IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Trimethoprim 10mg/ml Oral Suspension
Trimethoprim
PA1418/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Trimethoprim 10mg/ml Oral Suspension, from Athlone Pharmaceuticals Ltd on 3rd May 2024 for the treatment of infections caused by trimethoprim-sensitive organisms including urinary and respiratory tract infections and prophylaxis of recurrent urinary tract infections. Trimethoprim is indicated in adults and children aged over 12 years and children under 12 years (>6 weeks to <12 years old).

This was a national application. The legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.

This medicinal product is subject to prescription, which may not be renewed.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Trimethoprim 10mg/ml Oral Suspension
Name(s) of the active substance(s) (INN)	Trimethoprim
Pharmacotherapeutic classification (ATC code)	J01EA01
Pharmaceutical form and strength(s)	10mg/ml Oral Suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA1418/005/001
Marketing Authorisation Holder	Athlone Pharmaceuticals Ltd

II. QUALITY ASPECTS

II.1. Introduction

This application is for Trimethoprim 10 mg/ml Oral Suspension

II.2 Drug substance

The active substance is Trimethoprim, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each ml of oral suspension contains 10 mg Trimethoprim.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Trimethoprim 10 mg/ml Oral Suspension

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Monotrim 10 mg/ml Oral Suspension on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Trimethoprim 10 mg/ml Oral suspension is a generic product, it will not lead to an increased exposure to the environment. A justification for the absence of specific ERA studies on the basis of generic substitution was provided.

III.3 Discussion on the non-clinical aspects

This active substance has been available on the European/Irish market for more than 40 years. Preclinical data have been superseded by clinical experience.

Pharmacodynamic, pharmacokinetic and toxicological properties of Trimethoprim are well known. As Trimethoprim is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Non-clinical sections of the SmPC are in accordance with that accepted for the reference product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Trimethoprim is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Monotrim 10mg/ml Oral Suspension, marketed by Taw Pharma (Ireland) Ltd, formerly Chemidex Pharma Ltd, UK.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Trimethoprim 10mg/ml Oral suspension is compared with the pharmacokinetic profile of the reference product Monotrim 10mg/ml Oral suspension.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Trimethoprim 10mg/ml Oral suspension, was compared to the reference product Monotrim 10mg/ml Oral suspension, Chemidex Pharma Ltd, UK. Based on the pharmacokinetic parameters of active substance, the reference Monotrim 10mg/ml Oral suspension marketed by Chemidex Pharma Ltd, UK and test Trimethoprim 10mg/ml Oral suspension are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

IV.2 Pharmacokinetics

The pharmacokinetics of trimethoprim are well characterised.

Absorption
Trimethoprim is absorbed rapidly and almost completely following oral administration and maximal plasma concentrations are reached after 1-2 hours. Peak plasma concentrations of about 1 µg per ml have been reported after a single dose of 100mg.

Distribution
Trimethoprim is rapidly and widely distributed to various tissues and fluids, including kidneys, liver, spleen, bronchial secretions, saliva and prostatic tissue and fluid, and the tissue concentrations are generally higher than the plasma concentration. Trimethoprim is bound to plasma proteins to the extent of 42 to 46 % at therapeutic concentrations. Protein binding of trimethoprim is unchanged in uraemic plasma.

Metabolism
The half-life is about 10 hours in patients with normal renal function but up to 20-50 hours in anuric patients.

Elimination
Trimethoprim is predominantly excreted in the urine in unchanged form. Urinary concentrations are generally well above the MIC of common pathogens for more than 24 hours after the last dosage.

IV.3 Pharmacodynamics

Trimethoprim's selective inhibition of bacterial dihydrofolate reductase results in derangements of bacterial protein and nucleic acid synthesis. The critical metabolic pathway inhibited by trimethoprim is thymine synthesis.

Trimethoprim is effective in-vitro against most Gram-positive and Gram- negative aerobic organisms, including enterobacteria - *E. coli, Proteus, Klebsiella pneumoniae, Streptococcus faecalis, Streptococcus pneumonia, Haemophilus influenzae,* and *Staphylococcus aureus*.

It is not active against *Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Treponema pallidum,* or anaerobic bacteria.

Several mechanisms of bacterial resistance to trimethoprim have been described. Intrinsic resistance has been ascribed to cell wall permeability factors that exclude the drug from binding to dihydrofolate reductase, as occurs with Pseudomonas aeruginosa, or the presence of a dihydrofolate reductase that is less susceptible to trimethoprim inhibition, as occurs with *Neisseria meningitidis, Clostridium perfringens,* and *Bacteroides fragilis*. Susceptible strains can develop acquired resistance.

Susceptibility testing before starting trimethoprim should be considered.

IV.4 Clinical Efficacy

No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety

As this is a generic application, no other clinical safety data are required.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Trimethoprim 10mg/ml Oral Suspension.

Summary table of safety concerns in approved RMP:

Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Reports (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Trimethoprim 10mg/ml Oral suspension is a generic form of Monotrim 10mg/ml Oral Suspension. Monotrim 10mg/ml Oral Suspension is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Trimethoprim 10mg/ml Oral suspension demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.