Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Perrigo Cold & Flu Tablets Paracetamol 250 mg Guaifenesin 100 mg Phenylephrine hydrochloride 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient	**mg/Tablet**
Paracetamol	250
Guaifenesin	100
Phenylephrine Hydrochloride	5 (corresponding to 4.1 mg phenylephrine base)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White capsule shaped tablet, embossed with “PGP”, free from specks and blemishes.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms associated with colds and flu, including aches and pains, headache, blocked nose and sore throat, chills and chesty cough.

This medicine is indicated in adults, the elderly and adolescents aged 12 years and over.

4.2 Posology and method of administration

Posology:
Adults, the elderly and adolescentsaged 12 years and over:
Two tablets every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

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 medication. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours. The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (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 medication. 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 restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Method of administration
Route of administration: Oral.

Take tablets with water. Swallow whole, do not chew.

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).
Minimum dosing interval: 4 hours.

Dosage should not be continued for longer than 3 days without consulting a doctor.

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 (see Section 4.5).
· Hypertension.
· Cardiovascular disease
· Severe ischemic heart disease.
· Hyperthyroidism.
· Diabetes mellitus.
· Pheochromocytoma.
· Those taking tricyclic anti-depressant drugs or beta-blockers
· Angle closure glaucoma.
· Severe hepatic impairment
· Use in patients who are currently receiving other sympathomimetic drugs (see Section 4.5).
· Pregnancy
· Porphyria.

4.4 Special warnings and precautions for use

The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations).

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.These patients must seek medical advice before taking this medication. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

The product should be administered only with particular caution under the following circumstances:
• Circulatory disorders such as Raynaud's Phenomenon
• Chronic alcoholism
• Urinary retention or prostatic hypertrophy
• Gilbert's Syndrome (familial non-haemolytic jaundice)
• Concomitant treatment with medicinal products affecting hepatic function
• Glucose-6-phosphate dehydrogenase deficiency
• Haemolytic anaemia
• Glutathione deficiency
• Dehydration
• Chronic malnutrition
• The elderly, adults and adolescents weighing less than 50kg

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 hepaticenzymes 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.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Patients with prostatic hypertrophy may have increased difficulty with micturition.
Sympathomimetic-containing products should be used with great care in patients suffering from angina.

Sympathomimetic-containing products may act as cerebral stimulants giving rise to insomnia, nervousness, hyperpyrexia, tremor and epileptiform convulsions.

This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants).

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

Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid, since mild bronchospasms are reported in association with paracetamol (cross reaction).

Patients suffering from chronic cough or asthma should consult a physician before taking this product. Patients should stop using the product and consult a health care professional if cough lasts for more than 3 days or comes back, or is accompanied by a fever, rash or persistent headache. Do not take with a cough suppressant.

Concomitant use of other paracetamol containing products, decongestants or cold and flu medicines should be avoided.
Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

Do not exceed the recommended dose. Do not take with alcohol
If symptoms persist or worsen, consult your doctor. Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

PARACETAMOL
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding, 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.Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol particularly in overdose (see Section 4.9)

Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors because of a risk of hypertensive crisis (see Section 4.3).
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 since probenecid reduces the clearance of paracetamol by 50% since it prevents the conjugation of paracetamol with glucuronic acid.

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics but its validity has been criticised and evidence of a clinically relevant interaction appears to lack. Although no routine monitoring is needed, it is

important to bear in mind this potential interaction when these two medications are concomitantly administered, 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, especially in patients with risks factors (see section 4.4)

GUAIFENESIN
If urine is collected within 24 hours of a dose of this product a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary-5- hydroxyindolacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

PHENYLEPHRINEHYDROCHLORIDE
Phenylephrine may adversely interact with other sympathomimetics, vasodilators and beta blockers. Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.

Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors.

Sympathomimetic-containing products should be used with great care in patients receiving phenothiazines or tricyclic antidepressants.

Sympathomimetic-containing products should be used in caution in patients receiving digitalis, beta-adrenergic blockers, guanethidine, reserpine, methyldopa or anti-hypertensive agents.

Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

This medicine should not be used with enzyme inducers such as alcohol.

Phenylephrine should be used with caution in combination with Ergot alkaloids (ergotamine and methylsergide), increase risk of ergotism.

Medical advice should be sought before taking this medicine in combination with the following drugs.
Digoxin and cardiac glycosides: Concomitant use of phenylephrine may increase the risk of irregular heartbeat or heart attack.

