IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lemsip Multirelief capsules Paracetamol 500mg Phenylephrine hydrochloride 6.1mg Guaifenesin 100mg
Paracetamol
Phenylephrine hydrochloride
Guaifenesin
PA0979/053/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/1694/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 18th February 2020 under procedure number IE/H/1040/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0979/053/001
Marketing Authorisation Holder: Reckitt Benckiser Ireland Ltd

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Lemsip Max All In One Cold and Flu Capsules, for the relief of symptoms of colds and influenza, is approvable.

This application is made under Article 10a "bibliographic application" of Directive 2001/83 EC. The proposed product contains paracetamol 500 mg, phenylephrine 6.1 mg and guaifenesin 100 mg intended for self medication. The active ingredients in the proposed dose and dosing regimen have been in clinical use for many years with well established efficacy and an acceptable level of safety.

Colds and influenza (commonly known as flu) are amongst the most common illnesses to affect human populations worldwide. The common cold is caused by many different viruses, Rhinovirus and Coronavirus being the principal ones. Influenza is caused by influenza viruses A, B and C with multiple subtypes. The main presenting symptoms of the common cold and influenza can overlap to a considerable degree can include nasal congestion, headache and sore throat, bodily aches and pains, fever and malaise.

A large number of single and combination products containing and antipyretic/analgesic, anticongestant and espectorants are available for the relief of symptoms associated with cold and flu.

The proposed product is a combination of paracetamol 500 mg, phenylephrine 6.1 mg and guaifenesin 100 mg in the form of a capsule to be swallowed whole with water.

No new preclinical or clinical studies were conducted and none are required for an application of this type. The active substances have been in clinical use for many years with well established efficacy and an acceptable level of safety.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Name of the product in the Reference Member State	Lemsip Max All In One Cold & Flu Capsules

Name(s) of the active substance(s) (INN)	Paracetamol; Phenylephrine hydrochloride, Guaifenesin
Pharmacotherapeutic classification (ATC code)	N02BE51, "Paracetamol, combinations excl. psycholeptics"
Pharmaceutical form and strength(s)	Capsules, Paracetamol 500 mg, Phenylephrine hydrochloride 6.1 mg Guaifenesin 100 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1694/01/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 00063/0551
Name and address of the authorisation holder	Reckitt Benckiser Healthcare (UK) Limited Dansom Lane, Hull, HU8 7DS UK

II. QUALITY ASPECTS

III.1 QUALITYASPECTS
S. Active substance (1) General Information Nomenclature

rINN: Guaifenesin

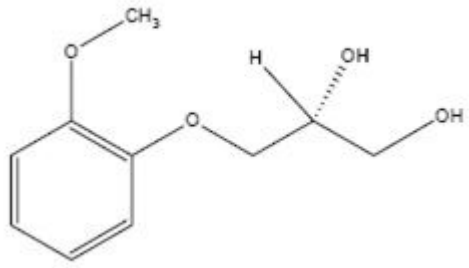
Compendial Name: Guaifenesin Ph Eur

Chemical Names: 3-(2-methoxyphenoxy)-1,2-propanediol

Company or laboratory code 15039
Other Non-Proprietary Name: Glycerylguaiacol Glyceryl Guaiacolate Glycerylginayacolum Guaiacol Glycerol ether Guajarolum Glycerdatum

Chemical Abstracts Service
(CAS) Registry Number: 93-14-1

Structure



Molecular formula: C10H14O4

Relative Molecular Mass: 198.22

General Properties
Guaifenesin is a white or almost white crystalline powder, sparingly soluble in water and soluble in alcohol.

Manufacture
All aspects of the manufacture and control of guaifenesin are supported by a European Directorate for the Quality of medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of guaifenesin for inclusion in the medicinal product.

The active substance, guaifenesin, is controlled by the Ph Eur monograph.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Guaifenesin is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Certificates of analysis of three batches have been provided by the active substance manufacturer and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a re-test period of 5 years. This is accepted.

