Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rowasip Max Strength Cold and Flu with Decongestant 1000 mg/12.2 mg Powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Sachet contains:
Paracetamol 1000 mg
Phenylephrine hydrochloride 12.2 mg corresponding to phenylephrine 10.0 mg

Excipients with known effect:
Sucrose 3.8 g
Aspartame (E951) 35 mg
Sorbitol (E420) 1 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral solution

Free flowing white powder with lemon odour

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short term symptomatic treatment of colds and influenza (aches, fever) when associated with nasal congestion.

Paracetamol/Phenylephrine is indicated in adults and children over 16 years of age.

4.2 Posology and method of administration

Posology

Adults and adolescents over 16 years

One sachet dissolved in a mug (250 ml) by stirring in hot water.

The dose may be repeated in 4-6 hours.
No more than four doses should be taken in 24 hours.

Paediatric Population

Children under 16 years of age:
Paracetamol/Phenylephrine is not recommended for use in children below the age of 16 years without medical advice.

Hepatic insufficiency
In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

Renal insufficiency
In case of severe renal insufficiency (creatinine clearance < 10 ml/min) the dosing interval should be at least 8 hours.

Older people:
There is no indication that dosage needs to be modified in the elderly.

Medical supervision is recommended if symptoms are not relieved or deteriorate within 3 days of therapy with Paracetamol/Phenylephrine.

Method of Administration

Oral administration after dissolution in water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Severe coronary heart disease
- Hypertension
- Glaucoma
- Hyperthyroidism
- Use in patients taking tricyclic antidepressants
- Use in patients who are currently taking or have taken monoamine oxidase inhibitors (MAOIs) within the last 2 weeks
- Severe impairment of liver function
- Acute Hepatitis
- Alcohol abuse

4.4 Special warnings and precautions for use

Use with caution in patients with
- Raynaud's phenomenon
- Diabetes
- Moderate and severe renal insufficiency
- Liver function disorders: mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh >9), acute hepatitis and concomitant treatment with medicinal products affecting hepatic functions
- haemolytic anaemia
- dehydration
- alcohol abuse
- chronic malnutrition
- glutathione depletion due to metabolic deficiencies
- prostatic hypertrophy
- phaechromocytoma

This product should not be combined with other medicinal products that contain paracetamol. Higher doses than recommended may lead to severe liver damage. Clinical signs of liver damage normally become evident 2 days after ingestion. Antidote should be given as soon as possible. See also section 4.9.
Alcoholic beverages should be avoided while taking this medicine because alcohol use in combination with paracetmol may cause liver damage.
Patients should not take other sympathomimetic containing products concomitantly, including other nasal or eye decongestant products.

Each sachet contains 3.9 g of sucrose

This should be taken into account in patients with diabetes mellitus.

Contains sucrose and sorbitol (E420). 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol
Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, anticonvulsants such as phenytoin, phenobarbital, methylphenobarbital and primidone, rifampicin, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.
The speed of absorption of paracetamol may be decreased by anticholinergic drugs (e.g., glycopyrronium, propantheline), and increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
Isoniazide reduces paracetamol clearance with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Probenecid reduces clearance of paracetamol by inhibiting conjugation with glucoronic acid.
Regular use of paracetamol possibly reduces metabolism of zidovudine (increased risk of neutropenia).
The elimination half-life of chloramphenicol may be prolonged by paracetamol.

Phenylephrine
Phenylephrine may adversely interact with other sympathomimetics, vasodilators, alpha- and beta-blockers and other antihypertensives (including guanethidine).
The vasopressor effects of phenylephrine can be potentiated by digoxin, MAO inhibitors, tricyclic antidepressants such as amitriptyline, amoxapine, clomipramine, desipramine and doxepine or tetracyclics such as maprotiline; antidepressants such as phenelzine, isocarboxylic acid, nialamide, tranylcipromine, moclobemide; Parkinson's disease drugs such as selegiline, and others such as furazolidone.
Contraindicated for patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors

Paediatric population
Frequency, type and severity of interactions in children over the age of 16 years are expected to be the same as in adult.

4.6 Fertility, pregnancy and lactation

Pregnancy
Paracetamol
Epidemiological studies in human pregnancy have shown no ill-effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

Phenylephrine
There are limited data on the use of phenylephrine in pregnant women. Vasoconstriction of uterine vessels and reduced uterine blood flow associated with use of phenylephrine may result in fetal hypoxia. Until more information is available, use of phenylephrine should be avoided during pregnancy.

Breast-feeding
Paracetamol
Paracetamol is excreted in breastmilk, but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Phenylephrine
There are no data available on whether phenylephrine is released into breast milk and no reports on the effects of phenylephrine on the nursing infant. Until more data are available, use of phenylephrine should be avoided in lactating woman.

In summary Paracetamol/Phenylephrine is not recommended during pregnancy and lactation.

Fertility
There is no evidence from non-clinical studies indicating effects of paracetamol on male or female fertility at clinically relevant doses. The effects of phenylephrine on male or female fertility have not been studied.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No such effects have been described to date.

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

System organ class	Frequency	Symptoms
Blood and lymphatic system disorders	Rare	Blood dyscrasias including platelet disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia
Immune system disorders	Rare	Allergic or hypersensitivity reactions including skin rashes, urticaria, anaphylaxis and bronchospasm
Gastrointestinal disorders	Very rare	Acute pancreatitis
Hepatobiliary disorders	Rare	Abnormal hepatic function (increase in hepatic transaminases), hepatic failure, hepatic necrosis, jaundice.
Skin and subcutaneous tissue disorders	Rare	Hypersensitivity including skin rash and urticaria, pruritus, sweating, purpura, angioedema
Renal and urinary disorders	Very rare	Interstitial nephritis after prolonged use of high doses of paracetamol Sterile pyuria (cloudy urine)

Erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported with a not known frequency.
Very rare cases of serious skin reactions have been reported.

