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Public Assessment Report

Scientific discussion

Clotic 10 mg/ml ear drops, solution in single-dose container
(Clotrimazole)

ES/H/0894/001/DC

Date: 05/11/2024

This module reflects the scientific discussion for the approval of Clotic 10 mg/ml ear drops, solution in single-dose container. The procedure was finalised at 05/08/2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This marketing authorisation application (MAA) via the decentralised procedure is made under Article 8.3 of Directive 2001/83/EC. It is a full-mixed application, where Module 4 and 5 of the eCTD consist of a combination of reports of limited non-clinical and clinical studies carried out by the Applicant and of bibliographical references. This medicinal product, under the tradename Clotic, contains an active substance, clotrimazole, that is considered a known active substance.

The product is indicated for the treatment of fungal otitis externa (otomycosis) in adults, adolescents and children over 1 month of age.
A comprehensive description of the indications and posology is given in the SmPC.

On 9 August 2023, having regard to the opinion of the Paediatric Committee (PDCO) issued on 21 July 2023, a decision was adopted by EMA (P/0332/2023) grating a product specific waiver for clotrimazole, ear drops, solution, auricular use for the treatment of fungal otitis externa, for all subsets of the paediatric population (EMEA-003431-PIP01-23), in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

II. QUALITY ASPECTS

II.1 Introduction

Clotic 10 mg/ml ear drops, solution in single-dose container contains clotrimazole as active substance. The solution is packed into LDPE ampoules which will be contained in an aluminium foil overwrap.

II.2 2.2 Drug Substance

Clotrimazole is the active substance which is an antifungal. The INN is clotrimazole and it is slightly hygroscopic and is practically insoluble in water and soluble in ethanol and in methylene chloride. It does not exhibit polymorphism.

The manufacturers of the drug substance and its responsibilities have been disclosed.

The drug substance is adequately characterized and is used according to the requirements laid down in the valid European Pharmacopoeia. The active substance has a CEP and it is submitted assuring the quality of the control tests and specifications for the drug substance. The retest period is included in the CEP.

II.3 Medicinal Product

The manufacturers and its responsibilities of the drug product have been disclosed. A brief description of the manufacturing process and the validation have been presented including satisfactory manufacturing process flow diagram annotated with all the in-process controls has been provided.

The excipients are commonly used for the manufacture of pharmaceutical preparations. The

finished product specifications have been set considering the ICH Q6A and ICH Q3B.

The batch results provided confirm the satisfactory uniformity of the product and indicate the manufacturing process is under control.

Stability studies have been conducted according to ICH stability guidelines. These stability results support the proposed shelf-life of 36 months. This medicinal product does not require any special temperature storage condition and the in-use shelf-life of 30 days with the storage condition “Stored below 25ºC”.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Introduction

Clotrimazole, an imidazole derivative, is used to treat superficial skin infections such as dermatophytes, pityriasis versicolor, and candidiasis. Since clotrimazole is already in use in humans for a long time, a combination of limited non-clinical literature references from published pharmaco-toxicological information from other formulations and routes of administration constitute the body of knowledge for the product, Clotic 10 mg/ml ear drops, solution in single-dose container.

III.2 Pharmacology

Clotrimazole exhibits a broad antifungal spectrum both *in vitro* and *in vivo*, with well-documented antifungal, antibacterial, and antiprotozoal activity. Its minimum inhibitory concentration (MIC) varies across species, with relevant MIC values for otomycosis-causing species such as Aspergillus and Candida being between 1 to 10 µg/mL.

In studies involving animal models like dogs, clotrimazole combined with other agents has proven effective in treating ear infections, eliminating 88% of infections after 10 days of treatment and reducing inflammation and other symptoms. However, these findings are specific to canine infections and may not directly apply to human conditions.

Clotrimazole has also demonstrated secondary pharmacological effects, including inhibition of calcium and potassium channels, reduction of steroid synthesis, and interaction with estrogen receptors in cancer models. These effects are independent of its antifungal action. Due to the low systemic absorption expected after otic administration, no significant off-target effects are anticipated.

As there is a sufficient well-documented clinical experience with clotrimazole, additional safety studies for topical or otic use are not considered necessary under current guidelines.

III.3 Pharmacokinetics

The pharmacokinetics of clotrimazole, based on existing literature, suggest minimal systemic absorption from 1% ear drops. While the ability of the product to penetrate an intact tympanic membrane hasn’t been tested, studies in dogs show that clotrimazole's plasma levels were below quantifiable limits after otic application. Similar results were observed with intravaginal administration, showing no detectable serum levels.

Clotrimazole, like other azole antifungals, inhibits CYP3A4 with high potency. Regarding excretion, more than 90% of clotrimazole is eliminated through feces and 2-4% via urine after oral or intravenous administration in rats.

III.4 Toxicology

No non-clinical toxicology studies were conducted with the new topical otic formulation of clotrimazole. Instead, the toxicological assessment was based on previous studies and literature on clotrimazole 1% from other formulations and routes of administration.

