Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Night Nurse Capsules Paracetamol 500 mg Promethazine Hydrochloride 10 mg Dextromethorphan Hydrobromide 7.5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
Paracetamol 500.0 mg
Promethazine Hydrochloride 10.0 mg
Dextromethorphan Hydrobromide 7.5 mg

Excipients:
Lactose 60.04 mg per capsule

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsule
No. 0 hard gelatin capsule with an opaque bright green cap and opaque white body, printed 'night nurse' in black on both halves and containing a white free-flowing powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the night-time relief of the symptoms of colds, chills and influenza, including cough.

4.2 Posology and method of administration

For oral administration only.

Adults aged 16 years and over:
Take two capsules just before bedtime.

Only one dose (two capsules) should be taken per night.

Elderly
The normal adult dose can be taken by the elderly.

Do not exceed the stated dose.
The lowest dose necessary to achieve efficacy should be used.

Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4000mg (including this product) in any 24 hour period.
Allow at least four hours between taking any paracetamol-containing product and this product.
Maximum duration of continued use without medical advice: 7 days

Should not be used at the same time or within a 4 hour period of taking other cough or cold medicines, or any other antihistamine containing products, including those used on the skin.

If symptoms persist, consult a doctor.

4.3 Contraindications

- Known hypersensitivity to the active ingredients or to any of the excipients.
- Use in children under 16 years of age.
- Hepatic or renal impairment.
- Patients who are taking or have taken monoamine oxidase inhibitors (MAOIs) in the last two weeks.
- With, or at risk of developing, respiratory failure (e.g. those with chronic obstructive airways disease or pneumonia, or during an asthma attack or an exacerbation of asthma).

4.4 Special warnings and precautions for use

Contains paracetamol. Do not use with any other paracetamol-containing products, antihistamines or cold and flu medicines. The concomitant use with other products containing paracetamol may lead to an overdose.

Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol.

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.

Concomitant use of decongestant containing medicines or alcohol should be avoided.
Concomitant use of other antihistamines, cough and cold medicines should be avoided.

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients with severe renal or severe hepatic impairment should seek medical advice before treatment with paracetamol. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Medical advice must be sought before taking this product in people with:

- Chronic or persistant cough, such as occurs with asthma and emphysema, chronic bronchitis or where cough is accompanied by excessive secretions

Caution in patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis.

Consult your doctor if you are taking warfarin.

In patients with asthma or other respiratory disorders, epilepsy, glaucoma, urinary retention, prostatic hypertrophy or cardiovascular problems the product should only be taken after consulting a doctor.

Night Nurse should only be used under medical supervision for persistent or chronic cough such as occurs with smoking, asthma or emphysema, or where cough is accompanied by excessive secretions.

Medical advice should be sought before taking this product in people taking tricyclic antidepressants; selective serotonin reuptake inhibitors (SSRI); drugs which cause CNS depression, such as antipsychotics, hypnotics and anxiolytics, as concurrent use may cause an increase in sedative effects; or drugs with anticholinergic effects (e.g. atropine and tricyclic antidepressants)

Use with caution in the elderly, who are more likely to experience anticholinergic adverse effects including confusion and paradoxical excitation. Avoid use in elderly patients with confusion.
Children are more likely to experience paradoxical excitation with sedating antihistamines.

Medical advice should be sought if symptoms persist, or are accompanied by high fever, skin rash or persistent headache.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

If symptoms persist, please consult your doctor.

Patients, who are taking other medication and/or are under the care of a physician, should consult their doctor before taking the product.

Cases of dextromethorphan abuse and dependence have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors. Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, treatment with Night Nurse should be discontinued.

Promethazine may interfere with immunologic urine pregnancy tests to produce false positive or negative results.

Do not exceed the recommended dose schedule.