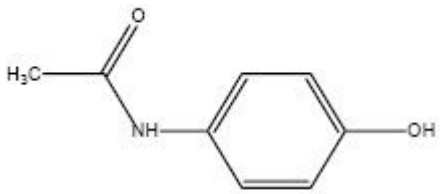
S. Active substance (2) General Information
Nomenclature

rINN: Paracetamol

Compendial Name: Paracetamol (Ph Eur)

Chemical Names: N-(4-Hydroxyphenyl) acetamide
(CAS) Registry Number: 103-90-2

Structure



Molecular formula $C_8H_9NO_2$
Relative Molecular Mass 151.2

General Properties

A white, crystalline powder which is sparingly soluble in water, soluble 1 in 20 of boiling water, 1 in 10 of alcohol and 1 in 15 of 1N sodium hydroxide. It is very slightly soluble in dichloromethane (methylene chloride) and in ether.

Manufacture
Two active substances manufacturers are listed for the manufacture of paracetamol. All aspects of the manufacture and control of paracetamol are supported by European Directorate for the Quality of medicines and Healthcare (EDQM) Certificates of Suitability. These certificates are accepted as confirmation of the suitability of paracetamol for inclusion in the medicinal product.

The active substance, paracetamol, is controlled by the Ph Eur monograph.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Paracetamol is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Certificates of analysis have been provided for all batches supplied by both active substance manufacturers and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

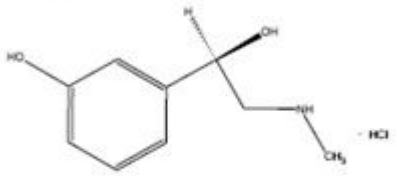
S. Active substance (3)

rINN: Phenylephrine hydrochloride

Chemical Names:
(S)-1-(3-Hydroxyphenyl)-2-methylaminoethanol hydrochloride

(CAS) Registry Number: 59-42-7

Structure



Molecular formula: $C_9H_{14}ClNO_2$
Relative Molecular Mass: 203.7

General properties
Phenylephrine is a white or almost white, crystalline powder, freely soluble in water and in alcohol

Manufacture
All aspects of the manufacture and control of phenylephrine hydrochloride is supported by are supported by a European Directorate for the Quality of medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of phenylephrine hydrochloride for inclusion in the medicinal product.
The active substance, phenylephrine hydrochloride, is controlled by the Ph Eur monograph. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance
with the relevant specifications.

Phenylephrine hydrochloride is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Batch analysis results have been provided for three production scale batches by the active substance manufacturer and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P Medicinal Product
Other ingredients consist of pharmaceutical excipients maize starch, croscarmellose sodium, sodium laurilsulfate, magnesium stearate and talc. All the ingredients within the body of the capsule comply with their relevant Ph Eur monographs.

The capsule shell contains: gelatin, brilliant blue-FD&C blue 1 (E133), red iron oxide (E172), yellow iron oxide (E172) and titanium dioxide (E171). Both titanium dioxide (E171) and gelatin comply with their relevant Ph Eur monographs. Red iron oxide (E172), yellow iron oxide (E172) comply with their relevant USP monograph and brilliant blue E133 comply with EEC monogragh.

The printing ink contains: shellac and titanium dioxide. Both shellac and titanium dioxide comply with their relevant Ph Eur monographs. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their respective monograph/specifications.

The only excipients used that contain material of animal or human origin is gelatin. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

The drug product contains three active ingredients – paracetamol, guaifenesin and phenylephrine hydrochloride, all of which have been used widely, both separately and in combination, in product marketed for the relief of cold and flu symptoms. The quality of the three active ingredients is suitably controlled by their respective Ph Eur monographs. The particle size of each active ingredient is additionally controlled by the drug product manufacturer to optimise blending of the powders and drug dissolution.

Characterisation of Impurities
The source and characterisation of impurities in the drug product have been outlined by the applicant and comply with the ICH guideline qualification limit for each of the potential impurities identified for the three active ingredients.

