SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fedril Night Cold and Flu, Oral Solution
Numark Night Cold and Flu, Oral Solution
Boots Night Cold & Flu Relief Oral Solution
Well Pharmaceuticals Night Cold & Flu Oral Solution
Care Night Cold & Flu Relief Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Constituents	mg/20 ml
Paracetamol	1000.0
Promethazine Hydrochloride	20.0
Dextromethorphan Hydrobromide Monohydrate	15.0

Excipients with known effect:
Each 20 ml of oral solution contains: 2916 mg of ethanol (18.08% v/v), 5180 mg of propylene glycol, 12.9 g of liquid maltitol and 23.52 mg of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

Clear green, mint flavoured, sugar free oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic night time relief of colds, chills and influenza consisting of headache, shivers, sore throat pain, tickly cough, runny nose, aches and pains.

4.2 Posology and method of administration

Route of administration

For oral use. To be taken at bedtime. Shake the bottle before use

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

Do not exceed the stated dose

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

Adults and children aged 16 years and over:
One measured 20 ml dose to be taken just before going to bed.

Children aged 12 to 15 years:
A 10 ml to 15 ml dose to be taken just before going to bed.

Not to be given to children under 12 years.

Elderly:
The normal adult dose can be used.

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

4.3 Contraindications

Hypersensitivity to paracetamol, dextromethorphan, promethazine or any of the other excipients listed in Section 6.1

Hepatic or renal impairment.

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.

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to subjects in, or at risk of developing respiratory failure.

This product is contraindicated in patients taking serotonin reuptake inhibitors (SSRIs, see section 4.5).

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

4.4 Special warnings and precautions for use

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

- Chronic or persistent cough, such as occurs with asthma, emphysema, or other respiratory disorders; or where the cough is accompanied by excessive secretions unless directed by a physician
- Epilepsy
- Narrow- angle glaucoma

- Urinary retention
- Prostatic hypertrophy
- Cardiovascular problems

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 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 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.

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.

There have been no specific studies of this product in renal or hepatic dysfunction. Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment. Underlying liver disease increases the risk of paracetamol-related liver damage.

This product should not be taken with any other cough and cold medicine.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

This product should be used with caution in atopic children due to histamine release.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the stated dose. Always use the measuring cup supplied with the pack.

Patients should be advised not to take other paracetamol-containing products or decongestant-containing medicines concurrently.

If symptoms persist consult your doctor.

Keep all medicines out of sight and reach of children.

Warning: May cause drowsiness. If affected, do not drive or operate machinery.

Avoid alcoholic drink.

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.

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).'

Serotonin Syndrome
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 this medicine should be discontinued.

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.

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.

Excipients: Ethanol, Propylene glycol, Sodium and Maltitol.

- Ethanol
  This medicinal product contains 2916 mg of ethanol (alcohol) in each 20 ml dose, which is 18.08 v/v %. A dose of 15 ml of this medicine administered to (a child 12 years of age and weighing 40 kg) would result in exposure to 55 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 9.1 mg/100 ml. A dose of 20 ml of this medicine administered to (an adult weighing 70 kg) would result in exposure to 42 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 7.0 mg/100 ml.

  For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

  The amount of ethanol in this medicine should be taken into account in the following patients/situations: children, patients driving or operating machinery, epilepsy, liver problems, pregnancy, breast-feeding or addiction to alcohol.

- Propylene glycol
  This medicinal product contains 5180 mg propylene glycol in each 20 ml, which is equivalent to 259 mg/ml or 220 mg/g. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

  Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following haemodialysis.
  Medical monitoring is required.

- Maltitol
  Patients with rare hereditary problems of fructose intolerance should not take this medicine.

- Sodium
  This medicinal product contains 23.52 mg of sodium (main component of cooking salt) in each 20 ml dose. This is equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interaction

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

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. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.
Anticholinergic drugs such as atropine, MAOIs and tricyclic antidepressants	As promethazine has some anticholinergic activity, the effects of some anticholinergic drugs may be potentiated.
Cholestyramine	The speed of absorption of paracetamol may be reduced by cholestyramine.
CNS depressant drugs such as antipsychotics, hypnotics or anxiolytics	Promethazine and dextromethorphan may potentiate the additive CNS depressant effects of other CNS depressant drugs or alcohol, antihistamines, psychotropics.
Metoclopramide and domperidone	The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
Monoamine-oxidase inhibitors (MAOIs)	Severe reactions, including serotonin syndrome (see below), may occur when this product is taken concomitantly, or within two weeks of taking, an MAOI. MAOIs may prolong and intensify the anticholinergic effects of antihistamines. Use of dextromethorphan in patients taking monoamine oxidase inhibitors should be avoided as severe reactions have been reported.
Selective serotonin re-uptake inhibitors (SSRIs), tricylic antidepressants or MAOIs	Dextromethorphan should not be used concurrently in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs as there is a risk of serotonin syndrome (e.g. hyperpyrexia, hallucinations, gross excitation or coma, mental status, hypertension, restlessness, myoclonus diaphoresis, shivering and tremor) Antihistamines have an added antimuscarinic effect with other antimuscarinic drugs including tricyclic antidepressants.

