Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Panadol Max Strength Cold & Flu Hot Berry plus Vitamin C Powder for Oral Solution Paracetamol 1000 mg Ascorbic Acid 70 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose sachet contains paracetamol 1000 mg and ascorbic acid 70 mg.

Excipients with known effect:
Each sachet contains 5.01 g of sucrose
Each sachet contains 120 mg of sodium
Each sachet contains 80 mg aspartame (E951)
Contains carmoisine (E122) and sunset yellow (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.
Pale pink powder with a characteristic fruity menthol odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The relief of symptoms of influenza, feverishness, chills and feverish colds including headache, and aches and pains.

4.2 Posology and method of administration

For oral use.

Adults (including the elderly) and children aged 16 years and over:
One sachet, dissolved in a cup or mug of hot water, to be taken every four hours up to a maximum of four sachets in any 24 hours.

Do not exceed the stated dose.

Do not take more often than every 4 hours.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Children under 16 years of age:
Not to be given to children under 16 years of age, except on medical advice.

4.3 Contraindications

This product is contraindicated in patients with hypersensitivity to paracetamol, ascorbic acid or to any of the excipients listed in section 6.1 and in patients with severe hepatic or renal impairment and in children under 16 years of age.

4.4 Special warnings and precautions for use

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, sepsis and in acute and chronic malnutrition (low reserves of hepatic glutathione).
Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Paracetamol should be administered with caution to patients with these risk factors.

Caution is also advised in conditions which may predispose to glutathione deficiency (see section 4.9).

Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

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

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.
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.

Do not exceed the stated dose.

Keep all medicines out of reach and sight of children.
Contains 5 g sucrose per dose. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains 120 mg sodium per dose, equivalent to 6% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 24% of the WHO recommended maximum daily intake for sodium. This product is considered high in sodium. This should be particularly taken into consideration for those on a low salt diet.
This medicinal product contains 80 mg of aspartame in each dose. Aspartame is a source of phenylalanine and may be harmful in patients with phenylketonuria (PKU)

Contains the colours carmoisine (E 122) and sunset yellow (E 110), which may cause allergic reactions including asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol is reported to increase the half-life of chloramphenicol.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. 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. The hepatotoxicity of paracetamol may be potentiated by other drugs that affect the liver. 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, especially in patients with risks factors (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity from paracetamol. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Lactation
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

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.

4.8 Undesirable effects

The following convention has been utilised 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).

Adverse event frequencies have been estimated from spontaneous reports received through post marketing data.

Paracetamol

Body system	Undesirable Effect	Frequency
Blood and lymphatic system disorders	Thrombocytopaenia	Very rare
Immune System disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among other, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis. Very rare cases of serious skin reactions have been reported. Bronchospasmin patients sensitive to aspirin and other NSAIDs	Very rare
Metabolism andnutrition disorders	High anion gapmetabolic acidosis*	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

* 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 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, website: www.hpra.ie.

4.9 Overdose

Paracetamol

Symptoms and signs

Symptoms of paracetamol overdose in the first 24 hours may include pallor, nausea, vomiting, anorexia and abdominal pain. Abnormalities of glucose metabolism and metabolic acidosis may occur. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Clinical signs of liver injury occur usually after 24 to 48 hours. Four to 6 days after initial ingestion, hepatic necrosis leading to hepatic failure may occur which may lead to coagulation defects, followed by hepatic encephalopathy and failure of multiple organs. Liver damage results when excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver
tissue. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrythmias have been reported and acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Biochemical evidence of maximal damage, however, may not be attained until 72-96 hours after ingestion of the overdose.

Some patients may be at increased risk of liver damage from paracetamol toxicity:
Risk factors include;
• Patients with liver disease
• Young children
• Patients who regularly consume ethanol in excess of recommended amounts
• Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Treatment
Immediate transfer to hospital.
Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion.
Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.
Symptomatic treatment should be implemented.

