Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg/Guaifenesin 100 mg/Phenylephrine hydrochloride 6.1 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Active Ingredient	mg/capsule
Paracetamol	500
Guaifenesin	100
Phenylephrine hydrochloride	6.1 (corresponding to 5mg phenylephrine base)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Capsule with translucent green body and opaque blue cap, 21mm long, filled with an off-white powder free from large aggregates and particulate contamination.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard is indicated in adults, the elderly and adolescents aged 16 years and over.

4.2 Posology and method of administration

Posology

Adults, the elderly and adolescents aged 16 years and over
2 capsules every 4 to 6 hours as needed to a maximum of 3 doses in 24 hours.
No more than 6 capsules (3g paracetamol) should be taken in any 24 hour period.

Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard should not be used in adults, the elderly and adolescents aged 16 years and over, who weigh less than 50 kg.

Paediatric population
Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard is not intended for use in children and adolescents under 16 years of age.

Elderly patients
Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing.

Renal impairment
Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medicine. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each dose to at least 6 hours (see section 4.4).

Hepatic impairment

Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medicine. The medicinal product should be used with caution in patients with mild or moderate hepatic impairment (see section 4.4). The medicinal product is contraindicated in patients with severe hepatic impairment (see section 4.3).

The maximum daily dose of paracetamol should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in the following situations, unless directed by a physician: (see section 4.4)

- Dehydration
- Malnutrition
- Chronic alcoholism

Method of administration

For oral use.
The capsules should be swallowed whole with water and should not be chewed.
The recommended daily dosage or the specified number of doses should not be exceeded because of the risk of liver damage (see section 4.4 and 4.9).

Treatment should be discontinued, and the patient should seek medical advice if:

- Symptoms persist for more than 3 days
- Symptoms get worse
- Any other symptoms occur

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients listed in section 6.1.
- Use in patients currently receiving, or within two weeks of stopping, therapy with monoamine oxidase inhibitors.
- Hypertension.
- Cardiovascular disease.
- Hyperthyroidism.
- Diabetes mellitus.
- Pheochromocytoma.
- Use in patients receiving therapy with tricyclic antidepressants, beta-blockers or other antihypertensive agents (see section 4.5).
- Angle closure glaucoma.
- Severe hepatic impairment
- Pregnancy
- Use in patients who are currently receiving other sympathomimetics (such as decongestants, appetite suppressants, amphetamine-like psychostimulants)

4.4 Special warnings and precautions for use

Underlying liver disease increases the risk of paracetamol-related liver damage. Paracetamol should be administered with caution to patients with renal impairment and mild or moderate hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

This medicine should be administered with particular caution under the following circumstances:

-Occlusive vascular disease (e.g. Raynaud's phenomenon).
-Gilbert's Syndrome (familial non-haemolytic jaundice).
-Glucose-6-phosphate dehydrogenase deficiency.
-Haemolytic anaemia.
-Glutathione deficiency.
-Dehydration.
-Elderly patients
-Urinary retention or prostatic hypertrophy.

-Chronic cough, asthma or emphysema.

Hepatotoxicity at therapeutic doses of paracetamol
Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2, 4.5 and 4.9).
Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation occurs or is suspected, treatment should be discontinued, and medical advice obtained. The diagnosis of medicine overuse headache is likely in patients who have frequent or daily headaches despite (or because of) the regular use of headache medicine.

Use with caution in patients with asthma who are sensitive to acetylsalicylic acid, since mild bronchospasms have been reported in association with paracetamol (cross reaction).

Patients should be advised not to take other paracetamol-containing products, cold and flu medicines or cough medicines concomitantly (see section 4.5). Due to the risk of irreversible liver damage, immediate medical advice should be sought in the event of overdose, even if the patient feels well (see section 4.9).

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of other paracetamol-containing products, cold and flu medicines or cough medicines should be avoided.

PARACETAMOL
The speed of absorption of paracetamol may be increased by metoclopramide (and raise its maximum plasma levels). As the total amount of paracetamol absorbed remains unchanged, this interaction is not likely to be clinically significant.

The speed of absorption of paracetamol may be increased by domperidone, and absorption reduced by colestyramine. Colestyramine should not be administered within one hour of taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding, although occasional doses have no significant effect.

