IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard
Paracetamol
Guaifenesin
Phenylephrine Hydrochloride
PA1186/025/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules, hard, from Chefaro Ireland DAC on 10th September 2021 for the short-term symptomatic relief of colds and flu including mild to moderate pains, headache, blocked nose and sore throat, chills and fever, and for relief from chesty coughs in adults, the elderly and adolescents aged 16 years and over.

This application for a marketing authorisation was submitted as a decentralised procedure application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application. The RMS is IE, with CMS' BG, CY, CZ, EE, EL, HR, HU, LT, LV, PL, PT, RO, SI and SK.

This is a non-prescription medicinal product however pack size restrictions may apply in the member states. In Ireland, pack sizes greater than 24 units are subject to prescription.

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

Name of the product	Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules, hard
Name(s) of the active substance(s) (INN)	Paracetamol, Guaifenesin, Phenylephrine Hydrochloride
Pharmacotherapeutic classification (ATC code)	N02BE51
Pharmaceutical form and strength(s)	500 mg/100mg/6.1mg Capsule, hard
Marketing Authorisation Number(s) in Ireland (PA)	PA1186/025/001
Marketing Authorisation Holder	Chefaro Ireland DAC
MRP/DCP No.	IE/H/1029/001/DC
Reference Member State	IE
Concerned Member State	BG CY CZ EE EL HR HU LT LV PL PT RO SI SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Paracetamol 500 mg, Guaifenesin 100 mg, Phenylephrine Hydrochloride 6.1 mg capsules, hard.

II.2 Drug substance

The active substances are paracetamol, guaifenesin and phenylephrine hydrochloride, each an established active substance described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications has been provided.

II.3 Medicinal product

P.1 Composition

Each capsule of the medicinal product contains: 500 mg Paracetamol, 100 mg guaifenesin and 6.1 mg phenylephrine hydrochloride.
The medicinal product also contains the excipients maize starch, croscarmellose sodium, sodium lauryl sulfate, talc and magnesium stearate. The capsule shell contains: gelatin, sodium lauryl sulfate, titanium dioxide (E171), Indigo carmine (E132), quinoline yellow (E104), erythrosine (E127) and purified water.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by EDQM have been provided for gelatin in the capsule and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules, hard.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Paracetamol, guaifenesin and phenylephrine hydrochloride are widely used and well-known active substances and their pharmacodynamic, pharmacokinetic and toxicological properties are well known. The applicant has not provided additional non-clinical safety studies and further studies are not required. An overview based on literature review is appropriate.

III.2 Pharmacology

The analgesic and antipyretic properties of paracetamol, the expectorant activity of guaifenesin and the nasal decongestant effect of phenylephrine are all well established.

Paracetamol blocks prostaglandin biosynthesis by inhibiting COX (cyclooxygenase). Prostaglandins produce pain and cause inflammation by local action. In addition, the mechanism of action may include effects on the serotonergic, opioidergic, or eicosanoid systems and/or nitric oxide-containing pathways.
Guaifenesin increases the volume and reduces the viscosity of tenacious sputum. It may therefore be used as an expectorant in cases of productive cough.
Phenylephrine is a sympathomimetic vasoconstrictor with agonist selectivity for the α1-receptor subtype, which has been used as a nasal decongestant for many years. Most of the α1-stimulant activity is due to direct action on receptors in pre-capillary and post-capillary blood vessels of the nasal mucosa. The resulting vasoconstriction decreases blood flow through the nasal mucosa and results in shrinkage of this tissue, thereby resulting in decongestion.

III.3 Pharmacokinetics

Absorption
Paracetamol is rapidly and completely absorbed after oral administration with peak plasma concentrations in humans usually occurring within 10-60 minutes after ingestion.
Guaifenesin is rapidly absorbed and has a short half-life in humans.
Phenylephrine is rapidly but erratically absorbed after oral administration to humans. Its bioavailability is about 40 % due to first-pass metabolism by monoamine oxidase in the gastrointestinal tract and liver.