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.
CYP2D6 inhibitors	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).

Promethazine may interfere with immunologic urine pregnancy test to produce false results.

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 Pregnancy and lactation

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

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.

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

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

There are also no known contraindications to the use of Promethazine during lactation. Promethazine may be excreted in breast milk. It should only be used when considered essential by a doctor.

It is not known whether dextromethorphan or its metabolites are excreted in breast milk.

As with all medicines, the advice of a doctor should be sought before use of the product in pregnancy and lactation, and it should only be used when considered essential by the doctor.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

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

Paracetamol

Adverse events of paracetamol 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. The frequency of these adverse is not known.

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome/toxic epidermal necrolysis
Respiratory thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction
Metabolism and nutrition disorders	High anion gap metabolic acidosis with frequency "Not known"[#]

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

[#]Description of selected adverse reactions
High anion gap metabolic acidosis
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.

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 are not known.

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

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

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as 'Not known'.

Body System	**Frequency**	**Adverse Drug Reaction (Preferred Term)**
General disorders and administration site conditions	Not known	drug withdrawal syndrome
Immune System Disorders	Not known Not known Not known Not known	Angioedema Pruritus Rash Urticaria
Psychiatric Disorders	Not known Not known Not known	Insomnia Confusional state Drug dependence (see section 4.4)
Nervous System Disorders	Not known Not known Not known Not known	Convulsion Dizziness Psychomotor hyperactivity Somnolence
Respiratory, thoracic and mediastinal Disorders	Not known	Respiratory depression
Gastrointestinal Disorders	Not known Not known Not known Not known Not known	Abdominal pain Diarrhoea Gastrointestinal disturbance Nausea Vomiting

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, angiodema and anaphylaxis, photosensitivity

Psychiatric disorders	Not known: Confusion*, disorientation*, paradoxical excitation*, **(e.g. increased energy, irritability, restlessness, nervousness, sleep disturbance), hallucinations, aggression
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 confusion, disorientation and paradoxical excitation
**Children are more susceptible to paradoxical excitation

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 the Yellow Card Scheme at 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).

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 overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12-48 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 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. Liver damage is possible in adults who have taken 10 g 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. 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, see BNF overdose section.
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.
Promethazine Hydrochloride

Symptoms and signs:
In children, Promethazine overdose can cause CNS stimulation and antimuscarinic effects. 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 (uncommon). Prolonged QT interval and cases of severe arrhythmias with fatal outcome have been described in overdose of phenothiazines.

Management:
If the patient is seen soon enough after ingestion, it should be possible to induce vomiting with ipecacuanha despite the antiemetic effect of promethazine; alternatively gastric lavage may be used. Treatment otherwise 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 anticonvulsants.

Dextromethorphan

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.
Other observed symptoms of overdose may include gastrointestinal disturbances, dizziness, restlessness, nervousness and irritability.

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.
- Other general symptomatic and supportive measures should be used including a clear airway and monitoring of vital signs until stable.
- 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: other analgesics and antipyretics, anilides.
Pharmacotherapeutic Group: Analgesics and Antipyretics, Anilides
ATC Code: N02B E01

Promethazine Hydrochloride: an antihistamine with anticholinergic activity.
Pharmacotherapeutic Group: Antihistamines for Systemic Use, Phenothiazine derivatives
ATC Code: R06A D02

Dextromethorphan Hydrobromide Monohydrate : an antitussive
Pharmacotherapeutic Group: Cough and Cold Preparations, Opium Alkaloids and derivatives
ATC Code: R05D A09

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 patient compound and ca. 10% as the sulphoxide metabolite being excreted in the urine over a 72 hour period.

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

Preclinical 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

ethanol

propylene glycol

liquid maltitol (hydrogenated glucose syrup)

sodium citrate

ascorbic acid

acesulfame k

citric acid monohydrate

natural mint flavour

patent blue v (E131)

quinoline yellow (E104)

purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

Shelf life after first opening: 1 month

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original container. Keep the bottle in the outer carton.

6.5 Nature and contents of container

Clear glass bottles – 200 ml with polypropylene child resistant closures.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited

Ballymacarbry

Clonmel

Co. Tipperary

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 04917/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th November 2009
Date of latest renewal: 4th November 2014

10 DATE OF REVISION OF THE TEXT

09/01/2026