Keep out of the sight and reach of children

4.5 Interaction with other medicinal products and other forms of interaction

Potentially clinically significant drug interactions are listed below. Medical advice should be sought before taking paracetamol-promethazine-dextromethorphan in combination with these drugs:

Medicine	**Drug interactio**n
Monoamine-oxidase inhibitors (MAOIs), Selective serotonin re-uptake inhibitors (SSRIs), tricylic antidepressants	Severe reactions, including serotonin syndrome, with changes in mental status, hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor, may occur when this product is taken concomitantly, with selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, or within two weeks of taking, an MAOI (see Contraindications). MAOIs may prolong and intensify the anticholinergic effects of antihistamines.
Anticholinergic drugs such as atropine, MAOIs and tricyclic antidepressants	As promethazine has some anticholinergic activity, the effects of some anticholinergic drugs may be potentiated.
Alcohol	Concomitant use of alcohol with dextromethorphan and promethazine may increase the CNS depressant effects of these drugs. The hepatotoxicity of paracetamol may be potentiated by excessive intake of alcohol.
CNS depressant drugs such as antipsychotics, hypnotics or anxiolytics	Promethazine may potentiate the sedative effects of other CNS depressant drugs.
Warfarin and other coumarins	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.
Anti-emetics such as Metoclopramide and Domperidone	The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
Cholestyramine	The speed of absorption of paracetamol may be reduced by cholestyramine.
	Dextromethorphan is metabolized by CYP2D6 and has an

Inhibitors of Cytochrome P450 2D6	extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.
Flucloxacillin	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)

4.6 Fertility, pregnancy and lactation

Pregnancy

This product should not be used during pregnancy without medical advice.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. 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. This product should not be used during pregnancy unless the expected benefit justifies the potential risk to the foetus.

Human and animal studies with paracetamol have not identified any risk to pregnancy or embryo-foetal development.

No relevant data are available for products containing dextromethorphan.

Human and animal studies with promethazine are insufficient to establish the safety of this drug during pregnancy. It should only be used when considered essential by a doctor.

Lactation

This product should not be used whilst breast-feeding without medical advice.

Human studies with paracetamol have not identified any risk to lactation or the breast-fed offspring. Paracetamol crosses the placental barrier and is excreted in breast milk, but not in a clinically significant amount.

No relevant data are available for dextromethorphan.

Promethazine may be excreted in breast milk. It should only be used when considered essential by a doctor.

4.7 Effects on ability to drive and use machines

This medicine may cause drowsiness, dizziness, blurred vision, cognitive and psychomotor impairment which can seriously affect the ability to drive and use machinery. Those affected should not drive or operate machinery.

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Paracetamol

Body System	Undesirable Effect	Frequency
Blood and lymphatic system disorders	Thrombocytopaenia	Very rare
Immune system disorders	Very rare cases of serious skin reactions have been reported. Cutaneous hypersensitivity reactions including among others, skin rashes, angioedema, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.	Very rare
Respiratory, thoracic and mediastinal disorders	Aggravation of bronchospasm reported in asthmatic patients known to be sensitive to aspirin and other non-steroidal anti-inflammatory drugs.	Very rare
Hepatobiliary	Liver disfunction	Very rare

Promethazine

Adverse events may occasionally occur with promethazine. The available clinical and post marketing data is insufficient to reliably determine event frequencies.

Body System	Undesirable Effect	Frequency
Nervous system disorders	Drowsiness	Very common
	Psychomotor impairment Dizziness Restlessness Disturbance in attention Headache	Common
Eye disorders	Blurred vision	Common
Gastrointestinal disorders	Gastrointestinal disturbance	Not known
	Dry mouth	Common
Skin and subcutaneous system disorders	Rash Photosensitivity Urticaria Angioedema	Not known
Renal and urinary disorders	Urinary retention	Not known
Psychiatric disorders	Confusion* Disorientation* Paradoxical excitation*, ** (e.g. increased energy, irritability, restlessness, nervousness, sleep disturbance)	Not known
Immune system disorders	Hypersensitivity reactions including rash, urticaria, angioedema, anaphylaxis and photosensitivity	Not known

* The elderly are more susceptible to confusion, disorientation and paradoxical excitation.
** Children are more susceptible to paradoxical excitation.
The elderly are more susceptible to anticholinergic effects of promethazine.