Distribution
Paracetamol is rapidly and evenly distributed into most body tissues in humans. It crosses the placenta and appears in breast milk at concentrations approximately 20% lower than those in serum. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration.
Guaifenesin. The pharmacokinetics of guaifenesin were determined in four rabbits after an oral dose of 200 mg/kg. The maximum plasma concentration was 94.85 µg/mL and the time to maximum plasma concentration (tmax) was assessed in one rabbit and found to be 0.5 hour.
Phenylephrine. Peak plasma concentrations of phenylephrine are attained 0.5–2 hours after oral dosing. Considerable inter-individual variations in peak serum levels have been observed. Phenylephrine shows extensive distribution into extravascular sites.

Metabolism
Paracetamol is metabolised predominantly in the liver, undergoing extensive biotransformation to sulphate and glucuronide conjugates. In addition, a small fraction of paracetamol is metabolized by cytochrome P450-dependent mixed-function oxidase to the reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI). Normally this metabolite undergoes conjugation with glutathione and is excreted as mercapturic acid and cysteine conjugates. In conditions of glutathione deficiency, such as following paracetamol overdose and in poor nutritional states, NAPQI accumulates and binds to hepatic proteins causing irreversible damage and necrosis, which may lead to hepatic failure
Guaifenesin is metabolised by oxidation and no unchanged drug is found in the urine.
Phenylephrine undergoes extensive intestinal and hepatic biotransformation with only a small fraction of an oral dose being excreted unchanged. The primary routes of metabolism are by sulphate conjugation to phenylephrine-3-O-sulphate or deamination to 3-hydroxymandelic acid and 3-hydroxyphenylglycol, which is itself sulphated to produce the 3-O-sulphate. Some glucuronidation of phenylephrine also occurs.

Excretion
Paracetamol. The mean plasma half-life of paracetamol after a therapeutic dose ranges from 1 to 4 hours with a total body clearance of about 5 mL/min/kg. Excretion is mainly in the urine as glucuronide and sulphate conjugates but about 2- 5 % is excreted unchanged.
Guaifenesin is metabolised by oxidation and no unchanged drug is found in the urine.
Phenylephrine and its metabolites are excreted almost entirely in the urine, with less than 20 % excreted as unchanged drug. The plasma clearance of phenylephrine is 2 L/h.

III.4 Toxicology

Since paracetamol, guaifenesin and phenylephrine act by different pharmacological mechanisms, their toxicological profiles may be expected to be independent of one another.

Single and repeat dose toxicity
Paracetamol
The most commonly affected organs in single-dose toxicity studies of paracetamol are the liver and kidneys; primarily involving hepatocellular necrosis and changes in renal function. The oral LD50 values of paracetamol are quoted as 338 mg/kg, 1944 mg/kg and 2620 mg/kg in the mouse, rat and guinea-pig respectively. The major toxicity concerns associated with paracetamol in humans are the adverse hepatic and renal effects which can occur following ingestion of high doses.
A 13-week oral toxicity study in which rats received continuous administration of paracetamol at doses above 700 mg/kg/day. This resulted in changes in the liver, kidney, ureter and bladder as well as body-weight loss or reduced weight gain. In addition, evidence of the hepatotoxicity of high-dose paracetamol is available from a study in which a dose of 400 mg/kg induced liver injury in mice (indicated by alanine aminotransferase activity and glutathione levels).
The hepatotoxicity of high doses of paracetamol is generally thought to be due to the accumulation of the reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI) which, under conditions of glutathione depletion or insufficiency, binds to proteins in hepatocytes, resulting in hepatocellular necrosis and possible hepatic failure. Similarly, the pathogenesis of paracetamol-induced nephrotoxicity is attributed to accumulation of the metabolites NAPQI and p-benzoquinone, accompanied by the production of free radicals.
Guaifenesin
A search of the PubMed database from 1945 to date failed to identify any toxicological studies of guaifenesin in the published literature. However, in view of the long history of safe use of guaifenesin in humans, the lack of toxicity data is not considered to be associated with a safety risk.

