LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mollisupradin
(efedrinhydroklorid, bromhexinhydroklorid)

Asp no: 2019-0756

Applicant: Unimedic Pharma AB

This module reflects the scientific discussion for the approval of Mollisupradin. The procedure was finalised on 2020-05-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Mollisupradin 0.5 mg/ml + 1.0 mg/ml, oral solution, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Unimedic Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Mollipect, 0.5 mg/ml + 1 mg/ml, oral solution, authorised in Sweden since 1974, with BioPhausia AB as marketing authorisation holder

No bioequivalence study has been performed, see section IV.1 for further information.

For approved indications, see the Summary of Product Characteristics.

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

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

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 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetic properties of the active substances
Bromhexine
Absorption: Bromhexine is rapidly absorbed and has an oral bioavailability of 20%, undergoing extensive first-pass metabolism. Maximal plasma concentrations occur at approximately 1 hour.

Elimination: About 85-90% is excreted in the urine mainly as metabolites. The metabolites have terminal half-life of up to about 12 hours. The half-life of unmetabolized drug is 6.5 hours.

Ephedrine
Absorption: Ephedrine is rapidly and fully absorbed.

Elimination: Major part is excreted into urine as unchanged ephedrine and a small amount as the metabolised form norephedrine. The excretion rate of all ephedrines is pH-dependant, whereof lower pH gives higher excretion rate. The terminal half-life in healthy subjects is approximately 6 hours.

Biowaiver
No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) since the product is an aqueous oral solution without excipients known to affect bioavailability. Almost the same excipients have been used in the applied product as in the reference product and these excipients are not known to affect the gastro-intestinal transit, absorption or in vivo stability of the active substance.

Discussion and overall conclusion
According to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution. However, if the excipients may affect gastrointestinal transit, absorption, solubility or stability, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for BCS-based biowaivers (Appendix III Section IV.2).

The EMA has clarified in Pharmacokinetics Q&A 6.3 on how to apply the reference made in Appendix II of the Bioequivalence Guideline, when waiving in vivo studies for oral studies. Differences in excipients could be handled more flexible with BCS class 1 drug substances, but qualitative similarity and very close quantitative similarity of excipients is expected in the case of BCS class 3 drug substances. The evaluation and comparison of excipients of solutions containing BCS class 2 and BCS class 4 drug substances, should be handled according to BCS 3 requirements. Non-relevant excipients, e.g. colorants, flavours, buffers, are not considered relevant in this context.

Both the test and the reference products contain bromhexine hydrochloride and ephedrine hydrochloride in the same concentrations (0.5 mg/ml and 1 mg/ml, respectively).

The excipients of the reference product Mollipect are:
Citric acid monohydrate,
Potassium sorbate,
Glycerol,
Polysorbate 20,
Ethanol 96 (per cent),
Levomenthol,
Peppermint flavour,
Blood orange flavor,
Sodium hydroxide (pH adjustment),
Water, purified

With the exception of difference in the flavour excipients and potassium sorbate used as preservative only present in the reference product, the same excipients and in similar amounts are used in both formulations. None of these excipients are considered as critical excipients. Waiving bioequivalence studies is therefore acceptable.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Mollisupradin.

Safety specification

An RMP version 0.2, signed 2019-11-21, has been submitted with the following table of Summary of safety concerns. The RMP is acceptable.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions • Serious skin reactions
Important potential risks	• Addiction
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.

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

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 2019-11-21, 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 MPA;
- 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Etrilect, SE/H/1624/01/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Mollisupradin is found adequate. There are no objections to approval of Mollisupradin, from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Mollisupradin, 0.5 mg/ml + 1.0 mg/ml, oral solution, was approved in the national procedure on 20200508.

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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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