Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Perrigo Cold & Flu powder for oral solution Paracetamol 500 mg, Guaifenesin 200 mg, Phenylephrine hydrochloride 10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains:
Active Substance mg/Sachet
Paracetamol 500
Guaifenesin 200
Phenylephrine hydrochloride 10

Excipients of known effect:
- Sucrose 2077 mg
- Aspartame (E951) 12 mg
- Sodium citrate (E331) 500 mg (contains 117.3 mg sodium)
- Sodium cyclamate (E952) 100 mg (contains 11.5 mg sodium)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

An off-white powder with a characteristic citrus/menthol odour.

The reconstituted solution is opalescent yellow with a characteristic citrus/menthol odour.

4 CLINICAL PARTICULARS

Each sachet contains:

Active Substance		mg/Sachet
Paracetamol		500
Guaifenesin		200
Phenylephrine hydrochloride		10

Excipients of known effect:
- Sucrose 2077 mg
- Aspartame (E951) 12 mg
- Sodium citrate (E331) 500 mg (contains 117.3 mg sodium)
- Sodium cyclamate (E952) 100 mg (contains 11.5 mg sodium)

For the full list of excipients, see section 6.1.

4.1 Therapeutic indications

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.

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

4.2 Posology and method of administration

Posology

For all indications:
Adults, the elderly and adolescents aged 12 years and over:
One sachet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

Do not give to children under 12 years old.
Do not give to patients with hepatic or severe renal impairment (see Section 4.3).

Medical advice should be sought if symptoms persist for more than 3 days.

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.

Method of administration

Route of administration: Oral.
Dissolve the contents of one sachet in a standard mug of hot, but not boiling water (250 ml). Allow to cool to a drinkable temperature. Drink all the yellow solution within 1½ hours.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hepatic or severe renal impairment.
- Heart disease and cardiovascular disorders.
- Hypertension.
- Hyperthyroidism.
- Diabetes.
- Phaeochromocytoma.
- Use in patients taking tricyclic antidepressants or beta-blocking drugs (see section 4.5).
- Patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors.
- Use in patients with closed angle glaucoma or urinary retention.
- Use in patients who are currently receiving other sympathomimetic drugs (such as decongestants, appetite suppressants and amphetamine-like psychostimulants).
- Pregnancy

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).
- 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.
- The product should be administered only with particular caution under the following circumstances :

    - Prostatic hypertrophy (patients may experience increased difficulty with micturition)
    - Occlusive vascular disease e.g. Raynaud's phenomenon
    - Cardiovascular disease
    - Myasthenia gravis – an autoimmune disorder
    - Severe gastrointestinal diseases
    - Glucose-6-phosphatedehydrogenase deficiency
    - Haemolytic anaemia
    - Glutathione deficiency
    - Chronic malnutrition
    - Chronic alcoholism
    - Gilbert's Syndrome (familial non-haemolytic jaundice)
    - Concomitant treatment with medicinal products affecting hepatic function
    - Dehydration

- The elderly, adults and adolescents weighing less than 50kg

- This medicine should only be recommended if all symptoms (pain and/or fever, nasal congestion and chesty cough) are present.
- 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.
- 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).
- Do not take with a cough suppressant.
- Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
- Concomitant use with alcohol should be avoided.
- Patients should be advised not to take other paracetamol-containing products concurrently. 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).
- 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.
- Hepatotoxicity at therapeutic doses of paracetamolCases 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.
- 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.
- Contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Contains aspartame (E951) a source of phenylalanine. May be harmful for people with phenylketonuria.
- This medicinal product contains 129 mg sodium per sachet, equivalent to 6.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

PARACETAMOL

Pharmacological interactions involving paracetamol with a number of other drugs have been reported. These are considered to be of unlikely clinical significance in acute use at the dosage regimen proposed.

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

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, although occasional doses have no significant effect.

The hepato-toxicity of paracetamol may be potentiated by excessive intake of alcohol.

Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol particularly after overdosage. Paracetamol is contraindicated

in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors because of a risk of hypertensive crisis.

Regular use of paracetamol probably reduces metabolism of zidovudine (increased risk of neutropenia).

