SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panadol Cold & Sinus 500mg / 30mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500 mg and pseudoephedrine hydrochloride 30mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

A bilayer (white/blue) film-coated capsule shaped tablet. The tablet is debossed with the number 2 in a circle on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Panadol Cold & Sinus is indicated in adults and in children and adolescents aged 12 years and over for the symptomatic relief of nasal congestion when combined with fever and/or pain such as, sore throat, sinus pain or headache in the common cold or influenza.

4.2 Posology and method of administration

Posology

Adults, including the elderly, and children 16 years and over:
Two tablets up to three times daily as required for relief of symptoms.
No more than eight tablets should be taken in 24 hours.

Elderly patients
Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing.

Paediatric population

Children aged 12 to 15 years old:
One tablet up to three times daily as required for relief of symptoms.

Not to be used in children under 12 years of age.

The dose should not be repeated more frequently than every four hours nor should more than three doses be given in any 24 hour period.

Do not exceed the stated dose.

Method of administration

For oral use.
The tablets should be taken with water.

Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage (see section 4.4 and 4.9).

Minimum dosing interval: 4 hours.

If pain or fever persist for more than 3 days or get worse, or if any other symptoms occur, treatment should be discontinued and a physician consulted.

Special Populations
Pseudoephedrine is primarily excreted renally. Pseudoephedrine should not be used by those with severe renal impairment (see Contraindications) and should be used with caution in those with moderate renal impairment (see 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetics).

Paracetamol and pseudoephedrine
Renal impairment
Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours. The kidney impairment restrictions relate to the use of both paracetamol and pseudoephedrine. (see section 4.4).

Paracetamol
Hepatic impairment
Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

4.3 Contraindications

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

The antibiotics furazolidone and linezolid should not be taken with Panadol Cold & Sinus (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Not to be used by patients with the following conditions:
- Hypertension

- Diabetes mellitus
- Severe coronary artery disease
- Cardiovascular disease
- Hyperthyroidism
- Prostatic hypertrophy
- Glaucoma
- Severe renal impairment
- Pheochromocytoma

Not to be used by patients currently receiving other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants).

Not to be used by patients taking beta-blockers (see 4.5 Interaction with other medicinal products and other forms of interaction).

Not to be used in children under 12 years of age.

4.4 Special warnings and precautions for use

Use with caution in patients with hepatic impairment or mild to moderate renal impairment or arrhythmias.

Use with caution in patients taking antihypertensives (see 4.5 Interaction with other medicinal products and other forms of interaction).

The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

This product may give rise to insomnia and nervousness.

Care is advised in the administration of Panadol Cold & Sinus to patients who will be undergoing general anesthesia within a few days.

Pseudoephedrine

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

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

Cases of PRES and RCVS have been reported with the use of pseudoephedrine-containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).

Pseudoephedrine should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment.

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 Panadol Cold & Sinus should be discontinued, and appropriate measures taken if needed.

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.

Risks of abuse
Pseudoephedrine carries the risk of abuse. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. The recommended maximum dose and treatment duration should not be exceeded (see section 4.2).

Paracetamol

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):
- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR ≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

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.

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).

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as with severe renal impairment and sepsis,

or in patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

If you are taking medication or are under medical care, consult your doctor or pharmacist.

Keep all medicines safely out of sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

The co-administration of this medicine with tricyclic antidepressants, the antidepressant moclobemide 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 moclobemide or MAOI's.

The antibiotic furazolidone is a monoamine oxidase inhibitor and the antibiotic linezolid is a reversible non-selective MAOI with weak MAO-inhibitory properties. Therefore neither should be taken with this medicine.

Pseudoephedrine may antagonize the effect of certain classes of antihypertensives (e.g., beta-blockers, methyl-dopa, reserpine, debrisoquine, guanethidine) (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

The rate of paracetamol absorption may be reduced by colestyramine. The interaction can be avoided by delaying administration of colestyramine by one hour, in order to maintain maximal analgesic effects.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of this medicine with increased risk of bleeding; occasional doses have no significant effect.

