SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Snip tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 325mg paracetamol, 15mg pseudoephedrine hydrochloride and 1mg clorpheniramine maleate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, flat, scored tablets embossed Snip.
The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Snip is indicated for:

- Relief of symptoms associated with cold and flu, such as: nasal congestion, rhinitis, sneeze, fever, mild to moderate pain of different origin
- Additional, for alleviating symptoms of hay fever and other allergies of upper respiratory tract associated with fever.

4.2 Posology and method of administration

Posology

Adults

Two tablets up to four times daily as required for relief of symptoms. The dose should not be repeated more frequently than every four hours nor should more than four doses be given in any 24 hour period.

Paediatric population

- Children 12 years and over: as for adults.
- For children 6 to 11 years old: 1 tablet every 4 to 6 hours, not to exceed 6 tablets per day. For children between 6 to 8 years old the maximum recommended dose is 5 tablets per day.

- Children under 6 years old: As with any antihistamine-containing product, use of Snip tablets in children under 6 years of age should be only under the advice and supervision of a physician.

Elderly: as for adults.

Renal/hepatic impairment
Consideration should be given to a reduced total daily dosage in patients with hepatic or renal impairment.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Not to be used by patients taking monoaminoxidase inhibitors (MAOI's) or for two weeks after stopping the MAOI drug.

4.4 Special warnings and precautions for use

Ischaemic colitis
Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine.
Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Severe Skin reactions
Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small

pustules are observed, administration of Snip should be discontinued and appropriate measures taken if needed.

Care is advised in the administration of Snip to patients with renal or hepatic impairment, cardiac or peripheral vascular disease, hypertension, hyperthyroidism, prostatic hypertrophy, diabetes mellitus or glaucoma, breathing difficulties such as emphysema or chronic bronchitis, epilepsy or thyrotoxicosis.
Do not exceed the stated dose.

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.

Chlorpheniramine may cause drowsiness, dizziness, blurred vision and psychomotor impairment, which can seriously hamper the patients' ability to drive and operate machinery.
Anginal pain may be precipitated in angina pectoris.
Patients should be advised not to take other paracetamol-containing products or sympathomimetic agents concurrently.
Patients should be advised to consult their doctor if their cold or flu symptoms persist.
Keep all medicines safely away from children.

4.5 Interaction with other medicinal products and other forms of interaction

The co-administration of Snip with tricyclic antidepressants, sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants), or with monoamine oxidase inhibitors (MAOI's) (or within two weeks of stopping MAOI's) which interfere with the catabolism of sympathomimetic agents, may occasionally cause a rise in blood pressure and may lead to hypertensive crisis in the case of MAOI's.
Because of its pseudoephedrine content, this product may partially reverse the hypotensive action of drugs, which interfere with sympathetic activity including alpha- and beta- adrenergic blocking agents and methyldopa.
Drowsiness caused by Chlorpheniramine can be exacerbated by concomitant use of alcohol, sedatives and tranquilizers. Chlorpheniramine inhibits phenytoin metabolism and can lead to phenytoin toxicity.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of Snip with increased risk of bleeding; occasional doses have no significant effect.

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).

Absorption of paracetamol is increased by drugs, which increase gastric emptying e.g. metoclopramide and domperidone and decreased by drugs which decrease gastric emptying e.g. tricyclic antidepressants, narcotic analgesics. The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol and anticonvulsants.
Patients should avoid alcohol while taking Snip.

4.6 Fertility, pregnancy and lactation

Do not use Snip if pregnant or breast-feeding without medical advice.

4.7 Effects on ability to drive and use machines

Chlorpheniramine can cause drowsiness; if affected patients should not drive or operate machinery.

4.8 Undesirable effects

The frequencies of the adverse reactions are defined as follows: Very common (≥11/10); Common (≥11/100 to <1/10); Uncommon (≥11/1,000 to <1/100); Rare (≥11/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Adverse effects of Snip are rare but a variety of allergic cutaneous reactions, with or without systemic features, have been reported.

Blood and lymphatic system disorders
Very rare: There have been very rare reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily causality related to Snip.

Psychiatric disorders
Rare: Hallucinations have been reported rarely.
Not known: nervousness

Nervous system disorders

Not known: dizziness, insomnia, agitation and restlessness have also been reported but these are usually mild, drowsiness.

Eye disorders

Not known: Ischaemic optic neuropathy.

Cardiac disorders

Not known: tachycardia.

Vascular disorders

Not known: hypertension.

Gastrointestinal disorders

Not known: Ischaemic colitis, dry mouth.

Skin and subcutaneous tissue disorders

Rare: Hypersensitivity including skin rash, angioedema have also been reported rarely.

Very rare: Very rare cases of serious skin reactions have been reported.

Not known: Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP).

Renal and urinary disorders

Not known: Urinary retention can occur in those patients with prostatic enlargement.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system.

4.9 Overdose

PARACETAMOL

Symptoms

Symptoms of paracetamol overdose 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, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been

reported. Liver damage is possible in adults who have taken 10g or more of paracetamol. It is considered that excess quantities of a 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 a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Gastric lavage or the administration of activated charcoal may be beneficial when performed within one hour of the overdose but can be considered for up to four hours after the overdose. Antidotes such as N acetylcysteine (NAC) and methionine protect the liver if administered within 12 hours of overdose. NAC is effective up to and possibly beyond 24 hours. General supportive measures must be available.

