal products. • Aged under 16 or over 60 years. • Drug Interactions
Important potential risks	<ul style="list-style-type: none"> • N/A
Missing information	<ul style="list-style-type: none"> • Use in children under 16

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

Not applicable

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**

Safety concern	Routine risk minimisation activities
Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> • previous history of sexually transmitted disease or exposure to partner with

	sexually transmitted disease.
More than two infections of candidal vaginitis in the last 6 months.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> more than two infections of candidal vaginitis in the last 6 months.
Pregnancy or suspected pregnancy.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> pregnancy or suspected pregnancy
Known hypersensitivity to imidazoles or other vaginal antifungal products.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> known hypersensitivity to imidazoles or other vaginal antifungal products.
Drug Interactions	<p>Warning is mentioned in SPC section 4,5, 4.8 and PIL section 3:</p> <p>Concomitant medication with Clotrimazole vaginal tablet and oral tacrolimus (FK506; immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.</p>

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

The marketing authorisation application for Clotrimazole 500mg tablets is being submitted under Article 10(a) of Directive 2001/83/EC.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease. More than two infections of candidal vaginitis in the last 6 months. Pregnancy or suspected pregnancy. Known hypersensitivity to imidazoles or other vaginal antifungal products. Aged under 16 or over 60 years. Drug Interactions
Important potential risks	<ul style="list-style-type: none"> N/A
Missing information	<ul style="list-style-type: none"> Use in children under 16

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)**III.1 Routine pharmacovigilance activities**

Routine pharmacovigilance activities for Clotrimazole vaginal tablet 500mg are as per within Directive 2001/83/EC and Regulation (EC) No 726/2004 include, but are not limited to:

- Expedited reporting of spontaneous Individual Case Safety Reports (ICSR) to Regulatory Authorities
- Collation and processing of ICSRs from Post Marketing Studies (PMS)
- Compliant management of information pertaining to cases and follow up information with defined structured and relevant regulatory guidelines
- Periodic reporting of PSUR'S and RMP'S to relevant authorities worldwide
- Signal evaluation and risk management activities
- Training of company personnel

To ensure compliance with current and relevant legislation, the Pharmacovigilance activities performed are regularly reviewed accordingly.

Routine pharmacovigilance activities shall be conducted to identify and characterise the risks of the product.

III.2 Additional pharmacovigilance activities

Not applicable

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)**Risk Minimisation Plan**

All risk minimization measures related to Clotrimazole vaginal tablet will be reviewed if any safety concern is identified in order to ensure that adverse reactions are minimized and the overall benefit-risk profile is maintained.

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

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.	Warning is mentioned in SPC section 4.4 and PIL section 2: Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable: <ul style="list-style-type: none"> previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.
More than two infections of candidal vaginitis in the last 6 months.	Warning is mentioned in SPC section 4.4 and PIL section 2: Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable: <ul style="list-style-type: none"> more than two infections of candidal vaginitis in the last 6 months.
Pregnancy or suspected pregnancy.	Warning is mentioned in SPC section 4.4 and PIL section 2: Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable: <ul style="list-style-type: none"> pregnancy or suspected pregnancy
Known hypersensitivity to imidazoles or other vaginal antifungal products.	Warning is mentioned in SPC section 4.4 and PIL section 2: Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable: <ul style="list-style-type: none"> known hypersensitivity to imidazoles or other vaginal antifungal products.
Drug Interactions	Warning is mentioned in SPC section 4,5, 4.8 and PIL section 3: Concomitant medication with Clotrimazole vaginal tablet and oral tacrolimus (FK506; immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus overdose, if necessary by determination of the respective plasma levels.

V.2. Additional Risk Minimisation Measures

Not applicable

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease. 	None
More than two infections of candidal vaginitis in the last 6 months.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> more than two infections of candidal vaginitis in the last 6 months. 	None
Pregnancy or suspected pregnancy.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> pregnancy or suspected pregnancy 	None
Known hypersensitivity to imidazoles or other vaginal antifungal products.	<p>Warning is mentioned in SPC section 4.4 and PIL section 2:</p> <p>Before using Clotrimazole vaginal tablet, medical advice must be sought if any of the following are applicable:</p> <ul style="list-style-type: none"> known hypersensitivity to imidazoles or other vaginal antifungal products. 	None
Drug Interactions	<p>Warning is mentioned in SPC section 4,5, 4.8 and PIL section 3:</p> <p>Concomitant medication with Clotrimazole vaginal tablet and oral tacrolimus (FK506; immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus overdose, if necessary by determination of the respective plasma levels.</p>	None

Part VI: Summary of the risk management plan

Summary of risk management plan for Clotrimazole vaginal tablet

This is a summary of the risk management plan (RMP) for Clotrimazole vaginal tablet. The RMP details important risks of Clotrimazole vaginal tablet, how these risks can be minimised, and how more information will be obtained about Clotrimazole's risks and uncertainties (missing information).

Clotrimazole vaginal tablet's summary of product characteristics (SmPC) and its package leaflet provides essential information to healthcare professionals and patients on how Clotrimazole vaginal tablet should be used.

I. The medicine and what it is used for

Clotrimazole vaginal tablet is authorised for the treatment of candidal vaginitis

Further information about the evaluation of Clotrimazole vaginal tablet benefits can be found in Clotrimazole's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Clotrimazole vaginal tablet, together with measures to minimise such 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment 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 Clotrimazole vaginal tablet is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Clotrimazole vaginal tablet 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 Clotrimazole vaginal tablet. 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);

List of important risks and missing information	
Important identified risks	<ul style="list-style-type: none"> • Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease. • More than two infections of candidal vaginitis in the last 6 months. • pregnancy or suspected pregnancy. • Known hypersensitivity to imidazoles or other vaginal antifungal products. • Aged under 16 or over 60 years. • Drug Interactions
Important potential risks	<ul style="list-style-type: none"> • N/A
Missing information	<ul style="list-style-type: none"> • Use in children under 16

II.B Summary of important risks

Important identified risks	<ul style="list-style-type: none"> • Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease. • More than two infections of candidal vaginitis in the last 6 months. • Pregnancy or suspected pregnancy. • Known hypersensitivity to imidazoles or other vaginal antifungal products. • Aged under 16 or over 60 years. • Drug Interactions
Important potential risks	<ul style="list-style-type: none"> • N/A

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 Clotrimazole vaginal tablets.

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

There are no studies required for Clotrimazole vaginal tablets.

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Annex 1 – EudraVigilance Interface***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 (if applicable)

Not applicable

Annex 7 - Other supporting data (including referenced material)

Not applicable

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	<At the time of authorisation> <procedure number> dd/mm/yyyy	New RMP <i>Safety concerns at approval include the following:</i> <ul style="list-style-type: none">• Previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.• More than two infections of candidal vaginitis in the last 6 months.• Pregnancy or suspected pregnancy.• Known hypersensitivity to imidazoles or other vaginal antifungal products.• Aged under 16 or over 60 years.• Drug Interactions• Use in children under 16