Salicylates/aspirin may prolong the elimination $t_{1/2}$ of paracetamol.

Concomitant paracetamol and NSAID's treatment increases the risk of renal dysfunction.

Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests.

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 may cause a colour interference with laboratory determinations of 5 hydroxyindoleacetic acid (5-HIAA) and vanillymandelic acid (VMA).

Guaifenesin potentiates the action of sedatives and muscle relaxants.

PHENYLEPHRINE HYDROCHLORIDE
Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported:

Monoamine oxidase inhibitors (including moclobemide)	Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see contraindications)
Sympathomimetic amines	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects
Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)	Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased
Tricyclic antidepressants (e.g. amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine
Phenothiazides used as sedatives	May potentiate CNS effects.
Ergot alkaloids (ergotamine and methylsergide)	Increased risk of ergotism
Cardiac glycosides (e.g. digitalis)	Increased risk of arrhythmia or heart attack
Halogenated anaesthetic agents (such as cyclopropane, halothane, enflurane, isoflurane)	May provoke or worsen ventricular arrhythmias

4.6 Fertility, pregnancy and lactation

Pregnancy

Perrigo Cold & Flu Powder for Oral Solution is contraindicated during pregnancy.

Paracetamol

A large amount of data on pregnant women indicate neither malformative nor feto/neonatal toxicity Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Guaifenesin

There are no or limited amount of data from the use of guaifenesin in pregnant women. The safety of guaifenesin during pregnancy has not been established.

Phenylephrine Hydrochloride

Based on human experience phenylephrine hydrochloride causes congenital malformations when administered during pregnancy. It has also been shown to have possible associations with fetal hypoxia. Phenylephrine should not be used during pregnancy.

Breast-feeding

The use of this medicine is not recommended whilst breastfeeding without medical advice due to insufficient data.

Paracetamol

Paracetamol / metabolites are excreted in human milk, but at therapeutic doses of the product no effects on the breastfed new-borns/infants of treated women are anticipated.

Guaifenesin / Phenylephrine Hydrochloride

There is insufficient information on the excretion of guaifenesin/ phenylephrine hydrochloride /metabolites in human milk.

Fertility

There are no or limited amount of data regarding the use of paracetamol, guaifenesin or phenylephrine hydrochloride and its impact on fertility.

4.7 Effects on ability to drive and use machines

Driving or operating machinery should be avoided if this medicine causes dizziness

4.8 Undesirable effects

The frequency of occurrence of undesirable effect is usually classified as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

PARACETAMOL
Adverse events from historical clinical trial data are both infrequent and from limited patient exposure. Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by MedDRA System Organ Class. Due to limited clinical trial data, the frequency of these adverse events is unknown (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare (≥1/10,000 to <1/1,000) and serious reactions are very rare (<1/10,000).

Body System	Undesirable effect
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis These are not necessarily causally related to paracetamol
Immune system disorders	Anaphylaxis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction
Gastrointestinal disorders	Acute pancreatitis

*There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Immune system disorders
• Rare (≥1/10,000, <1/1000): allergies (not including angioedema).

Skin and subcutaneous tissue disorder
• Very rare (<1/10,000):

- Cutaneous hypersensitivity reactions including skin rashes and angioedema.
- Very rare cases of serious skin reactions have been reported.
- Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS).
- Pruritus, sweating, purpura and urticaria.
- Drug-induced dermatitis, Acute generalized exanthematous pustulosis (AGEP).

Renal and urinary disorders:

• Very rare (<1/10,000): sterile pyuria (cloudy urine).

GUAIFENESIN

Body system	Undesirable effect	Frequency
Immune system disorders	Allergic reactions, angioedema, anaphylactic reactions	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Rare
Gastrointestinal disorders	Nausea, vomiting, abdominal discomfort, diarrhoea	Rare
Skin and subcutaneous disorders	Rash, urticaria	Rare

PHENYLEPHRINE HYDROCHLORIDE
The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events, though actual frequencies are not available.

