LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Entolex

Mentha × piperita L., aetheroleum
(peppermint oil)

SE/H/2369/01/DC

This module reflects the scientific discussion for the approval of Entolex. The procedure was finalised on 2024-02-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Entolex, Gastro-resistant capsule, soft.

The active substance is peppermint oil. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Entolex, Gastro-resistant capsule, soft, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS), and with DK, FI and NO as concerned member states (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

A European Union monograph on *Mentha* x *piperita* L., aetheroleum, has been established in accordance with directive 2001/83/EC. The EU monograph was first adopted in 2007, and subsequently updated and re-adopted in 2020. According to this monograph, peppermint oil, in gastro-resistant capsules, has been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. The reader is referred to the monograph and pertinent assessment report for details.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise and Good Agricultural and Collection Practice, respectively).

II.1 Herbal Substance / Herbal Preparation

The herbal preparation is peppermint oil (Ph. Eur.) obtained by steam distillation of the herbal substance peppermint (*Mentha* × *piperita* L.).

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Herbal Medicinal Product

The drug product is a gastro-resistant soft capsule with the only fill ingredient peppermint oil. The drug product is packed in blister strips (PVC/PVdC/Al).

The development of the product has been described, the choice of excipients is justified, and their functions explained. The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been adequately described.

Manufacture of the bulk product (encapsulation) is Ayanda GmbH Co. KG, Germany.
Wiewelhove GmbH, Germany is responsible for coating, packaging and batch release of the finished product.

The release specification covers relevant parameters for this dosage form. Acceptable validations of the analytical methods have been presented.
Batch analysis results show that the finished product meets specification requirements.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
The principal pharmacodynamic effect of peppermint oil relevant to the GI tract is an antispasmodic effect on the smooth musculature.

The presented data, which is in agreement with the EU monograph on *Mentha x piperita L.*, aetheroleum and the HMPC assessment report on *Mentha x piperita L.*, folium and aetheroleum, is considered sufficient for a well-established use application.

Pharmacokinetics
In animals, peppermint is rapidly absorbed and the major biliary metabolite of the main constituent, menthol, is menthol glucuronide, which undergoes enterohepatic circulation.
Data on the excretion of single constituents of peppermint oil into breast milk in animals are lacking.

The bibliographic review is sufficient for an application based on well-established use.

Toxicology
Genotoxicity studies on the extract included in Entolex, gastro-resistant soft capsule (peppermint oil), showing no genotoxicity, were performed according to guidelines. Overall, presented data including published literature, indicates a very weak or totally absent genotoxicity of peppermint oil and thus constitutes no cause for safety concern.

Adequate tests on carcinogenicity have not been performed. Overall, based on public data for peppermint oil or its major constituent menthol, a carcinogenic potential was not identified.

With the proposed posology, Entolex does not cause exposure to pulegone and menthofuran that would exceed the recommended upper limits posed by the HMPC in ‘Public statement on the use of herbal medicinal products containing pulegone and menthofuran’.

There is no information on reproductive and developmental toxicity.

In summary, available non-clinical information constitutes no cause for safety concern.

Environmental Risk Assessment (ERA)
According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00) herbal medicinal products are exempted from environmental risk assessment due to the nature of their constituents.

IV. CLINICAL ASPECTS

Pharmacokinetics
The proposed Section 5.2 of the SmPC of Entolex is in agreement with the EU monograph on *Mentha* x *piperita* L., aetheroleum.

Pharmacodynamics
The proposed section 5.1 of the SmPC of Entolex is in agreement with the EU monograph on *Mentha* x *piperita* L., aetheroleum.

Clinical efficacy
By reference to the EU monograph on *Mentha* x *piperita* L., aetheroleum and bibliographic data on clinical efficacy, the Applicant has adequately shown that peppermint oil (Entolex) has a well-established medicinal use with a recognised efficacy in EU.

Clinical safety
The Applicant refers to the safety conclusions in the well-established use EU herbal monograph on *Mentha* x *piperita* L., aetheroleum, the HMPC assessment report on *Mentha* x *piperita* L., folium and aetheroleum and the HMPC 'Public statement on the use of herbal medicinal products containing pulegone and menthofuran'.

In general, the safety information in the SmPC of Entolex is in agreement with the EU herbal monograph on *Mentha* x *piperita* L., aetheroleum.

The use in children under 8 years of age is not recommended due to a lack of data on safety and efficacy and due to the presence of pulegone and menthofuran. In the absence of sufficient data, the use during pregnancy and breast-feeding is not recommended. The use in special populations i.e. children and pregnant and breast feeding women are in agreement with the EU herbal monograph.

Furthermore, in agreement with the EU herbal monograph, Entolex is contraindicated in patients with hypersensitivity to peppermint oil, menthol or to any of the excipients listed in SmPC section 6.1. Moreover, in agreement with the EU herbal monograph, the use in patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders is contraindicated.

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 Entolex.

Safety specification

Summary of safety concerns	
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.

Summary of the RMP
The Risk Management Plan is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 PL was Norwegian.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

According to the currently valid EU herbal monograph on *Mentha x piperita L.*, aetheroleum, peppermint oil in gastro-resistant oral dosage forms, such as Entolex, has a well-established medicinal use with recognised efficacy and an acceptable level of safety for use in the therapeutic indication "for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome in children from 8 years of age, adolescents, adults and elderly". This application was based on the EU herbal monograph on *Mentha* x *piperita* L., aetheroleum and the product information for Entolex, is in harmonisation with the EU herbal monograph.

In addition, the posology does not cause exposure to pulegon and menthofuran that would exceed the recommended limits for exposure to pulegone and menthofuran in the HMPC 'Public statement on the use of herbal medicinal products containing pulegone and menthofuran'.

The quality of Entolex is found adequate. There are no objections to approval of Entolex, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Entolex, Gastro-resistant capsule, soft was positively finalised on 2024-02-22.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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