Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medisip with Decongestant Powder for Oral Solution
Paracetamol 500mg
Phenylephrine hydrochloride 12.2mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Sachet contains:

Paracetamol	500 mg
Phenylephrine hydrochloride	12.2 mg
corresponding to phenylephrine	10.0 mg

Excipients with known effects:

Sucrose	1829.7 mg
Aspartame (E951)	17.5 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.

The reconstituted solution is visually colourless, slightly opalescent, free from particles and precipitates.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Medisip with Decongestant Powder for Oral Solution is indicated in adults and children over 16 years of age.

4.2 Posology and method of administration

Posology

Adults:
One sachet dissolved by stirring in half a mug of hot water (approx. 125 ml).
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:
Medisip with Decongestant Powder for Oral Solution is not recommended for use in children below the age of 16.

Adolescents over 16 years of age:

One sachet dissolved by stirring in half a mug of hot water (approx. 125 ml).
The dose may be repeated in 4-6 hours.
No more than four doses should be taken in 24 hours.

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

Renal insufficiency
Medisip with Decongestant Powder for Oral Solution should be used with caution in the presence of renal insufficiency and increased interval between doses is recommended in case of severe renal insufficiency. When creatinine clearance is lower than 10 ml/min. the minimum interval between two administrations should be 8 hours.

Hepatic insufficiency
Medisip with Decongestant Powder for Oral Solution should be used with caution in the presence of hepatic insufficiency or Gilbert's syndrome. The dose should be reduced or the dosing interval prolonged.

Medical supervision is recommended if symptoms are not relieved or deteriorate within 3 days of therapy with Medisip with Decongestant Powder for Oral Solution.

Monotherapy should be used if one of the symptoms is dominant.

Method of Administration

Oral administration after dissolution in water.

4.3 Contraindications

Hypersensitivity to the active substances paracetamol or phenylephrine or to any of the excipients listed in section 6.1.
Severe coronary heart disease and cardiovascular disorders
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 mellitus
- Moderate and severe renal insufficiency
- Liver function disorders:
  mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), concomitant treatment with medicinal products affecting hepatic functions
- haemolytic anaemia,
- dehydration
- chronic malnutrition
- glutathione depletion due to metabolic deficiencies
- prostatic enlargement
- 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.

Patients should not take other sympathomimetic containing products concomitantly, including other nasal or eye decongestant products.

Each sachet contains approximately 1.9 g of carbohydrates. 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.

Aspirin-hypersensitive asthmatics may also be hypersensitive to Medisip with Decongestant Powder for Oral Solution.

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).

Phenylephrine
Phenylephrine may adversely interact with other sympathomimetics, vasodilators and beta-blockers and other antihypertensives.
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 adolescents over the age of 16 years are expected to be the same as in adult.

4.6 Fertility, 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.

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.

Breastfeeding
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 Medisip with Decongestant Powder for Oral Solution is not recommended during pregnancy and lactation.

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
Skin and subcutaneous tissue disorders	Rare	Hypersensitivity including skin rash and urticaria, pruritus, sweating, purpura, angioedema
Immune system disorders	Rare	Allergic or hypersensitivity reactions including skin rashes, urticaria, anaphylaxis and bronchospasm
Hepatobiliary disorders	Rare	Abnormal hepatic function (increase in hepatic transaminases), hepatic failure, hepatic necrosis, jaundice.
Renal and urinary disorders	Very rare	Interstitial nephritis after prolonged use of high doses of paracetamol Sterile pyuria (cloudy urine)
Gastrointestinal disorders	Very rare	Acute pancreatitis

Very rare cases of serious skin reactions have been reported.

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.

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

Phenylephrine

System organ class	Frequency	Symptoms
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
Immune system disorders	Rare	Allergic or hypersensitivity reactions including skin rash, urticaria, anaphylaxis and bronchospasm

Paediatric population
Frequency, type and severity of adverse reactions in adolescents 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: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol
Immediate medical advice should be sought in the event of overdosage because of the risk of irreversible liver damage.

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 and this may be manifested in increasing pro-thrombin time, which is a reliable indicator of deteriorating liver function. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, coma 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.
Liver damage is likely in adults who have taken 10g or more of Paracetamol. Acute or chronic ingestion of Paracetamol above the recommended dose may lead to liver damage particularly if the patient has risk factors.

Risk Factors
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 deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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.

Management

Immediate treatment is essential in the management of Paracetamol overdose. Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentrations should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Or any patient who have ingested about 7.5g or more of Paracetamol in the preceding 4 hours should undergo gastric lavage. Plasma paracetamol concentrations should be measured at 4 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 8 hours post indigestion.

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. General supportive measures must be available.

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

Phenylephrine hydrochloride
Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression. Treatment includes early gastric lavage and symptomatic and supportive measures. Hypertensive effects may be treated with an i.v. alpha-receptor blocking agent.

Phenylephrine overdose is likely to result in: nervousness, headache, dizziness, insomnia, increased blood pressure, nausea, vomiting, mydriasis, acute angle closure glaucoma (most likely to occur in those with closed angle glaucoma), tachycardia, palpitations, allergic reactions (e.g. rash, urticaria, allergic dermatitis), dysuria, urinary retention (most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy).

Additional symptoms may include, hypertension, and possibly 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 that required to cause paracetamol-related liver toxicity.

Treatment should be as clinically appropriate. Severe hypertension may need to be treated with alpha blocking medicinal products such as phentolamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paracetamol combinations excl. psycholeptics
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.

Mechanism of action 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.
In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations.
In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

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

3 years

Duration of storage after reconstitution:
The reconstituted solution in hot water is stable for 1 hour at room temperature, although immediate consumption is advised.

6.4 Special precautions for storage

Store in the original packaging in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Laminated aluminium paper foil sachets.

5, 6, 8, 10, 12, 16, 20 sachets are contained in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjördur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/160/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th March 2015

10 DATE OF REVISION OF THE TEXT

June 2016