Paediatric population
Frequency, type and severity of adverse reactions in children over the age of 16 years are expected to be the same as in adults.

Phenylephrine

System organ class	Frequency	Symptoms
Immune system disorders	Rare	Allergic or hypersensitivity reactions including skin rash, urticaria, anaphylaxis and bronchospasm
Nervous system disorders	Very rare	Insomnia, nervousness, tremor, anxiety, restlessness, confusion, irritability, dizziness and headache may occur
Cardiac disorders	Rare	Tachycardia, palpitation
Vascular disorders	Rare	Blood pressure increase
Gastrointestinal disorders	Common	Anorexia, nausea and vomiting

Paediatric population
Frequency, type and severity of adverse reactions in children over the age of 16 years are expected to be the same as in adults.

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: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

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 (single dose of 10 g or more of paracetamol). Ingestion of a single dose of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

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 include:
If the patient;
a. Is on long-term treatment with carbamazepine, phenobarbitone, 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 depleted 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.
After prolonged use of high doses of paracetamol hypokalemia may develop.

Emergency Procedure:
Immediate transfer to hospital
Blood sampling to determine initial paracetamol plasma concentration
Gastric lavage
IV (or oral if possible) administration of the antidote N-acetylcysteine as soon as possible and before the 10th hour of the overdose
Symptomatic treatment should be implemented

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other analgesics and antipyretics
ATC- Code: N02BE51

Mechanism of action
Paracetamol
In vivo, paracetamol has both analgesic and antipyretic activity, which is believed to be mediated through inhibition of the cyclooxygenase (COX) pathway within the central nervous system. Although this mechanism is shared with the nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol does not have significant anti-inflammatory activity nor does it inhibit production of pro-clotting thromboxanes. Additional pathways such as the serotonergic descending pain pathways may be involved in the antinociceptive effect of paracetamol.

Phenylephrine
Phenylephrine is a potent alpha1-adrenoceptor agonist. Its action on the peripheral $alpha_1$ receptors induces vasoconstriction, which in the nasal mucosa, reduces oedema and nasal swelling. When given intravenously, phenylephrine consistently increases total peripheral resistance (TPR), systolic (SBP) and diastolic (DBP) blood pressure, while heart rate declines as a result of reflex bradycardia. The hemodynamic alterations brought about by IV phenylephrine may differ according to age and baseline blood pressure. Young normotensive subjects will show larger heart rate decreases and lower SBP increases than young hypertensives and old normotensives, while old hypertensives show the least pronounced reflex bradycardia and most pronounced SBP rise. The orally administered drug has not demonstrated consistent cardiovascular effects at the recommended doses of 10 – 12.2 mg QID, and oral doses of 40 to 60 mg are needed to elicit clinically meaningful cardiovascular effects such as increased diastolic blood pressure and reflex cardiac slowing.

Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors. Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs.

5.2 Pharmacokinetic properties

Paracetamol
Absorption/Distribution
The absolute bioavailability of orally administered paracetamol is 75 %, and is probably subject to first-pass metabolism. Tmax, though formulation-dependent, is usually between 30 and 120 minutes. The extent of absorption is however not formulation-dependent.

Elimination
Half-life is approximately 2 - 2.5 hours.

Biotransformation
The major metabolites are glucuronide and sulphate conjugates (>80 %) which are excreted in urine. A small amount (<10 %) of paracetamol is oxidized in the liver by cytochrome P4502E1 (CYP2E1). This reaction produces the highly reactive metabolite N-acetyl- p-benzoquinone imine (NAPQI), which is responsible for the characteristic centrilobular hepatotoxicity associated with paracetamol overdoses.

Phenylephrine
Absorption/Distribution
When administered by intravenous infusion, free 3H-phenylephrine concentration peaks at the end of the infusion, after serum concentration declines in a biexponential pattern, with an 80 % decline in the first 15 minutes, followed by a slower decline with an average half-life of 2 hours. When taken orally, phenylephrine is absorbed from the gastrointestinal tract with a serum peak between 45 and 75 minutes.

Elimination
Following a short phase of fast elimination, the average elimination half-life is 2.5 hours. At steady state, the volume of distribution is 340 l, indicating storage in certain organ compartments. Renal clearance is only a fraction of total plasma clearance.

Biotransformation
Due to extensive first-pass metabolism, total phenylephrine bioavailability is approximately 38 %, of which 1% is active, non-conjugated parent phenylephrine.

Phenylephrine retains activity as a nasal decongestant when given orally, the drug distributing through the systemic circulation to the vascular bed of nasal mucosa. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4-6 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid,
Sucrose,
Aspartame (E951),
Lemon flavours (containing: natural lemon oils and natural and nature identical flavouring substances, maltodextrin, mannitol (E 421), gluconolactone, acacia gum, sorbitol) (E420), silica colloidal anhydrous and α-tocopherol (E 307)),
Saccharin sodium,
Silica colloidal anhydrous,
Citric acid anhydrous,
Sodium citrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Reconstituted solution in hot water: 1 hour.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions

Store in the original packaging in order to protect from light and moisture.

6.5 Nature and contents of container

Laminated aluminium paper foil sachets in a carton box.

Pack sizes:

10 sachets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/227/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th December 2014

10 DATE OF REVISION OF THE TEXT