IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Perrigo Cold & Flu powder for oral solution Paracetamol 500 mg Guaifenesin 200 mg Phenylephrine hydrochloride 10 mg
Paracetamol
Guaifenesin
Phenylephrine hydrochloride
PA1186/023/001

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/6413/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12/02/2019 under procedure number IE/H/0949/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/023/001
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 member states considered that the applications for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution (PL 02855/0311; UK/H/6411/001/DC) and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for oral solution (PL 02855/0312; UK/H/6413/001/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and the following Concerne Member States (CMS):

For UK/H/6411/001/DC - Estonia, Croatia, Hungary, Lithuania, Latvia, Portugal, Slovenia and Spain
For UK/H/6413/001/DC - Bulgaria, Ireland and Romania

These products are General Sales List medicines (legal classification GSL).

The applications were submitted according to Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference product is Beechams All-in-One Liquid Oral solution (PL 00079/0320) which was granted a Marketing Authorisation to Beecham Group plc, in the UK, on 19 October 1994.

The pharmaceutical forms are different in that the Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for oral solution are presented as powders for dissolution in approximately 250 mL of hot water prior to ingestion as an aqueous oral solution. By contrast, the reference medicinal product is presented as a pre-prepared oral solution containing the same quantities of the active substance in a unit dose of 20 mL.

Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution is indicated in adults, the elderly and children aged 15 and over, for the short-term symptomatic relief of colds and flu including aches and pains, headache, blocked nose and sore throat, chills and fever, and for relief from chesty coughs.

Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for oral solution is indicated in adults, the elderly and children aged 12 and over, for the short-term symptomatic relief of colds and flu including aches and pains, headache, blocked nose and sore throat, chills and fever, and for relief from chesty coughs.

These products contain the active ingredients paracetamol, guaifenesin and phenylephrine hydrochloride.

Paracetamol has analgesic and anti-pyretic actions. The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation. Paracetamol probably produces antipyresis by acting on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Guaifenesin is a well-known expectorant. Such expectorants are known to increase the volume of secretions in the respiratory tract and therefore to facilitate their removal by cilary action and coughing.

Sympathomimetic amines, such as phenylephrine, act on alpha-adrenergic receptors of the respiratory tract to produce vasoconstriction, which temporarily reduces the swelling associated with inflammation of the mucous membranes lining the nasal and sinus passages. In addition to reducing mucosal lining swelling, decongestants also suppress the production of mucus, therefore preventing a build-up of fluid within the cavities which could otherwise lead to pressure and pain.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being similar to an originator product that has been licensed for over 10 years.

These products are aqueous oral solutions at the time of administration and in line with the *guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

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

The RMS and CMS considered that the applications could be approved at the end of procedure on 22 September 2017. After a subsequent national phase, licences were granted in the UK on 19 October 2017.

II. QUALITY ASPECTS

Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for Oral Solution are off-white powders with a characteristic citrus/menthol odour. The reconstituted solutions are opalescent yellow with a characteristic citrus/menthol odour. Each sachet contains 500 mg paracetamol, 200 mg guaifenesin and 10 mg phenylephrine hydrochloride.

The other ingredients consist of the pharmaceutical excipients, namely sucrose, citric acid E330, tartaric acid E334, sodium cyclamate E952, sodium citrate E331, acesulfame potassium E950, aspartame E951, powdered menthol flavour [contains natural menthol, corn maltodextrin and arabic gum (E414)], lemon flavour [contains flavouring preparation, natural flavouring substance, corn maltodextrin, arabic gum E414, sodium citrate E331, citric acid E330 and butylated hydroxyanisole E320 (0.01%)], lemon juice flavour [contains flavouring preparation, natural flavouring substance(s), maltodextrin, modified starch E1450 and butylated hydroxyanisole E320 (0.03%)], quinoline yellow E104.

These products are packaged in an ionomer (product contact layer)/aluminium foil /low density polyethylene/ paper (outer layer) laminated sachet in a pack size of 5, 6, 10, 14, 15 and 20 sachets. Not all pack sizes may be marketed.