Phenylephrine
Acute toxicity studies of phenylephrine performed in the 1960s and reported in the RTECS database give oral LD50 values of 120 mg/kg in the mouse and 350 mg/kg in the rat. In 12-week repeat dose toxicity studies, body weight gains decreased in a dose-related manner and food consumption was lower in treated rats. Deaths occurred in male rats and mice treated with dietary concentrations of 10,000 or 20,000 mg/kg. One of the 10 male rats treated with 5,000 mg/kg also died. An approximate estimate of dose levels achieved in these dietary studies indicates only minor effects after two years of continuous oral administration at doses up to about 60 mg/kg/day in rats and up to about 170 mg/kg/day in mice. These doses are substantially higher than the dose of phenylephrine provided by the proposed product in the recommended regimen.

Genotoxicity
Paracetamol does not cause gene mutations in either bacteria or mammalian cells, but it consistently produces chromosomal aberrations in in-vitro studies. The clastogenicity is concentration- and incubation time- dependent with clastogenic effects generally absent until cytotoxic concentrations are reached.
Guaifenesin
A literature search from 1945 to date failed to identify any genotoxicity studies of guaifenesin in the published literature. In view of the long history of safe use of guaifenesin in humans, the lack of data is not considered to be associated with a safety risk.
Phenylephrine
In an Ames test, phenylephrine-hydrochloride was not mutagenic in four strains of Salmonella typhimurium (TA100, TA1535, TA1537, and TA98) with or without S9 mix, and gave equivocal results in the mouse lymphoma L5178Y/TK+/- assay in the absence of S9 mix.
Phenylephrine-hydrochloride did not induce chromosomal aberrations in Chinese hamster ovary cells

Carcinogenicity
Paracetamol

Studies in mouse and rat were conducted within the US National Toxicology Program and were probably carried out in compliance with GLP. These studies indicated that paracetamol is non-carcinogenic when given at doses of up to 300 mg/kg/day.

Guaifenesin

A literature search from 1945 to date failed to identify any carcinogenicity studies of guaifenesin in the published literature. In view of the long history of safe use of guaifenesin in humans, the lack of data is not considered to be associated with a safety risk.

Phenylephrine

Two-year NTP studies in groups of 50 4-6-week-old F344/N rats and B6C3F1 mice of both genders showed no evidence of carcinogenicity of phenylephrine hydrochloride at the studied dietary concentrations of up to 1250 ppm for rats or 2500 ppm for mice. No increases in neoplasms were seen in any treatment group in either rats or mice.

Reproductive and developmental toxicity

Paracetamol

In a study assessing the reproductive effects of paracetamol over two generations in mice, there were no effects on gestation, parturition, lactation and offspring development at doses up to 1400 mg/kg/day. The greatest toxicity was on the growing neonate and seen as reduced weight gain during nursing. Some studies report conflicting effects for testicular abnormalities. Recent animal data indicated that cognition and behaviour may be altered following exposure to therapeutic doses of paracetamol during early development. However, no firm conclusion about the relevance of these observations to humans can be drawn.

Guaifenesin

Significant developmental toxicity associated with guaifenesin, particularly at high doses, was observed in a study of groups of five female Sprague-Dawley rats. Foetal mortality occurred at doses of 350, 500 and 600 mg/kg. There was a significant decline in foetal weight, full body length, skull length, forelimb length, hindlimb length, and tail length in all guaifenesin-treated groups.

