SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Night Nurse Hot Lemon Menthol Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituents	mg/sachet
Paracetamol	1000.0
Promethazine hydrochloride	20.0
Dextromethorphan hydrobromide	15.0

Excipients	mg/sachet
Aspartame	35.0
Sodium (as sodium citrate dihydrate)	117.3

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic relief of colds, chills and influenza at night.

4.2 Posology and method of administration

Route of Administration

Oral

Adults and children 16 years and over:

Empty contents of one sachet into a mug. Half fill with very hot water. Stir well. Add cold water as necessary.

One sachet to be taken just before going to bed.

Not to be given to children under 16 years except on medical advice.

Maximum daily dose: Only one sachet should be taken per night.

Do not exceed the stated dose

Maximum duration of continued use without medical advice: 3 days.

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.

Should not be used with other cough or cold medicines, or any other antihistamine-containing products, including those used on the skin.

4.3 Contraindications

Hypersensitivity to paracetamol, dextromethorphan, promethazine or any of the other constituents.

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).

Patients taking or have taken monoamine oxidase inhibitors (MAOIs) in the last two weeks.

4.4 Special warnings and precautions for use

Contains paracetamol. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Avoid use of other antihistamine-containing preparations, including topical antihistamines and cough and cold medicines.

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

- Severe renal or hepatic impairment. Underlying liver disease increases the risk of paracetamol-related liver damage. The hazards of overdose are greater in those with non-cirrhotic liver disease.
- Chronic or persistant cough, such as occurs with asthma and emphysema, chronic bronchitis or where cough is accompanied by excessive secretions.
- Narrow-angle glaucoma
- Cardiovascular problems
- Prostatic hypertrophy
- Urinary retention
- Epilepsy

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.

Medical advice should be sought before taking this product in people taking the following medications (See interactions):

- 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
- drugs with anticholinergic effects (e.g. atropine)

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 antihistamine.

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

Patients with rare glucose-galactose malabsorption should not take this

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

liver disease. Do not exceed the stated dose.
Patients should be advised not to take other paracetamol-containing products or decongestant-containing medicines
concurrently. If symptoms persist consult
your doctor.
Keep out of the sight and reach of children.
Avoid alcoholic drink.

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.

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.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Drug withdrawal syndrome

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

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).

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

Special label warnings
Do not take with any other paracetamol-containing products.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Special leaflet warnings
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

This medicinal product contains 18% v/v ethanol (alcohol), i.e. up to 3.6ml (2.9g) per dose, equivalent to 72 ml beer, 30 ml wine per dose.
Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Each 20 ml dose contains 12.8 g glucose. This should be taken into account by patients with diabetes mellitus.

Each 20 ml dose contains 37 mg sodium. This should be taken into account by patients on a controlled sodium diet.

QT interval
As phenothiazines can prolong the QT interval, caution is advised in treated patients with pronounced bradycardia, cardiovascular disease, with a hereditary form of prolongation of the QT interval and concomitant use with other products leading to QT prolongation.

4.5 Interaction with other medicinal products and other forms of interaction

Medical advice should be sought before taking paracetamol-promethazine-dextromethorphan in combination with these drugs:

Monoamine-oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs) or tricyclic 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. 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.
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 increase risk of bleeding; occasional doses have no significant effect.
Inhibitors of cytochrome P450 2D6	Dextromethorphan is metabolized by CYP2D6 and has an 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 due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

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

Special caution is required when promethazine is used concurrently with other products leading to QT prolongation, including medicinal products such as antipsychotics, i.e., some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, amisulpride, tiapride), pimozide, haloperidol, droperidol, citalopram, halofantrin, methadone, pentamidine, and moxifloxacine.

4.6 Fertility, pregnancy and lactation

Pregnancy

This product should not be used during pregnancy without medical advice. This product should not be used during pregnancy unless the expected benefit justifies the potential risk to the foetus.The lowest effective dose and shortest duration of treatment should be considered.

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.

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 the doctor.

Lactation

This product should not be used whilst breast feeding without medical advice. This product should not be used while breast feeding unless the benefits to the mother outweigh the risks to the infant.. If used, the lowest effective dose and shortest duration of treatment should be considered.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Promethazine may be excreted in breast milk. It should only be used when considered essential by a doctor.

In lactating/breastfeeding women, dextromethorphan and its active metabolite, dextrorphan are distributed and excreted into breast milk in minor quantities.

There is a lack of data available on the effect of infant exposure through breast milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following convention has been utilized for the classification of undesirable effects: very common (≤ 1/10), common (≤ 1/100, <1/10), uncommon (≤ 1/1000, < 1/100), rare (≤ 1/10,000, < 1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Paracetamol

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 class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post- marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Body System	Undesirable effect

Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome/toxic epidermal necrolysis
Metabolism and nutrition disorders	High anion gap metabolic acidosis * (frequency not known)
Respiratory thoracic and mediastinal disorders	Bronchospasm**
Hepatobiliary disorders	Hepatic dysfunction

* 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.

