SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Guaifenesin/Phenylephrine Hydrochloride Wrafton 500mg/200mg/10mg Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient	**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.

Sachets containing the drug product, an off-white powder with a characteristic citrus/menthol odour.

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

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 children aged 12 and over.

4.2 Posology and 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 of the yellow solution within 1½ hours.

For all indications:

Adults, the elderly and children aged 12 years and over:

One sachet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

Children under 12 years:

Not to be used unless recommended by a doctor.

Dosage should not be continued for longer than 5 days without consulting a doctor

4.3 Contraindications

Hypersensitivity to paracetamol, guaifenesin, phenylephrine hydrochloride or to any of the excipients listed in section 6.1.

Hepatic or severe renal impairment

Heart disease and cardiovascular disorders, including severe haemolytic anaemia.

Hypertension

Hyperthyroidism

Diabetes

Phaeochromocytoma

Those taking tricyclic antidepressants or beta-blocking drugs (see section 4.5)

Those currently taking other paracetamol-containing products (see section 4.4)

Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors (see section 4.4).

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).

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.

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

Medical advice should be sought before taking this product in patients with these conditions:

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.

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, or is accompanied by a fever, rash or persistent headache.

Patients should stop using this product and consult a health care professional if cough lasts for more than 5 days or comes back.

Do not take with a cough suppressant.

Care is advised in the administration of paracetamol to patients with severe

renal or hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Concomitant use with alcohol should be avoided.

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 of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Special label warnings

Contains paracetamol. Do not take with any other paracetamol-containing products.

Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Do not take with other flu, cold or decongestant products.

Special leaflet warnings

Contains paracetamol. Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

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, although occasional doses have no significant effect. The hepato-toxicity of paracetamol may be potentiated by excessive intake of alcohol.

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.

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. 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 t1/2 of 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.

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

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

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

Paracetamol

A large amount of data on pregnant women indicate no malformative nor feto/neonatal toxicity of paracetamol. Paracetamol can be used during pregnancy if clinically needed 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. 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 unless the clinical condition of the woman requires treatment.

Breast-feeding

This product should not be used whilst breast feeding without medical advice.

Paracetamol

Paracetamol / metabolites are excreted in human milk, but at therapeutic doses of the product no effects on the breastfed newborns/infants are anticipated.

Guaifenesin

There are no or limited amount of data from the use of guaifenesin in pregnant women. Phenylephrine Hydrochloride
There is insufficient information on the excretion of Phenylephrine Hydrochloride/metabolite excreted 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)
Commo
n (>
1/100 to
< 1/10)
Uncom
mon (>
1/1,000
to <
1/100)
Rare (>
1/10,00
0 to
1/1,000)
Very rare (< 1/10,000)
Not known (incidence cannot be assessed on the basis of 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).

Very rare cases of serious skin reactions have been reported.

Body System	Undesirable effect
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis These are not necessarily causally related to paracetamol
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome, toxic epidermal necrolysis

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.

GUAIFENESIN

The frequency of these events is unknown but considered likely to be rare

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

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
Nervous system disorders	Headache, dizziness, insomnia
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).

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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

PARACETAMOL

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

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 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 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 overdosage 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. This allows the free drainage of the sinusoidal fluid from the sinuses.

In addition to reducing mucosal lining swelling, decongestants also suppress the production of mucous, therefore preventing a build up of fluid within the cavities which could otherwise lead to pressure and pain.

5.2 Pharmacokinetic properties

PARACETAMOL

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. 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.

GUAIFENSIN

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Citric acid E330

Tartaric acid E334

Sodium cyclamate E952

Sodium citrate E331

Acesulfame potassium E950

Aspartame E951

Powdered menthol flavour [contains natural menthol, corn maltodextrin and arabic gum (E414)]

Lemon flavour [contains flavouring preparation, natural flavouring substance, corn maltodextrin, arabic gum E414, sodium citrate E331, citric acid E330 and butylated hydroxyanisole E320 (0.01%)]

Lemon juice flavour [contains flavouring preparation, natural flavouring substance(s),

maltodextrin, modified starch E1450 and butylated hydroxyanisole E320 (0.03%)]

Quinoline yellow E104.

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 30°C.

6.5 Nature and contents of container

Pack sizes:

5 sachets

6 sachets

10 sachets

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

Wrafton Laboratories Limited

Braunton

Devon

EX33 2DL

8 MARKETING AUTHORISATION NUMBER(S)

PL 12063/0126

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

16/03/2017