Phenylephrine

Seminal vesicle atrophy and ovarian atrophy have been reported after high repeated doses of phenylephrine in the repeated-dose studies. The α-adrenergic stimulant effects of phenylephrine could cause constriction of uterine vessels and reduce uterine blood flow, thereby producing foetal bradycardia and hypoxia. Phenylephrine crosses the placenta in humans. Sympathomimetic agents are known to be teratogenic in some animal species. Phenylephrine has been reported to potentiate the teratogenic effect of acetazolamide in a dose-related manner in rats.

III.5 Ecotoxicity/environmental risk assessment

Since Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine Hydrochloride 6.1mg Capsule, hard, is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

As paracetamol, guaifenesin, and phenylephrine are well-known active substances, this is a bibliographic application with no new non-clinical studies conducted by the applicant. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

No clinical studies were submitted and none are required as this is a bibliographic application based upon literature.

Paracetamol, guaifenesin and phenylephrine hydrochloride are well-known active substances with established efficacy and tolerability when used in combination.

IV.2 Pharmacokinetics

In vitro dissolution data demonstrates the release profile of Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules with approximately 50% of the active substances released after 5 minutes.

PARACETAMOL
Absorption:
Paracetamol is rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring between 10 and 60 minutes after oral administration.

Distribution:
Paracetamol is relatively uniformly distributed throughout most bodily fluids and exhibits variable protein binding. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Biotransformation:
Paracetamol is metabolised in the liver.

Elimination:
Paracetamol is mostly excreted in the urine. Ninety percent of the ingested dose is eliminated via the kidneys within 24 hours as the glucuronide (60-80%) and sulphate conjugates (20-30%). Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours.

GUAIFENESIN
Absorption:
Guaifenesin is absorbed in the gastrointestinal tract after oral administration.

Metabolism and elimination:
Guaifenesin is rapidly metabolised by the liver by oxidation to -(2-methoxy-phenoxy)lactic acid which is excreted in the urine.

PHENYLEPHRINE HYDROCHLORIDE
Absorption:
Phenylephrine hydrochloride is irregularly absorbed from the gastrointestinal tract. Peak plasma levels occur within 2 hours.

Metabolism:
Phenylephrine hydrochloride undergoes first-pass metabolism by monoamine oxidase in the gut and liver. Therefore, orally administered phenylephrine has reduced bioavailability.

Elimination:
Phenylephrine hydrochloride is excreted in the urine almost entirely as the sulphate conjugate.

IV.3 Pharmacodynamics

PARACETAMOL
Paracetamol is an analgesic and antipyretic.

GUAIFENESIN
Guaifenesin is a well-known expectorant.

PHENYLEPHRINE HYDROCHLORIDE
Phenylephrine hydrochloride is a sympathomimetic amine which acts as a decongestant.

IV.4 Clinical Efficacy

The analgesic and antipyretic properties of paracetamol, the expectorant activity of guaifenesin and the nasal decongestant effect of phenylephrine are all well-established and the proposed indications and dosing is supported by literature data.

IV.5 Clinical Safety

The Applicant has given an adequate overview of the safety profiles of paracetamol, guaifenesin and phenylephrine hydrochloride based on literature data. The recommendations, contraindications, precautions and warnings in the proposed Summary of Product Characteristics are appropriate and consistent with these.

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 Paracetamol/Guaifenesin/Phenylephrine Hydrochloride.

Summary of safety concerns:

Important Identified Risks	Hepatotoxicity (paracetamol)
Important potential risks	None
Missing information	None

Routine pharmacovigilance activities and routine risk minimisation activities are suggested, which is endorsed.

Periodic Safety Update Reports (PSURs) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

This application is based on well-established use and therefore the clinical dossier is based upon published literature. Paracetamol, guaifenesin and phenylephrine hydrochloride are well-known active substances with established efficacy and tolerability.

V. OVERALL CONCLUSIONS

The overall assessment outcome of Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules, hard from Chefaro Ireland DAC, is positive.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Paracetamol 500mg, Guaifenesin 100mg, Phenylephrine hydrochloride 6.1mg capsules, hard demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

10.06.2026

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