Paracetamol is metabolized in the liver and can therefore interact with other medicines that follow the same pathway, or may inhibit or induce this route causing hepatotoxicity, particularly in overdose (see section 4.9).

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced because probenecid reduces the clearance of paracetamol by 50% by preventing the conjugation of paracetamol with glucuronic acid.

Alcohol may increase the hepatotoxicity of paracetamol, particularly after overdosage, and consumption should be avoided during treatment with this medicine.

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics, but its validity has been criticised and there is no evidence of a clinically relevant interaction. Although no routine monitoring is needed, it is important to bear this potential interaction in mind when these two medications are administered concomitantly, especially in malnourished patients.

```Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion ```gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).
GUAIFENESIN
Guaifenesin may interfere with diagnostic measurements of urinary 5-hydroxyindoleacetic acid or vanillylmandelic acid.

PHENYLEPHRINEHYDROCHLORIDE

Digoxin and cardiac glycosides. Concomitant use of phenylephrine may increase the risk of irregular heartbeat or heart attack.

Monoamine oxidase inhibitors. Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors. Concomitant use is contraindicated (see section 4.3).

Sympathomimetic amines. Concomitant administration of phenylephrine with sympathomimetic amines may increase the risk of cardiovascular side effects. Concomitant use is contraindicated (see section 4.3).

Ergot alkaloids (e.g. ergotamine and methysergide). Concomitant use of phenylephrine may cause increased risk of ergotism.

Beta-blockers and other antihypertensive agents (including debrisoquin, guanethidine, reserpine, methyldopa). Phenylephrine may reduce the efficacy of beta-blockers and antihypertensive agents. Concomitant use of phenylephrine may increase the risk of hypertension and other cardiovascular side effects. Concomitant use is contraindicated (see section 4.3).

Tricyclic antidepressants (e.g. amitriptyline). Concomitant use of phenylephrine may increase the risk of cardiovascular side effects. Concomitant use is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard is contraindicated during pregnancy.
Based on human experience, phenylephrine hydrochloride causes congenital malformation when administered during pregnancy. It has also been shown to have possible associations with foetal hypoxia.

A large amount of data on pregnant women indicate no malformative nor feto/neonatal toxicity of paracetamol. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

There are no data from the use of guaifenesin in pregnant women.

Lactation

Paracetamol and phenylephrine may be excreted in breast milk. It is not known whether guaifenesin is excreted in breast milk. Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard should not be used whilst breastfeeding without medical advice.

Fertility

There are no available human data regarding the influence of Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard on fertility.

4.7 Effects on ability to drive and use machines
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Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard has minor influence on the ability to drive and use machines. Patients should avoid driving or operating machinery if affected by dizziness.

4.8 Undesirable effects

The active ingredients are usually well tolerated in normal use.
Events reported in published literature at therapeutic/labelled dose and considered attributable, as well as events identified during post-marketing use of paracetamol, guaifenesin and phenylephrine are tabulated below by MedDRA System Organ Class.

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

PARACETAMOL

SystemOrganClass	**Undesirableeffect**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia, agranulocytosis, leukopenia, pancytopenia, neutropenia	Very rare
Immune system disorders	Anaphylaxis and allergic/hypersensitivity reactions	Rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to acetylsalicylic acid and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare
Skin and subcutaneous disorders	Cutaneous hypersensitivity reactions including skin rashes, pruritis, sweating, purpura, urticaria, and angioedema. Very rare cases of serious skin reactions have been reported. Toxic epidermal necrolysis (TEN), drug induced dermatitis, Stevens Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP)	Very rare
Renal and urinary disorders	Sterile pyuria	Very rare
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known

GUAIFENESIN

SystemOrganClass	**Undesirableeffect**	**Frequency**
Immune system disorders	Allergic reactions, angioedema, anaphylactic reactions	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea (reported in association with other symptoms of hypersensitivity)	Rare
Gastrointestinal disorders	Nausea, vomiting, abdominal discomfort, diarrhoea	Rare
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria)	Rare

PHENYLEPHRINEHYDROCHLORIDE

SystemOrganClass	**Undesirableeffect**	**Frequency**
Immune system disorders	Hypersensitivity, urticaria, allergic dermatitis	Not known
Psychiatric disorders	Nervousness, insomnia	Not known
Nervous system disorders	Headache, dizziness	Not known
Eye disorders	Mydriasis, acute angle glaucoma, most likely to occur in those with closed angle glaucoma	Rare
