LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Coldmexin

(bromhexine hydrochloride)

Asp no: 2017-0578

This module reflects the scientific discussion for the approval of Coldmexin. The procedure was finalised on 2018-07-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Orifarm Generics A/S has applied for a marketing authorisation for Coldmexin, 8 mg, Tablet. The active substance is bromhexine hydrochloride (known to have expectorant and mucolytic activity).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a (well established use, WEU) of Directive 2001/83/EC.

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 Pharmacology

The pharmacology of bromhexine hydrochloride is well known. The Applicant provided literature based data on the pharmacology of bromhexine hydrochloride, since this application is based on well-established use of the substance.
The non-clinical overview is compiled by the applicant mainly to give a concise review of the current non-clinical literature in order to support marketing authorisation of Bromhexine tablets 8 mg for oral use. The proposed indication is productive cough ("Hosta med segt slem").
This is considered acceptable.

III.2 Pharmacokinetics

The pharmacokinetics of bromhexine hydrochloride is well known. The Applicant provided literature based data on the pharmacokinetics of bromhexine hydrochloride, since this application is based on well-established use of the substance. This is considered acceptable.

III.3 Toxicology

The toxicology of bromhexine hydrochloride is well known. The Applicant provided literature based data on the toxicology of bromhexine hydrochloride, since this application is based on well-established use of the substance. This is considered acceptable.

III.4 Ecotoxicity/environmental risk assessment

Since Coldmexin is intended for substitution, this will not lead to an increased exposure of bromhexine hydrochloride to the environment. Therefore, no additional environmental risks are expected for Coldmexine.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bromhexine is a synthetic derivative of natural herbal substance vasicine, known to have expectorant and mucolytic activity.
Currently bromhexine is authorised in the all member states of the European Union (as well as in Norway and Iceland) except the United Kingdom, and is available in the form of over-the-counter (OTC) preparations in different formulations, including tablets. Bromhexine under the trade name Bisolvon was approved in Sweden 1973.

IV.2 Pharmacokinetics

The pharmacokinetics of bromhexine is considered well known. The applicant has submitted relevant litterature data in support of the proposed labelling. In summary, bromhexine is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism

in the liver. Bromhexine is widely distributed to body tissues and is highly (up to 99%) bound to plasma proteins. Ambroxol is an active metabolite of bromhexine. About 85% to 90% of a bromhexine dose is excreted in the urine mainly as metabolites. It has a terminal elimination half-life of up to about 12 h. The effective half-life is approximately 1 hour. Pharmacokinetics in special populations has not been studied.

IV.3 Pharmacodynamics

Bromhexine´s mechanism of action can be regarded as well-known and recognised with studies dating back to the 1960´s. Bromhexine is considered to have mucolytic properties, which can facilitate the expectoration of vicious mucus. The proposed dosage of bromhexine in the present application is 8 mg three times per day, i.e. 24 mg daily. This proposed posology (8 mg three times daily) has support in bibliographic data referred to by the applicant. Plausibility that a relevant pharmacological effect can be observed using the suggested posology has thus some support.

IV.4 Clinical efficacy

The fairly large number of articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of bromhexine. The proposed indication “hosta med segt slem” is in line with the medicinal use of bromhexine in the EU. Most of the studies seem to report a positive clinical response to bromhexine although the applicant has also included negative studies, which is acknowledged.
The majority of studies report a positive treatment effect, although the effect is deemed to be small in some studies. Coherence of positive study results are thus considered supported.
It is noted that the studies are from a rather limited time period, i.e. 1968–1974. For a WEU application older studies are acceptable, and in this case it is not surprising since bromhexine has been in clinical use for many years.

IV.5 Clinical safety

The applicant has provided adequate information regarding the clinical safety of bromhexine. Supportive to the safe use of Coldexin is that bromhexine has a documented long-standing use as an expectorant and mucolytic drug. The WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are considered supported.
No new alarming safety findings regarding bromhexine have been presented by the applicant.

IV.6 Risk Management Plans

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 Coldmexin.

Safety specification

Important identified risks	Hypersensitivity including severe cutaneous reactions
Important potential risks	None
Missing information	Use during lactation

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan, version 1.1, signed 02.11.2017, 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 Bromhexin Apofri, 0.8 and 1.6 mg/ml, oral solution, Diarienummer 111:2011/16694 och 111:2011/16758.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bromhexine´s mechanism of action can be regarded as well-known and recognised with studies dating back to the 1960´s. The fairly large number of articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of bromhexine. The proposed indication “hosta med segt slem” is in line with the medicinal use of bromhexine in the EU. Overall, included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

The applicant has provided adequate information regarding the clinical safety of bromhexine. Supportive to the safe use of Coldmexin is that bromhexine has a documented long-standing

use as an expectorant and mucolytic drug. Bromhexine under the trade name Bisolvon was approved in Sweden 1973 and is currently approved in all EU-states except the UK.

OTC-status has been granted previously in Sweden to bromhexine (Bisolvon), 8 mg tablets and OTC-status was granted for Coldmexin as well.

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

Coldmexin, 8 mg, Tablet was approved in the national procedure on 2018-07-24.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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