Ascorbic Acid
High doses of ascorbic acid (>3000mg) may cause transient osmotic diarrhoea and gastrointestinal effects such as nausea and abdominal discomfort.

Effects of overdose of ascorbic acid would be subsumed by serious liver toxicity caused by paracetamol overdose.

General Considerations
If overdose is confirmed or suspected, seek immediate advice from your Poison Centre. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage.
Where a Poison Information Centre is not available, refer patient to the nearest Emergency Medical Centre for management and expert treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paracetamol combinations excluding psycholeptics.
ATC Code: N02BE 51

Paracetamol is an analgesic, antipyretic drug substance.

The antipyretic activity of paracetamol is thought to be mediated by its ability to selectively inhibit prostaglandin synthesis in the central nervous system.

The precise mechanism for the analgesic properties of paracetamol remains to be established. Data suggest that central prostaglandin synthetase inhibition is likely to be of primary importance. Paracetamol is a weak inhibitor of COX-1 and COX-2 leading to the suggestion that there may be another form of COX which is more sensitive to inhibition by paracetamol.

Paracetamol does not appear to inhibit the peripheral generation of prostaglandins, e.g., it does not alter the gastric mucosal generation of prostaglandins and serious gastro-intestinal adverse events associated with paracetamol are rare. Paracetamol is, therefore, particularly suitable for patients with a history of acid peptic disease or on concomitant medication where peripheral prostaglandin inhibition would be undesirable, e.g., with gastro-intestinal bleeding, cardiovascular disease or in the elderly.

Ascorbic acid (Vitamin C) is commonly included in combination cold products to compensate for vitamin C losses that may occur in the initial stages of acute viral infections, including the common cold. Vitamin C is also a dietary supplement.

5.2 Pharmacokinetic properties

Absorption and Distribution

Oral paracetamol is readily absorbed from the upper small intestine to give peak plasma concentrations of 15-20 mcg/ml in 30 to 120 minutes after oral administration of a 1000 mg dose in adults. The speed of gastric emptying modifies the rate of absorption. Plasma protein binding is minimal and there is distribution to all tissues.

Metabolism and Excretion
There is limited first-pass metabolism of paracetamol after oral administration and about 80% of a 1000 mg dose is bioavailable. Paracetamol is metabolised primarily in the liver. After a 1000 mg oral dose in adults, 50-60% is recovered in the urine as the glucuronide conjugate, 25-35% as the sulphate conjugate, up to 5% as unchanged paracetamol and 2-5% as the cysteine or mercapturate metabolites.

The latter are formed from the combination of glutathione with the oxidation metabolite of paracetamol, N-acetyl-p-benzoquinoneimine (NAPQI). Excretion via the urine is rapid and the plasma half-life after oral administration is 1-4 hours.

5.3 Preclinical safety data

Preclinical (Nonclinical) safety data on the drug substances in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product, which have not already been mentioned elsewhere in the SPC.

The toxicity of paracetamol is well documented.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Effects of chronic toxicity in rats and mice include gastrointestinal lesions, blood count changes, degeneration and necrotic changes in testicular and lymphoid tissue in addition to hepatic and renal necrosis.

Long-term studies in rats and mice give no conclusive evidence of carcinogenic effects. There is no evidence of embryo- or foeto-toxicity from paracetamol in animal studies.

Paracetamol hepatotoxicity is directly dependent on the plasma concentration in relation to time. In man, plasma concentrations above 1.2 mmol/l at 4 hours, 0.6 mmol/l at 8 hours, and 0.3 mmol/l at 12 hours are criteria for immediate antidote treatment to prevent irreversible damage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate, anhydrous
Tartaric acid
Aspartame (E951)
Blackcurrant Flavour (contains carmoisine (E122), sunset yellow (E110) and green S (E142))
Berry fruits flavour (contains menthol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Individual single dose aluminium laminate sachets containing 7.605g of powder.
Supplied in packs of 5 or 10 sachets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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