Dextromethorphan

Adverse effects may occasionally occur with dextromethorphan. The available clinical and post-marketing data is insufficient to reliably determine event frequencies.

Body System	Undesirable Effect	Frequency

Nervous system disorders	Drowsiness, Dizziness. Serotonin syndrome (with changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor and hypertension) has been reported when dextromethorphan has been taken concurrently with MAOIs or serotonergic drugs such as SSRIs	Not known
Respiratory, thoracic and mediastinal disorders	Bronchoconstriction Dyspnoea	Not known
Gastrointestinal disorders	Gastrointestinal disturbance, nausea, vomiting, abdominal discomfort	Not known
Renal and urinary disorders	Urinary retention	Not known
Immune system disorders	Allergic reactions e.g. rash, urticaria, angioedema	Not known

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

Symptoms and Signs

Paracetamol

Paracetamol overdose can result in liver damage, which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise pallor, nausea, vomiting, anorexia, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause 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 patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

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

Acute renal failure with acute tubular necrosis may also develop even in the absence of severe liver damage.
Cardiac arrhythmias have also been reported.

Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Promethazine

In children, promethazine overdose can cause CNS stimulation and antimuscarinic effects. In severe cases in both adults and children, CNS depression with coma and convulsions may occur. Additional symptoms may include delirium, agitation, hallucinations, dystonic reactions, hypotension and ECG changes.
Large overdose may cause convulsions, toxic psychosis, arrhythmias, coma and cardiorespiratory depression.

Dextromethorphan

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability, dizziness, excitation, and gastrointestinal disturbances.
Following large overdoses, additional symptoms may include restlessness, nervousness and irritability, dystonia, and psychosis.
In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Treatment

Paracetamol

Emergency Procedure:

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.

Promethazine

Treatment should be supportive and directed towards specific symptoms, with attention to maintenance of adequate respiratory and circulatory status. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

Dextromethorphan

Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

Supportive and symptomatic care should be provided as required. If overdose is severe, naxalone may be helpful, particularly for patients with respiratory depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code/ Pharmacotherapeutic group: NO2 BE51

Paracetamol - an analgesic and antipyretic

Promethazine - an antihistamine with anticholinergic activity

Dextromethorphan hydrobromide - an antitussive

5.2 Pharmacokinetic properties

Paracetamol – is readily absorbed from the upper gastrointestinal tract. It is metabolised predominantly in the liver and excreted in the urine, mainly as glucuronide and sulphate conjugates.

Promethazine hydrochloride – is readily absorbed from the gastrointestinal tract, undergoes first pass metabolism in the liver and is excreted mainly as metabolites in the urine.

Dextromethorphan hydrobromide – is well absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted as demethylated metabolites including dextrorphan, and as a minor proportion of unchanged dextromethorphan. In a small proportion of individuals, metabolism proceeds more slowly and dextromethorphan predominates in blood and urine.

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

5.3 Preclinical safety data

Pre-clinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not already been mentioned elsewhere in this summary.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder Excipients
Lactose monohydrate
Dimeticone
Colloidal anhydrous silica

Capsule Shell
Patent blue V (E131)
Quinoline yellow (E104)
Titanium dioxide (E171)
Gelatin

Printing Ink
Shellac
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide yellow (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

The capsules are packed into opaque blister strips of polyvinylchloride backed with aluminium foil. The complete strip is contained in a boxboard carton containing 10 capsules.

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

Haleon Ireland Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 February 1990

Date of last renewal: 08 February 2010

10 DATE OF REVISION OF THE TEXT

May 2023