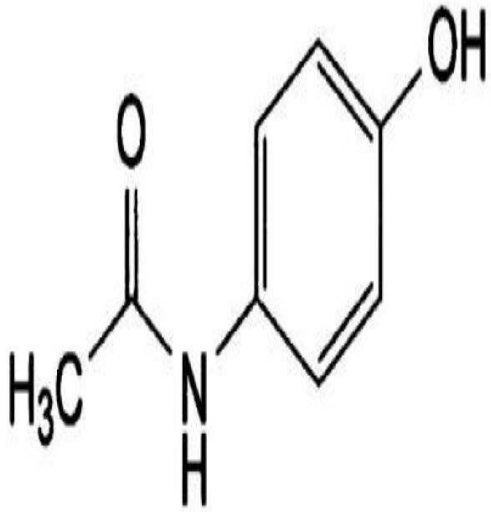
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Paracetamol

Chemical name(s): N-(4-hydroxyphenyl)acetamide

Structure:



Molecular formula: $C_8H_9NO_2$

Molecular weight: 151.2

Appearance: White, crystalline powder

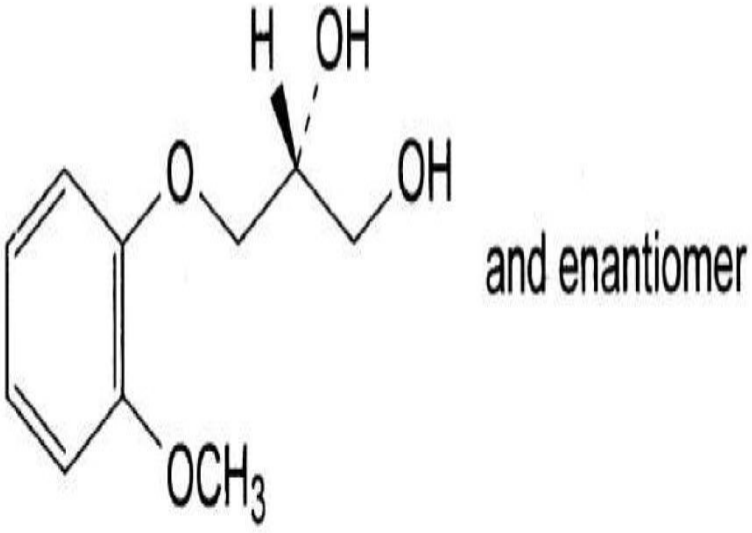
Solubility: Sparingly soluble in water, freely soluble in alcohol and very slightly soluble in dichloromethane

All aspects of the manufacture and control of the active substance paracetamol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Guaifenesin

Chemical name(s): (2RS)-3-(2-methoxyphenoxy)propane-1,2-diol

Structure:



and enantiomer

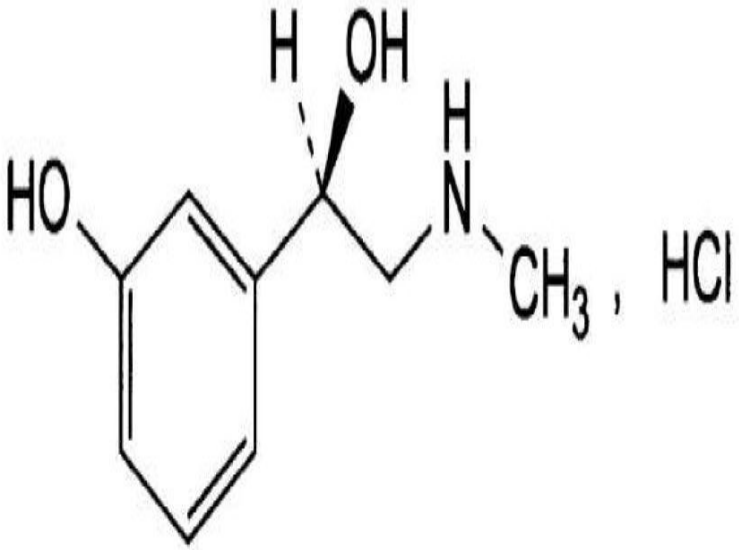
Molecular formula:	$C_{10}H_{14}O_4$
Molecular weight:	198.22
Appearance:	White or almost white, crystalline powder
Solubility:	Sparingly soluble in water and soluble in ethanol

All aspects of the manufacture and control of the active substance guaifenesin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Phenylephrine hydrochloride

Chemical name(s): (1R)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol

Structure:



Molecular formula: $C_9H_{13}NO_2.HCl$

Molecular weight: 203.7

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water and in ethanol.

All aspects of the manufacture and control of the active substance phenylephrine hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate robust and stable powders for oral solution, which could be considered hybrid medicinal products of the currently licensed product Beechams All-in-One Liquid Oral solution (PL 00079/0320; Beecham Group plc).