Dissolution profiles
Dissolution profiles of three batches have been presented and are satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

Manufacturing process
Satisfactory batch formula have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three pilot batches have been provided and are satisfactory. The applicant has committed to validate the first three full scale batches and to report any out of specification results as well as have the data available for inspection. Certificates of analysis have been provided for any working standards used.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch analysis data for three pilot scale batches have been provided and demonstrate compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The product is packaged in blister packs composed of unplasterised polyvinylchloride (uPVC) blister with foil/paper laminate with a soft-temper aluminium foil backed with child resistant paper. The blister strips are packed in an outer carton in pack sizes of 2,4,6,8,10,12,14 and 16. Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 15 months has been set, which is satisfactory. Storage conditions are "Do not store above 25°C".

Conclusion
It is recommended that Marketing Authorisations are granted for this application.

III. NON-CLINICAL ASPECTS

Paracetamol has both analgesic and antipyretic activity, which are mediated through inhibition of prostaglandin synthesis within the central nervous system.

Guaifenesin is reported to increase the volume and reduce the viscosity of tenacious sputum, acting as an expectorant for productive coughs. Additionally, a study in mice has indicated that guaifenesin may enhance the analgesic activity of paracetamol.

Phenylephrine hydrochloride is a selective α1-adrenergic agonist acting at the post-synaptic level, causing vasoconstriction within the nasal mucosa to reduce nasal congestion.

The pharmacodynamics, pharmacokinetics and toxicology of paracetamol, guaifenesin and phenylephrine hydrochloride are well established and will not be reviewed here. The active ingredients in combination or individually have been in use for many years and there is a wealth of clinical data available. As such, no new preclinical studies have been performed in support of this application and the applicant has provided a literature review.

The nonclinical overview has been written by a suitably qualified person. The overview comprised a thorough review of the pharmacology and toxicology of paracetamol, guaifenesin and phenylephrine hydrochloride with 137 publications up to year 2007.

Studies on impurities
The applicant has included a brief discussion on the impurities associated with the drug substances stating that all are well controlled and within the limits set out in ICH guidelines and in the European Pharmacopeia. As such, no toxicological qualification is necessary.

Environmental riskassessment
An environmental risk assessment has not been submitted. The applicant states that an environmental risk assessment is not considered necessary for Lemsip Max All in One Capsules as it contains actives (500 mg paracetamol, 100 mg guaifenesin and 6.1 mg phenylephrine hydrochloride per capsule) that are well-established with many years of sales and marketing in the EU. None of the actives have been shown to have an environmental impact. Lemsip products have been marketed continuously in the UK since 1971 and in addition to the UK all three actives have been in widespread use globally as non-prescription products for over 30 years by both Reckitt Benckiser and other companies. It is envisaged that any increase in the marketing of Lemsip Max All in One Capsules globally would not significantly increase the exposure levels of paracetamol, guaifenesin or phenylephrine hydrochloride because consumers would simply be switching from their pre-existing brands containing these actives to Lemsip. This justification is considered to be satisfactory.

Assessor'soverallconclusions
The applicant has supplied a satisfactory review of the relevant literature. As the active ingredients have been in clinical use for many years any gaps in the preclinical knowledge base are compensated for by clinical experience. As such, no nonclinical concerns are raised by these applications and granting of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

INTRODUCTION

Type of Application and aspects on development
This is a decentralised application for Lemsip Max All in One Capsules indicated for the relief of symptoms of colds and influenza, submitted under article 10(a) 'well established use application'.
The active ingredients are paracetamol, phenylephrine hydrochloride and guaifenesin and the applicant is seeking approval of the following indications (derived from section 4.1 of the proposed SPC):

4.1 Therapeutic indications
For the relief of symptoms of cold and influenza, including the relief of aches and pains, sore throat, headache, nasal congestion, lowering of temperature and chesty coughs.

4.2 Posology and method of administration
Adults (over 16 years and over): Two capsules every 4-6 hours to a maximum of four doses in any 24 hours.

Do not exceed eight capsules in any 24 hours.

Children (12-15 years): One capsule every 4-6 hours to a maximum of four doses in any 24 hours.

Do not exceed 4 capsules in any 24 hours. Swallow whole with water. Do not chew.
Not recommended for children under 12 years of age.

Assessor's comments
The proposed therapeutic indications, posology and method of administration have been suitably justified and are satisfactory.