PSEUDOEPHEDRINE

Symptoms

As with other sympathomimetics pseudoephedrine overdose will result in symptoms due to central nervous system and cardiovascular stimulation e.g. excitement, irritability, restlessness, tremor, hallucinations, hypertension, palpitations, arrhythmias and difficulty with micturition. In severe cases, psychosis, convulsions, coma and hypertensive crisis may occur. Serum potassium levels may be low due to extracellular to intracellular shifts in potassium.

Management

Treatment should consist of standard supportive measures. Beta-blockers should reverse the cardiovascular complications and the hypokalaemia.

CHLORPHENIRAMINE

Symptoms

Symptoms and signs of chlorpheniramine overdose include sedation, paradoxical stimulation of CNS, toxic psychosis, seizures, apnoea, convulsions, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.

Management

Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route treatment should include gastric lavage or induced emesis. Following these measures activated charcoal and cathartics may be administered to minimise absorption. Treat hypotension and arrhythmias vigorously. CNS convulsions may be treated with i.v. diazepam or phenytoin. Haemoperfusion may be used in severe cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paracetamol, combinations without psycholeptics. ATC code: N02BE51

The analgesic and antipyretic actions of paracetamol are believed to be due, at least in part, to inhibition of prostaglandin synthesis in the central nervous system. Paracetamol 1 g has been shown to be an effective analgesic and antipyretic.

Pseudoephedrine is predominantly an indirect-acting sympathomimetic amine. Pseudoephedrine 60 mg has been shown to be an effective nasal decongestant, as measured by nasal airflow, in patients with the common cold and rhinitis.

At therapeutic doses, pseudoephedrine has no clinically significant effect on blood pressure in normotensive patients. Studies in patients with controlled hypertension have demonstrated that pseudoephedrine 60 mg has no, or minimal, effect on blood pressure and does not have sedative effects.

Chlorpheniramine produces a dose-dependent inhibition of histamine-induced wheal and flare in healthy subjects. Following a single dose of chlorpheniramine 4 mg, the effect is apparent within one hour and lasts at least 12 hours. Chlorpheniramine produces sedation in man although the effect is variable and tolerance develops. The anti-cholinergic properties of chlorpheniramine have been demonstrated in man. These anticholinergic properties are relevant clinically in conditions associated with rhinorrhoea since the seromucosal glands of the nose are under anticholinergic control.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and completely absorbed from the gastro-intestinal tract with peak plasma levels occurring about 0.25-2 hours after dosing. The absolute bioavailability is about 80% and is independent of dose in normal therapeutic doses (5-20 mg/kg). It is not bound to plasma proteins. The volume of distribution is about 0.9 l/kg. The plasma half-life ranges from 1-3 hours and is largely unaffected by age. It is metabolised in the liver and excreted in the urine as the glucuronide and sulphate conjugates. In overdose situations, saturation of the detoxification of a minor metabolite, N-acetyl-p-benzoquinoneimine, by conjugation with glutathione occurs and this leads to its accumulation and resultant liver damage.

Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract after oral administration, with no presystemic metabolism. Peak plasma levels are achieved after 1-2 hours. No protein binding data are available. The volume of distribution ranges from 2.64 to 3.51 l/kg in both single and multiple dose studies. The plasma half-life varies from 4.3-7.0 hours in adults. There is little metabolism of pseudoephedrine in man with approximately 90% being excreted in the urine unchanged. Approximately 1% is eliminated by hepatic metabolism, by N-demethylation to norpseudoephedrine.

As a weak base, the extent of renal excretion is dependent on urinary pH. At low urinary pH, tubular resorption is minimal and urine flow rate will not influence clearance of the drug. At high pH (>7.0),

pseudoephedrine is extensively reabsorbed in the renal tubule and renal clearance will depend on urine flow rate.

Hepatic disease is unlikely to affect the pharmacokinetics of pseudoephedrine. Renal impairment will result in increased plasma levels.

Chlorpheniramine has relatively low oral bioavailability (25-50%) indicating extensive first pass metabolism in the liver. Administration with food reduces bioavailability. Peak plasma levels occur 2-3 hours following administration of immediate release and 6-8 hours following administration of immediate release formulations. The drug is extensively metabolised via demethylation in the liver to mono and didesmethyl derivatives and by deamination to polar alcoholic and acidic derivatives. There is considerable inter-subject variation in the half-life of the drug: the overall mean from a range of studies in adults was 20.4 hours with a range from 3-43 hours. The half-life of the d-isomer is approximately 60% longer than that of the l-isomer suggesting stereoselective metabolism. The half-life in children appears shorter. Chlorpheniramine is primarily excreted via the kidneys. At steady state, approximately 34% of chlorpheniramine is excreted as the parent drug. Since clorpheniramine is a weak base, renal excretion will vary with urinary pH.

5.3 Preclinical safety data

Preclinical safety data on paracetamol, pseudoephedrine and chlorpheniramine in the literature have not revealed findings which are of relevance to the recommended dosage and use of the product and which have not been mentioned elsewhere in the summary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Microcrystalline cellulose 101
Microcrystalline cellulose 105
Croscarmellose sodium
Powdered cellulose
Magnesium stearate

<u>Paracetamol DC 90</u>
Pregelatinized starch
Corn starch
PVP K-30
Stearic Acid (Type 50)
Sodium Start Glycolate (Type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 years.

6.4 Special precautions for storage

Store below 30°C in the original package.

6.5 Nature and contents of container

Packs containing 10, 20 and 30 tablets in PVC/Alu blisters are available.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

08478/08037/VAR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/09/2011

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10. DATE OF REVISION OF THE TEXT