A satisfactory account of the pharmaceutical development has been provided.

With the exception of the powdered menthol flavour, the lemon juice flavour and the quinoline yellow, which are controlled to an in-house specification, all the excipients comply with their respective European Pharmacopoeia monographs. No material from animal or human source and no genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on three production scale batches of finished product. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf life of 36 months, with the special storage conditions of "Do not store above 25°C".

The shelf life after reconstitution is 1½ hours.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for Paracetamol/Guaifenesin /Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for Oral Solution.

III. NON-CLINICAL ASPECTS

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III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol, guaifenesin and phenylephrine hydrochloride are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology

No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As the products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to the active substances is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Paracetamol/Guaifenesin /Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for Oral Solution.

IV. CLINICAL ASPECTS

IV.2 Pharmacokinetics

A bioequivalence study was not submitted as the product meets the criteria regarding oral solutions specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). These products are aqueous solutions when administered and none of the excipients are expected to significantly affect absorption or gastrointestinal transit time.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

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.

The MAH has submitted an RMP, 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 Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for Oral Solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity (Paracetamol/Phenylephrine Hydrochloride/Guaifenesin)	**Section 4.3. Contraindication** **Section 4.8. Undesirable effects**	None proposed
Hepatic toxicity (Paracetamol)	**Section 4.1. Therapeutic indications** **Section 4.2. Posology and method of administration** **Section 4.3. Contraindications** **Section 4.4. Special warnings and precautions for use** **Section 4.5. Interaction with other medicinal products and other forms of interaction** **Section 4.8. Undesirable effects** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC)) **Section 4.9. Overdose**	None proposed
Use in patients with hepatic and renal disorders (Paracetamol)	**Section 4.3. Contraindications** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC) and Coldrex Junior syrup) **Section 4.4. Special warnings and precautions for use** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC) and Coldrex Junior (tablets)) **Section 4.8. Undesirable effects** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC))	None proposed
Overdose – intentional and non-intentional (Paracetamol)	**Section 4.9. Overdose**	None proposed
Serious cutaneous reactions (Paracetamol)	**Section 4.8. Undesirable effects**	None proposed

Drug interaction with warfarin and other coumarins (Paracetamol)	**Section 4.5. Interaction with other medicinal products and other forms of interaction**	None proposed
Increased blood pressure (Phenylephrine Hydrochloride)	**Section 4.3. Contraindications** **Section 4.4. Special warnings and precautions for use** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC)) **Section 4.5. Interaction with other medicinal products and other forms of interaction** **Section 4.8. Undesirable effects** **Section 4.9. Overdose** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC))	None proposed
Acute angle closure glaucoma (Phenylephrine Hydrochloride)	**Section 4.3. Contraindications** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC)) **Section 4.8. Undesirable effects** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC))	None proposed
Urinary retention (Phenylephrine Hydrochloride)	**Section 4.3. Contraindications** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC)) **Section 4.8. Undesirable effects** (for Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500mg/200mg/10mg Powder for oral solution (UK/H/6413/01/DC and UK/H/6411/01/DC))	None proposed

Drug interactions with MAOIs, sympathomimetic amines, beta-blockers and other antihypertensives, tricyclic antidepressants, digoxin and cardiac glycosides (Phenylephrine Hydrochloride)	**Section 4.3. Contraindications** **Section 4.5. Interaction with other medicinal products and other forms of interaction**	None proposed
Pregnancy, lactation and fertility (Phenylephrine Hydrochloride/ Guaifenesin)	**Section 4.6. Fertility, pregnancy and Lactation**	None proposed

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Paracetamol/Guaifenesin /Phenylephrine Hydrochloride Omega Pharma 500mg/200mg/10mg Powder for oral solution and Paracetamol/Guaifenesin/Phenylephrine Hydrochloride 500/200/10 mg Powder for oral solution.

V. USER CONSULTATION

A user consultation with target patient groups on the patient information leaflet (PIL) has been performed on the basis of a bridging report making reference to for the Irish product Multi-Action Cough & Cold Capsules (PA 1120/1/2). The bridging report submitted by the applicant is acceptable. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's products and the reference product are interchangeable. Extensive clinical experience with paracetamol, guaifenesin and phenylephrine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment is therefore considered to be positive.

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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VI. REVISION DATE

21/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/6413/1/DC to IE/H/0949/1/DC			