Cardiac disorders	Increased blood pressure, tachycardia, palpitations, reflex bradycardia, cardiac arrhythmias	Rare
Gastrointestinal disorders	Vomiting, diarrhoea, nausea	Not known
Skin and subcutaneous disorders	Allergic reactions, tingling and coolness of the skin, rash	Not known
Renal and urinary disorders	Dysuria, urinary retention, most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.	Not known

Description of selected adverse reactions
High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reportingofsuspectedadverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

PARACETAMOL
There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal in these cases. Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain.
An overdose of paracetamol, administered as a single dose, in adults or children can induce complete and irreversible liver cell necrosis resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.
Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors
If the patient:
a) is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
or
b) Regularly consumes ethanol in excess of recommended amounts.
or
c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.
Management
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.
Treatment with activated charcoal should be considered if the overdose has been taken within one hour. Plasma paracetamol concentration should be measured at four hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to eight hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

GUAIFENESIN
Symptoms
Very large doses of guaifenesin can cause nausea and vomiting.
When taken in excess, guaifenesin may cause renal calculi.

Management

Vomiting should be treated by fluid replacement and monitoring of electrolytes.
Renal calculi should be treated according to established treatment guidelines for urolithiasis.

PHENYLEPHRINE HYDROCHLORIDE

Symptoms

Phenylephrine hydrochloride overdose is likely to result in symptoms similar to the undesirable effects listed in Section 4.8. Additional symptoms may include irritability, restlessness, hypertension, reflex bradycardia, hyperpyrexia and tremor. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However, the amount of Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard required to produce serious phenylephrine hydrochloride toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Management

Symptoms should be treated according to established guidelines, as appropriate. Severe hypertension may need to be treated with an alpha blocking drug such as phentolamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Other analgesics and antypiretics, anilides, paracetamol, combinations excluding psycholeptics

ATC code: N02BE51

Mechanism of action

PARACETAMOL

Paracetamol is an analgesic and antipyretic.
Analgesic:
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. The relative lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Antipyretic:
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

Guaifenesin is a well-known expectorant. Such expectorants are known to increase the volume and water content of secretions in the respiratory tract, which facilitates their removal by ciliary action and coughing. This changes an unproductive cough to a cough that is more productive and less frequent.

PHENYLEPHRINE HYDROCHLORIDE

Phenylephrine hydrochloride is a well-known sympathomimetic amine which acts on alpha-adrenergic receptors of the respiratory tract to produce vasoconstriction. This temporarily reduces the swelling associated with inflammation of the mucous membranes lining the nasal and sinus passages, allowing free drainage of the sinusoidal fluid from the sinuses.

In addition to reducing swelling of the mucosal lining, phenylephrine hydrochloride also suppresses the production of mucus, thereby preventing a build-up of fluid within the cavities which could otherwise lead to pressure and pain.

5.2 Pharmacokinetic properties

In vitro dissolution data demonstrates the release profile of Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard capsule, 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 following two major metabolic pathways, with formation of glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

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.

In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, with the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects.

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 β-(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.

5.3 Preclinical safety data

Paracetamol 500mg/Guaifenesin 100mg/Phenylephrine hydrochloride 6.1mg capsules, hard has a well-established safety profile. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Croscarmellose sodium
Sodium lauryl sulfate

Magnesium stearate
Talc

Gelatin capsule:
Gelatin
Sodium lauryl sulfate
Quinoline yellow (E104)
Indigo carmine (E132)
Erythrosine (E127)
Titanium dioxide (E171)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pack sizes of 8, 16, 24 and 32 capsules are available.

Child resistant PVC blister lidded with paper/aluminium foil containing gelatin capsules with a green body and blue cap filled with an off-white powder.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC,
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/025/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th September 2021

Common Renewal Date: 6th October 2026

10 DATE OF REVISION OF THE TEXT

June 2026