Sodium bicarbonate alkalinizes the urine and may reduce the renal elimination of pseudoephedrine, a reduction in dose may be necessary.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especiallyin patients with risks factors (see section 4.4).

The use of drugs which induce hepatic microsomal enzymes, such as anticonvulsants and oral contraceptive steroids, may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentrations of the drug and a faster elimination rate. Drugs which induce hepatic microsomal enzymes, such as alcohol and barbiturates, may increase the hepatotoxicity of paracetamol, particularly after overdose.

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

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics, but its validity has been criticized and evidence of a clinically relevant interaction appears to be lacking. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use of paracetamol-pseudoephedrine combination products in pregnancy has not been established despite widespread use over many years.

The product should be avoided during pregnancy, particularly during the first trimester, as defective closure of the abdominal wall (gastroschisis) has been reported very rarely in new-borns after first trimester exposure.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/fetal development and postnatal development. The use of this medicine during pregnancy is therefore not recommended.

Breast-feeding

Pseudoephedrine is excreted in breast milk, in amounts leading to increased risk of effects in the infants even at therapeutic doses. May suppress lactation. This product should not be used whilst breastfeeding without medical advice.

Fertility

There are no data available regarding the influence of paracetamol and pseudoephedrine hydrochloride on fertility.

4.7 Effects on ability to drive and use machines

Dizziness is one of the most frequent adverse effects. This could affect driving or using machines.

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. The following convention has been utilized for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

The following adverse reactions have been reported with products containing paracetamol and/or pseudoephedrine.

System Organ Class (SOC)	**Frequency**	**Adverse Drug Reaction**

Blood and the lymphatic system	Very Rare	Blood dyscrasia, including thrombocytopenia and agranulocytosis
Immune system disorders	Rare	Hypersensitivity*
	Very Rare	Anaphylaxis
Psychiatric disorders	Common	Nervousness, insomnia
	Uncommon	Agitation, restlessness
	Rare	Hallucinations
Nervous system disorders	Common	Dizziness
	Not known	Posterior reversible encephalopathy syndrome (PRES) (see section 4.4), Reversible cerebral vasoconstriction syndrome (RCVS) (see section 4.4)
Eye disorders	Not Known	Ischaemic optic neuropathy
Gastrointestinal disorders	Common	Dry mouth, nausea, vomiting
	Not known	Ischaemic colitis
Skin and subcutaneous tissue disorders	Rare	Rash, dermatitis allergic*
	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	Uncommon	Urinary retention**, dysuria
Cardiovascular disorders	Uncommon	Minor tachycardia
	Rare	Cardiac arrhythmias, hypertension
Hepatic disorders	Very Rare	Hepatic dysfunction
Respiratory disorders	Very Rare	Bronchospasm is more likely in patients sensitive to aspirin or NSAIDs.
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis***

*A variety of allergic skin reactions, with or without systemic features such as bronchospasm, angioedema have been reported following use of pseudoephedrine. Hypersensitivity reactions, including skin rashes, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, angioedema and anaphylaxis have been reported very rarely with paracetamol.

**Urinary retention is most likely to occur in those with bladder outlet obstruction such as prostatic hypertrophy.

*** Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below). Liver damage may become apparent 12 to 48 hours after ingestion.
Cardiac arrhythmias and pancreatitis have been reported.

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

Symptoms
Symptoms of paracetamol overdose usually occur within the first 24 hours and are pallor, nausea, vomiting, anorexia and abdominal pain.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin time that may appear 12 to 48 hours after administration. Abnormalities of glucose metabolism and metabolic acidosis may occur. Clinical symptoms of liver damage are usually evident initially after 2 days, and reach a maximum after 4 to 6 days.

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. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of 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 in accordance with established treatment guidelines.