4.6 Fertility, pregnancy and lactation

Pregnancy
This product 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.

This product should not be used whilst breastfeeding without medical advice.
Fertility
There are no available human data regarding the influence of this medicine on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. 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

System Organ Class	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia, agranulocytosis	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 tissue 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 (cloudy urine)	Very rare
Gastrointestinal disorders	Acute pancreatitis	Not known

GUAIFENESIN

System Organ Class	Undesirable effect	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	Rare
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria)	Rare

PHENYLEPHRINE HYDROCHLORIDE

System Organ Class	Undesirable effect	Frequency
Immune system disorders	Hypersensitivity, urticaria, allergic dermatitis	Not known
Psychiatric disorders	Nervousness, irritability, restlessness, excitability, 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 Cutaneous hypersensitivity reactions including skin rashes, angioedema, and Stevens Johnson syndrome, toxic epidermal necrolysis. Pruritus, sweating, purpura and urticaria. Drug-induced dermatitis, Acute generalized exanthematous pustulosis (AGEP).	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
Investigations	Increased Blood Pressure	Rare

Reporting of suspected adverse 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@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. Overdose of paracetamol in a single administration in adults or in children causes liver cell necrosis likely to induce complete and irreversible 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, see British National Formulary (BNF) overdose section.

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. Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

GUAIFENESIN

Symptoms:
Gastrointestinal discomfort has occasionally been reported with Guaifenesin. When taken in excess, guaifenesin may cause renal calculi.
Management:
Very large doses of guaifenesin can cause nausea and vomiting. Vomiting should be treated by fluid replacement and monitoring of electrolytes. Treatment of renal calculi should be done according to scientific guidelines for urolithiasis.

PHENYLEPHRINE HYDROCHLORIDE

Phenylephrine Hydrochloride may elevate blood pressure with headache, vomiting and rarely palpitations, tachycardia or reflex bradycardia, tingling and coolness of the skin. There have been rare reports of allergic reactions.

Symptoms:

Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions.Symptoms of overdosage include irritability, palpitations, hypertension, difficulty in micturition, nausea, vomiting, thirst and convulsions.

Severe overdosage of phenylephrine may produce hypertension and associated reflex bradycardia, haemodynamic changes and cardiovascular collapse with respiratory depression.
However, the amount required to produce serious phenylephrine toxicity would be greater than required to cause paracetamol-related liver toxicity.

Management
Treatment measures include early gastric lavage and symptomatic and supportive measures. The hypertensive effects may be treated with an alpha-receptor blocking agent (such as phentolamine mesylate 6 – 10 mg) given intravenously, and the bradycardia treated with atropine, preferably only after the pressure has been controlled. In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken, particularly with regard to cardiovascular and respiratory systems. Convulsions should be controlled with intravenous diazepam. Chlorpromazine may be used to control marked excitement and hallucinations. Severe hypertension may need to be treated with an alpha-adrenoreceptor blocking drug, such as phentolamine. A beta blocker may be required to control cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Other analgesics and antipyretics &
Other cold combination preparations

ATC code: N02B E51

Mechanism of action
Paracetamol
Paracetamol is an analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Guaifenesin
Guaifenesin is an expectorant. It is thought to reduce sputum viscosity by increasing the volume and water content of the bronchial secretion, thereby facilitating the expectoration of sputum.

Phenylephrine
Phenylephrine Hydrochloride is a sympathomimetic decongestant with mainly direct effects on adrenergic receptors (predominantly alpha-adrenergic activity) producing nasal decongestion.
The active ingredients are not known to cause sedation.

5.2 Pharmacokinetic properties

PARACETAMOL
Absorption:
Paracetamol is rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring between 10 and 120 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 375 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 absorbed after oral administration. It 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 and undergoes first-pass metabolism by monoamine oxidase in the gut and liver. Therefore, orally administered phenylephrine thus has reduced bioavailability.

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

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber additional to that already covered in other sections of the SPC. 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

Core:
Microcrystalline cellulose
Stearic acid
Povidone

Film Coat:
Hypromellose
Polyethylene glycol

6.2 Incompatibilities

None known.

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

Child Resistant PVC/Al blister.

Pack sizes: 8, 10, 12, 16, 20 and 24 tablets, although not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st July 2010
Date of last renewal: 15th April 2015

10 DATE OF REVISION OF THE TEXT

October 2022