Single-dose toxicity data indicate that the LD_{50} for clotrimazole ranges between 700-900 mg/kg in rodents and 1000-2000 mg/kg in rabbits. Repeated-dose toxicity studies in animals, though not GLP-compliant, showed liver toxicity at higher doses. Reversible liver and adrenal gland changes were noted in both rats and dogs at doses of 50-100 mg/kg.

After daily topical application of clotrimazole 1% solution plus PEG to the middle ear of rats for 5-days, a toxic effect on cochlear function of the inner ear was observed. PEG and other alcoholic solvents have been reported to cause cochlear ototoxicity.

Genotoxicity studies showed no potential for genetic damage, and carcinogenicity studies were deemed unnecessary due to the short treatment duration (up to 14 days).

Reproductive toxicity studies in animals revealed no malformations at doses up to 100 mg/kg/day, though higher doses caused some embryotoxic and fetotoxic effects in rats. Lower doses of 50 mg/kg/day showed no significant maternal or fetal harm.

No studies on dermal irritation or hypersensitivity were conducted due to existing clinical experience.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Given that the levels of clotrimazole to be dosed to patients with this otic medicine are not relevant compared to already approved products and, it is intended for use in acute manifestations of the disease and not chronic administration, a significant increased exposure to the environment is not expected. However, a final conclusion on potential risk of clotrimazole to the environment cannot be drawn as the Applicant did not provide additional ERA studies in this procedure.

The following table summarizes the literature information provided in the procedure.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	4.1	Not potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.1	not B
	BCF	1,691 L/kg	not B
Persistence	DT50 or ready biodegradability	-	-
Toxicity	NOEC or CMR	-	-
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.000364	µg/L	Not > 0.01 threshold
Other concerns (e.g. chemical class)	Potential antibiotic and endocrine effects		Yes

Conclusions on studies:
According to publicly available data, clotrimazole PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

IV. CLINICAL ASPECTS

IV.1 Introduction

Otomycosis, or fungal otitis externa, is a superficial fungal infection of the external auditory canal. The most frequently isolated pathogen is *Aspergillus* spp., followed by *Candida* spp. Otomycosis generally presents with localized pain, pruritus, otorrhea and hearing loss. Worldwide incidence is estimated to be between 5% and 80% of the total number of otitis externa cases, and the highest incidence is observed in tropical or subtropical climates (regions with high temperature and humidity). Known risk factors for otomycosis include pre-existing inflammatory conditions of the ear, participation in aquatic sports and previous use of topical antibiotics for the treatment of otitis. Current therapies for otomycosis include aural toileting and auricular use of antifungal or antiseptics products. In the European Union, only a few medicinal products are authorised in some member states for the treatment of otomycosis. Availability of authorised medicinal products (specially for auricular use) is limited in the European Union and off- label use is common.

Clotrimazole belongs to the azole class of antifungals. Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane.

IV.2 Pharmacokinetics

The Applicant hasn't conducted any pharmacokinetic studies. The Applicant has claimed that, after auricular use of the recommended dose of clotrimazole 10 mg/ml ear drops solution, the measurable systemic levels of active ingredient are expected to be below the levels that are associated with safety concerns of the component. In support of that, the Applicant has claimed that:

a) the available bibliographical data demonstrate the lack of significant systemic exposure following clotrimazole topical administration

b) the permeability characteristics of the skin of the external ear to those and the tympanic membrane are similar to those of the skin in other parts of the body and

c) this is clinically supported by the lack of systemic adverse events observed in the patients treated with clotrimazole for auricular use in clinical trials

IV.3 Pharmacodynamics

Clotrimazole is a known active substance and its mechanism of action is well-described in the literature. There is sufficient bibliographical evidence to corroborate the antifungal *in vitro* activity of clotrimazole against the relevant pathogens in otomycosis (*Aspergillus* spp. and *Candida* spp.). This is

further supported by the antimycological susceptibility testing performed with EUCAST method in the clinical isolates obtained from patients with otomycosis in the phase III trials (CLEAR-1 and CLEAR-2), as well as the efficacy results observed in these studies (mycological eradication and clinical endpoints).

IV.4 Clinical efficacy

The design of the phase III trials CLEAR-1 and CLEAR-2 is generally acceptable. The comparison with placebo is acknowledged taking into account the limited treatment options authorized for otomycosis in the European Union. The selected endpoints were adequate for the clinical and mycological evaluation of otomycosis. Therapeutic cure was defined as both absence of symptoms (pruritus, otalgia, ear fullness and otorrhea) and mycological eradication, and it was evaluated at test of cure (TOC) in a follow-up visit one week after the end of treatment (EOT). The primary analysis was performed only in patients with a positive fungal culture at baseline (MITT). Supportive analysis were planned in the different population analysis sets (CITT and MPP), as well as sensitivity analysis with different imputation methods. The secondary endpoints are valuable to assess the consistency of the efficacy results (separate clinical and mycological endpoints, individual symptoms and a global symptomatic score and evaluation at different timepoints).