Paracetamol concentrations in blood should be measured not less than 4 hours after overdose in order to be able to assess the risk of developing liver damage (using the paracetamol overdose nomogram). However, N-acetylcysteine (NAC) treatment should be started immediately when massive overdose is suspected.

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.

Intravenous (IV) infusion (or oral administration if IV infusion is not possible) of the antidote N-acetylcysteine should be started if possible before the 8th hour. The effectiveness of the antidote declines sharply after this time. N-acetylcysteine can, however, give some degree of protection even after 8 hours, and up to 24 hours, but in these cases prolonged treatment is given. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Symptomatic treatment should be implemented.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides, ATC Code: N02B E51

Panadol Cold & Sinus is a mild to moderate analgesic, antipyretic and decongestant.

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 1g has been shown to be an effective analgesic and antipyretic.

Pseudoephedrine acts on the alpha adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results is shrinkage of swollen nasal mucous membranes, reduction of nasal congestion and increase in nasal airway patency.

Pseudoephedrine 60mg 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 60mg has no, or minimal, effect on blood pressure and does not have sedative effects.

A clinical study was conducted in patients with symptoms of cold and flu to assess relief of pain and nasal congestion. The study compared this medicine (taken three times daily as required for three days) with paracetamol alone, pseudoephedrine alone and placebo. Results demonstrated that this medicine gives significantly ($p<0.05$) greater pain relief than either placebo or pseudoephedrine and that this medicine has a significantly ($p<0.05$) greater decongestant effect than either placebo or paracetamol. Panadol Cold & Sinus demonstrated an additive effect for relief of pain and nasal congestion compared to paracetamol or pseudoephedrine. For a single dose of this medicine there was significantly greater ($P<0.05$) relief of pain and nasal congestion (nasal airflow) compared to placebo at one hour post dose.

5.2 Pharmacokinetic properties

Paracetamol

Absorption
The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood saliva and plasma. Protein binding is low.

Biotransformation
Paracetamol is metabolised mainly in the liver, following two major metabolic pathways: Glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalyzed by the Cytocrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulphate conjugates (20-30%). Less than 5% is eliminated in unchanged form.
Elimination half life is about 2 hours.

Renal insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly subjects: Conjugation capacity is not modified.

Pseudoephedrine

Absorption
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.

Distribution
Pseudoephedrine is rapidly distributed throughout the body. 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.

Biotransformation
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.

Elimination**:**
The plasma half-life varies from 4.3-7.0 hours in adults. As a weak base the extent of renal excretion is dependent on urinary pH. At low 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.

Renal insufficiency: Renal impairment will result in increased plasma levels.

Elderly subjects: Elimination capacity is not modified.

A steady state pharmacokinetic interaction study in healthy volunteers has demonstrated that the rate (C_{max}, t_{max}) and extent ($AUC_{0\text{-}6\ hours}$) of absorption from this medicine is equivalent to those of paracetamol alone and of pseudoephedrine alone.

In the same study the median t_{max} values for the paracetamol and pseudoephedrine components of this medicine were 0.7 hours and 1.2 hours, respectively.

5.3 Preclinical safety data

Paracetamol / pseudoephedrine has a well-established safety profile.
There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline E 460
Silica, Colloidal anhydrous E 551
Stearic acid E 570
Magnesium stearate E 572
Starch pregelatinised
Povidone
Crospovidone

Croscarmellose sodium E 468
Hypromellose E 464
Macrogol
Carnauba wax E 903
Indigo carmine E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Opaque blister strips of PVC/ PE/ PVdC backed with aluminium foil. Blisters are packed into cartons and each carton contains 2, 5, 6, 10, 12, 16, 18, 24, 30 or 32 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Omega Pharma Ltd,
Wrafton, Braunton,
Devon, EX33 2DL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 02855/0076

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/11/2012

10 DATE OF REVISION OF THE TEXT

28/01/2025