Body System	Undesirable effect
Psychiatric disorders	Nervousness, irritability, restlessness, and excitability. Insomnia.
Nervous system disorders	Headache, dizziness
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, Vomiting, diarrhoea

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown but likely to be rare (≥1/10,000 to <1/1,000).

Body System	Undesirable effect
Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, allergic dermatitis).

	Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics.
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

Immune system disorders
• Rare (≥1/10,000, <1/1000): hypersensitivity, urticaria, allergic dermatitis.

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, website: www.hpra.ie

4.9 Overdose

PARACETAMOL
Paracetamol overdose can result in liver damage which may be fatal.

Signs and Symptoms
Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.
Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels. Overdose of paracetamol can cause liver cell necrosis, and, 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 also develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have also been reported.

Risk factors
Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
Some patients may be at increased risk of liver damage from paracetamol toxicity:
Risk factors include;
• Patients with liver disease;
• Elderly patients;
• Young children;
• Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes;
• Patients who regularly consume ethanol in excess of recommended amounts;
• Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

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

GUAIFENESIN

Symptoms and signs

Very large doses of guaifenesin can cause nausea and vomiting.

Treatment

Vomiting should be treated by fluid replacement and monitoring of electrolytes if indicated.

PHENYLEPHRINE HYDROCHLORIDE

Symptoms and signs

Phenylephrine overdose is likely to result in effects similar to those listed under adverse reactions.Additional symptoms may include hypertension and possibly associated reflex bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur, however the amount required to produce serious phenylephrine toxicity would be greater than required to cause paracetamol-related toxicity.

Treatment

Clinically appropriate treatment measures should be instituted and may 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 blood pressure has been controlled.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Paracetamol combinations excl. psycholeptics

ATC code: N02BE51

PARACETAMOL

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.

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 of secretions in the respiratory tract and therefore to facilitate their removal by cilary action and coughing.

PHENYLEPHRINE HYDROCHLORIDE

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.

The active ingredients are not known to cause sedation.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Following the ingestion of paracetamol dissolved in a hot drink, paracetamol absorption was both significantly faster and greater over the first 60 min post dose compared with standard tablets, as evidenced by a more rapid appearance of paracetamol in the plasma (median time to reach $t_{0.25\mu g/ml}$ of 4.6 min for the hot drink and 23.1 min for the standard tablets). In addition, t_{max} was significantly shorter for the hot drink compared with standard tablets. Such differences may be explained by a more rapid gastric emptying of the hot drink. Peak plasma concentrations are attained 10-60 minutes following oral dosing. Paracetamol is primarily metabolised in the liver via three pathways: glucuronidation, sulphation and oxidation. It is excreted in the urine, mainly as the glucuronide and sulphate conjugates. The elimination half-life ranges from 1 to 3 hours.

Guaifenesin is rapidly absorbed from the gastrointestinal tract after oral administration with maximum blood levels occurring within 15 minutes of administration. It is rapidly metabolised in the kidneys by oxidation to β-(2 methyoxy-phenoxy) lactic acid, which is excreted in the urine. The elimination half life is one hour.

Phenylephrine hydrochloride is irregularly absorbed from the gastrointestinal tract and undergoes firstpass metabolism by monoamine oxidase in the gut and liver; orally administered phenylephrine thus has reduced bioavailability. It is excreted in the urine almost entirely as the sulphate conjugate. Peak plasma levels occur between 1 and 2 hours and the plasma half life ranges from 2 to 3 hours.

5.3 Preclinical safety data

Preclinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use in the product and which have not already been mentioned elsewhere in this Summary.

Conventional studies using the currently accepted standards for the evaluation of toxicity of paracetamol to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Citric acid E330
Tartaric acid E334
Sodium cyclamate E952
Sodium citrateE331
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

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf life: 36 months.

Shelf life after reconstitution: 1½ hours.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Pack sizes:
5 sachets
6 sachets
10 sachets
14 sachets
15 sachets
20 sachets

Not all pack sizes may be marketed.

The sachet laminate comprises:
Ionomer (product contact layer)/aluminium foil /low density polyethylene/ paper (outer layer).

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused 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

PA1186/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th February 2018
Date of last renewal: 21st December 2021

10 DATE OF REVISION OF THE TEXT

August 2023