IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Perrigo Cold & Flu Multi Relief Max Powder for Oral SolutionParacetamol 1000 mg, Guaifenesin 200 mg, Phenylephrine 12.2 mg
Paracetamol
Guaifenesin
Phenylephrine hydrochloride
PA1186/021/003

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/1197/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 10th April 2019 under procedure number IE/H/0986/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/021/003
Marketing Authorisation Holder: Chefaro Ireland DAC

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 Beechams Ultra All In One hot Lemon Menthol Powder for Oral Solution for the relief of symptoms associated with colds and flu and the pain and congestion of sinusitis, including aches and pains, headache, blocked nose and sore throat, chills, lowering of temperature, and to loosen stubborn mucous and provide relief from chesty coughs is approvable.

This is an "Abridged" Standard Bibliographical decentralised application submitted in accordance with Directive 2001/83/EC Article 10a. The active ingredients (drug substances) are well established and literature references are provided in support of the safety and efficacy of the product.

The combination of paracetamol, guaifenesin and phenylephrine was first registered in the UK on 19 October 1994 (Beecham's All-in-One). This is the basis of this submission under Article 10(a) well-established use. In the current submission paracetamol (1000 mg), guaifenesin (200 mg) and phenylephrine hydrochloride (12.2 mg) are used in combination in a sachet. The pharmacokinetics of each drug substance has been well documented in the literature.

No new preclinical or clinical studies were conducted and none are required for an application of this type. The pharmacodynamics, pharmacokinetics and toxicology of both paracetamol, guaifenesin and phenylephrine hydrochloride are well established and the non- clinical dossier is based on a review of published literature. An acceptable justification for the absence of an environmental risk assessment has been provided.
The pharmacokinetics of paracetamol, guaifenesin and phenylephrine are well known. This is a bibliographical submission as required by Article 10(a). The clinical overview reviews 33 publications the most recent dating from 2006. No bio-availability and/or bio-equivalence studies or safety data are presented and none are required for an application of this type.

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.

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.

ABOUT THE PRODUCT

Product Name	Beechams Ultra All in One Hot Lemon menthol, Powder for Oral Solution
Type of Application	Bibliographic, 10a
Active Substance	Guaifenesin Paracetamol

	Phenylephrine Hydrochloride
Form	Powder for oral solution
Strength	Guaifenesin 200mg/sachet Paracetamol 1000mg/sachet Phenylephrine Hydrochloride 12.2mg/sachet
MA Holder	Wrafton Laboratories Limited (T/A Perrigo)
RMS	UK
CMS	Ireland
Procedure Number	UK/H/1197/001/DC
Timetable	Day 210 - 08/07/2009

II. QUALITY ASPECTS

Active substance(1)
General Information

Nomenclature

rINN: Guaifenesin

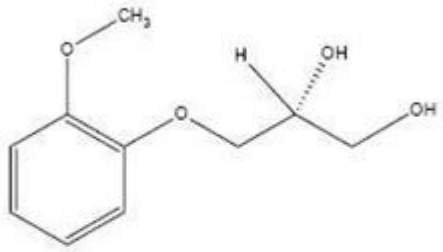
Compendial Name: Guaifenesin Ph Eur

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: $C_{10}H_{14}O_4$

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.

Active substance (2)

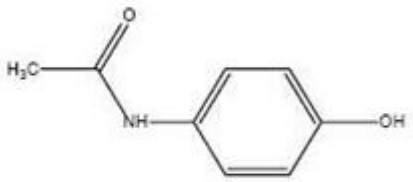
General Information
Nomenclature

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.

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

Certificates of analysis of three batches are provided by each of the 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.

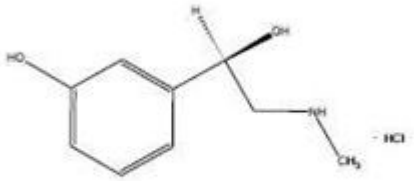
Active substance (3)

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
Two active substances manufacturers are listed for the manufacture of phenylephrine hydrochloride. All aspects of the manufacture and control of phenylephrine hydrochloride 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 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.

Batches analysis results have been provided for three production scale batches by each of the 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.

Medicinal Product
Other ingredients consist of pharmaceutical excipients sucrose, citric acid, tartaric acid, sodium citrate, acesulfame potassium, aspartame, powdered menthol flavour, lemon flavour and quinoline yellow.

All excipients used comply with their respective European Pharmacopoeial monograph with the exception of lemon flavour, powdered menthol flavour and quinoline yellow, in the absence of Ph Eur monographs comply with in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

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.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on six pilot-scale batches, this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in sachets composed of either low density polyethylene (LDPE) and paper (outerlayer) or 'Surlyn' 25 gm-2 (product contact layer)/aluminium foil / LDPE and paper (outer layer). Specifications and a certificate of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is available in pack sizes of five and ten sachets.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory with the specific storage conditions of 'Do not store about 25°C.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III. NON-CLINICAL ASPECTS

No new non-clinical data have been provided. The pharmacodynamics, pharmacokinetics and toxicology of both paracetamol, guaifenesin and phenylephrine hydrochloride are well established and the non-clinical dossier is based on a review of published literature. An acceptable justification for the absence of an environmental risk assessment has been provided.

IV. CLINICAL ASPECTS

Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. This is an "Abridged" Standard Bibliographical application submitted in accordance with Directive 2001/83/EC Article 10a. The active ingredients (drug substances paracetamol, guaifenesin and phenylephrine) are well established and literature references are provided in support of the safety and efficacy of the product. The first combination to use these three molecules in combination for the over the counter (OTC) market was Beecham's All-in-One which was first authorised on 19th October 1994.

Pharmacokinetics
The pharmacokinetics of paracetamol, guaifenesin and phenylephrine are well known. No new data has been submitted and none is required.

Clinical efficacy and Clinical safety
This is a bibliographical submission as required by Article 10(a). The clinical overview reviews 33 publications the most recent dating from 2006. No new efficacy or safety data have been submitted and none are required for an application as this type. No bio-availability and/or bio-equivalence studies or safety data are presented for the same reasons.

Conclusion:
The clinical overview adequately covers the needs of this submission.

V. OVERALL CONCLUSIONS

QUALITY
The important quality characteristics of Beechams Ultra All in One Hot Lemon Menthol Powder for Oral Solution 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.

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

December 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/1197/001/DC to IE/H/0986/001/DC	N/A	N/A	N/A	Approved 10/04/2019