The baseline characteristics of the patients were comparable between the clotrimazole group and the placebo (including age, gender, baseline pathogen, bilateral otomycosis and risk factors for otomycosis). A significant proportion of patients were ≥ 65 years (32.5%). Overall in both trials, 42.1% (166/393) of the patients were excluded from the MITT because they did not had a positive baseline culture for *Aspergillus* spp. and/or *Candida* spp. In the MITT, *Aspergillus* spp. was the most frequent fungal pathogen isolated, followed by *Candida* spp. Baseline isolates of both a bacterial and a fungal pathogen in the same patient were common, as well as isolates of both *Aspergillus* spp. and *Candida* spp.

The superiority of clotrimazole 1% solution for auricular use over placebo has been demonstrated for the treatment of fungal otitis externa in adult patients. The results of the primary analysis for the primary efficacy endpoint were statistically significant and clinically relevant in both studies, although the magnitude of the benefit was higher in CLEAR-2 than CLEAR-1 (mean difference in response rate [95% CI]: 30.8% [12.7%, 48.9%] in CLEAR-1 vs 55.8% [39.1%, 72.5%] in CLEAR-2).

The supportive analysis of the primary efficacy endpoint provided statistically significant results in the different population analysis sets (CITT and MPP). In the CITT, that included patients without a baseline fungal pathogen, the magnitude of the benefit was lower than the MITT (primary analysis).
The subgroup analysis provided did not raise any special concerns. The secondary efficacy endpoints indicated that a meaningful benefit was observed from both clinical and mycological variables when evaluated separately at TOC. Considering different timepoints, clotrimazole improved therapeutic cure (clinical+mycological cure) since the EOT. During treatment (Visit 2), a statistically significant improvement was also observed in mycological outcomes and in reduction of total sign/symptoms score (TSSS), but not in clinical cure.

IV.5 Clinical safety

The safety data provided includes the two phase III pivotal trials (CLEAR-1 and CLEAR-2) and a non-inferiority trial with clotrimazole 1% solution for auricular use as the reference drug (EBEROT). A total of 356 clotrimazole-treated patients were evaluated. The proportion of clotrimazole-treated patients that experienced at least one treatment-emergent adverse event (TEAE) was 6.7% in the safety group SG2 (CLEAR-1, CLEAR-2 and EBEROT) and 8.0% in the safety group SG1 (CLEAR-1 and CLEAR-2). Most of the TEAEs were mild and only one TEAE of severe intensity was reported: one case of headache in the EBEROT that was considered not related to the study drug. There were two non-serious TEAE that lead to discontinuation of study drug: application site pain in two patients and tympanic membrane

perforation in one patient. There were no serious adverse events (SAE) or deaths in the clotrimazole-treated patients.

Patients with a perforated tympanic membrane were excluded from the phase III trials CLEAR-1 and CLEAR-2. In the scientific literature, the use of clotrimazole 1% solution (often containing propylene glycol) for auricular administration has been associated with adverse effects such as prolonged pain, stinging and burning sensation in patients with a perforated tympanic membrane. Auricular administration of clotrimazole solution is not recommended in patients with a perforated tympanic membrane since the risk of adverse reactions, including ototoxicity, has not been adequately investigated in clinical studies. If a patient with a perforated tympanic membrane requires treatment with Clotic, close monitoring of adverse reactions is necessary.

IV.6 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 Clotic 10 mg/ml ear drops, solution in single-dose container.

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There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Clotic 10 mg/ml ear drops, solution in single-dose container.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Benefit/risk assessment

The CLEAR-1 and CLEAR-2 phase III trials provide compelling efficacy data on the treatment of fungal otitis externa (otomyocis) in adult patients. The superiority of clotrimazole 1% solution for auricular use over placebo has been sufficiently demonstrated. The results of the primary efficacy endpoint were statistically significant and clinically and mycologically relevant in both studies. The supportive analysis of the primary endpoint and the secondary endpoints further support the robustness and consistency of the results. In the subgroup analysis performed, no cause for concern was identified.

The safety database comprises 356 adult patients that received clotrimazole 1% solution for auricular use in three phase III trials (CLEAR-1, CLEAR-2 and EBEROT). Most of the AEs reported were mild and there were no serious AEs (SAEs) or deaths in the clotrimazole-treated patients. There were three patients that experienced a non-serious AEs that lead to discontinuation of study drug: application site pain in two patients and tympanic membrane perforation in one patient.

The safety and efficacy data obtained in adult patients can be extrapolated to paediatric patients over 1 month of age.

Overall conclusion and recommendation

Based on the review of the data on quality, safety and efficacy, the risk/benefit ratio for the application for Clotic is considered positive and the product information is acceptable. The application is therefore recommended for approval.