The clinical expert in the clinical overview argues that the active ingredients (paracetamol, phenylephrine hydrochloride, guaifenesin) are drug substances for which efficacy and safety is well-established and it was not considered necessary to conduct additional clinical studies.

Assessor's comments
In vivo bioequivalence studies were not considered necessary. This is acceptable.

GCP aspects

No clinical studies have been submitted with this application.

Pharmacokinetics

Both paracetamol and phenylephrine have similar pharmacokinetic profiles with Tmax of up to 1 hour and elimination half-lives of 1-3 hours.

Guaifenesin is readily absorbed after oral administration and rapidly metabolised by oxidation to β-(2-methoxyphenoxy) lactic acid. Half-life in plasma is approximately 1 hour.

Pharmacodynamics
Paracetamol
Paracetamol has both analgesic and antipyretic activity, which has been recognised for many years. It is believed that these actions are mediated principally through its inhibition of prostaglandin synthesis within the central nervous system.

Guaifenesin
Guaifenesin is a mucolytic expectorant used to reduce the viscosity of the bronchial mucus. It acts through stimulation of the vagal afferent nerves in the gastric mucosa, which serve the bronchial glands stimulationg increased secretion of bronchial fluids. This results in a decrease in mucus viscosity.

Phenylephrine hydrochloride
Phenylephrine hydrochloride is a selective α1-adrenergic agonist acting at the post-synaptic level. It has a low cardiac β1-adrenoreceptor affinity and minimal central stimulant activity. α1-Adrenergic agonists are used extensively as nasal decongestants and phenylephrine acts by vasoconstriction within the nasal mucosa to reduce nasal congestion.

Clinical efficacy
The efficacy of paracetamol in symptomatic treatment of pain and pyrexia is well established.
No new studies were conducted. The clinical expert discusses a number of studies from published literature.

Guaifenesin is a widely used product. Its efficacy has been studied in a placebo controlled study involving 239 patients which reported that guaifenesin reduced cough frequency and intensity in patients with dry or productive cough and helped to thin sputum compared to placebo.

Phenylephrine hydrochloride is a decongestant which acts by vasoconstriction to reduce oedema and swelling of the nasal mucosa. By this means nasal discharge may be reduced and obstruction associated with colds and influenza may be relieved.

Clinical safety
Paracetamol
The safety profile of paracetamol in the proposed dose is well established. No new safety studies were submitted. Hepatotoxicity is a recognised problem associated with paracetamol overdose, but there is little evidence that paracetamol is hepatotoxic in the recommended dosage. However, in patients with compromised hepatic function or who use paracetamol chronically, saturation of the detoxification pathway is possible.

Guaifenesin
Guaifenesin at doses of 200 mg has been reported to prolong the activating plasma clotting time and to significantly reduce platelet adhesiveness. However, guaifenesin has no effect on bleeding time and volunteers tested showed no tendency for bleeding.

In a study published in 1998 guaifenesin when used during the first trimester of pregnancy has been associated with an increased risk of neural tube defects in the foetus.

Phenylephrine Hydrochloride
The adverse event profile of phenylephrine in the proposed dose is well recognised. The applicant presents a review of safety and discusses adverse events such as tachycardia and increase in blood pressure. Adequate warnings are included in the SPC.

Administration of sympathomimetics has been reported to pose a risk for patients with glucose intolerance or type 1 diabetes because of increased glucose levels. A warning regarding use of by diabetics is included in the SPC.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
The Risk Management Plan is acceptable.

Periodic Safety UpdateReport (PSUR)
The applicant has not requested adifferent PSUR cycle upon approval. The RMS considers the submission of 6-monthly PSURs not necessary.

BENEFIT RISK ASSESSMENT
Paracetamol and phenylephrine hydrochloride have been in clinical use either as monotherapy or in combination for many years. The efficacy and safety profiles are well established. The risk benefit balance is considered positive.

V. OVERALL CONCLUSIONS

QUALITY
The important quality characteristics of Lemsip Max All In One Cold & Flu are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No new data are submitted and none are required for this type of application. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol, guaifenesin and phenylephrine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

VI. REVISION DATE

May 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/1694/001/DC to IE/H/1040/001/DC	N/A	N/A	N/A	Approved 18/02/2020