**There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Dextromethorphan

The following adverse events have been observed in published clinical studies and are likely to represent uncommon adverse reactions to dextromethorphan.

Body system	**Undesirable effect**
Nervous system disorders	Drowsiness, dizziness
Gastrointestinal disorders	Gastrointestinal disturbance, nausea, vomiting, abdominal discomfort

Adverse reaction identified during post-marketing use with dextromethorphan are listed below. The frequency of these reactions is unknown but likely to be very rare.

Body system	**Undesirable effect**
Immune system disorders	Allergic reactions (e.g. rash, urticaria, angioedema)

Nervous system disorders	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

The frequency of drug dependence and withdrawal reactions is unknown:

Body system	**Undesirable effect**
Psychiatric disorders	Drug dependence (see section 4.4)
General disorders and administration site conditions	Drug withdrawal syndrome

Promethazine

Adverse reactions which been observed in published clinical studies with promethazine and which are considered to be common or very common are listed below by MedDRA system Organ Class. The frequency of other reactions identified during post-marketing use is not known, but these reactions are likely to be uncommon or rare.

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Not known: Thrombocytopenia
Immune system disorders	Not known: Hypersensitivity reactions including rash, urticaria, angioedema and anaphylaxis, photosensitivity
Psychiatric disorders	Not known: Confusion*, disorientation*, paradoxical excitation*, **(e.g. increased energy, irritability, restlessness, nervousness, sleep disturbance), hallucinations, aggression *The elderly are more susceptible to confusion, disorientation and paradoxical

	excitation **Children are more susceptible to paradoxical excitation
Nervous system disorders	Very common: Drowsiness Common: Psychomotor impairment, disturbance in attention, dizziness, headache. Not known: neuroleptic malignant syndrome, psychomotor hyperactivity
Eye disorders	Common: Blurred vision
Cardiac disorders	Not known : QT prolongation, Torsade de pointes
Gastrointestinal disorders	Common: Dry mouth Not Known: Gastrointestinal disturbance
Renal and urinary disorders	Not known: Urinary retention

The elderly are more susceptible to anticholinergic effects of promethazine.

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).

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 and signs

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. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy,

haemorrhage, hypoglycaemia, cerebral oedema, 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.

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. 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 current best practice guidelines – see current BNF.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration 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-ingestion. The effectiveness of the antidote declines sharply after this time. 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. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

<u>Promethazine Hydrochloride</u>

Symptoms and signs

Promethazine overdose is likely to result in effects similar to those listed under Adverse Reactions. Additional symptoms may include delirium, agitation, hallucinations, dystonic reactions, hypotension, and ECG changes. Large overdose may cause convulsions, toxic psychosis, arrythmias, coma and cardiorespiratory depression. Prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines.

Management

Treatment is supportive with attention to maintenance of adequate respiratory and circulatory status. Convulsions and marked CNS stimulation should be treated with parenteral diazepam or other suitable anti-convulsants.

<u>Dextromethorphan</u>

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms and signs

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. In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Management

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.

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if overdose is severe and if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol an analgesic and antipyretic.

Promethazine hydrochloride – 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, but undergoes extensive first pass metabolism in the liver, with only 25% of the oral dose reaching the systemic circulation unchanged. After oral therapy therapeutic effects are identifiable at 15-30 minutes and peak plasma concentrations at 2 to 3 hours. Estimates of terminal half life in blood plasma are in the range of 4-6 hours. It is extensively plasma protein bound. It is eliminated mainly as metabolites, predominantly by the faecal (via biliary)

route, with < 1% of the parent compound and ca. 10% as the sulphoxide metabolite being excreted in the urine over a 72 hour period.

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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltodextrin

Sucralose

Citric acid

Tartaric acid

Sodium citrate

Acesulfame potassium E 950

Aspartame E 951

Powdered menthol flavour

Lemon flavour

Quinoline yellow E 104

6.2 Incompatibilities

Maltodextrin

Sucralose

Citric acid

Tartaric acid

Sodium citrate

Acesulfame potassium E 950

Aspartame E 951

Powdered menthol flavour

Lemon flavour

Quinoline yellow E 104

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25□C.

6.5 Nature and contents of container

Pack sizes of five sachets are available.

The sachet laminate comprises:

‘Surlyn’ 25 gm-2 (product contact layer)/aluminium foil 15 microns/low density polyethylene 12 gm-2 /bleached paper 45 gm-2 (outer layer).

6.6 Special precautions for disposal

No special requirements for disposal and handling.

7 MARKETING AUTHORISATION HOLDER

Haleon UK Trading Limited
The Heights
Weybridge
Surrey
KT13 0NY
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0192

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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