Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Four Flu Oral Solution
Paracetamol 1000mg/20ml
Diphenhydramine hydrochloride 25mg/20ml
Pseudoephedrine hydrochloride 45mg/20ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 ml contains:

Diphenhydramine hydrochloride 25 mg
Paracetamol 1000 mg
Pseudoephedrine hydrochloride 45 mg

Also contains:

Ethanol
Ponceau 4R (E 124)
Sodium
Fructose
E306 Natural tocopherols extract (from soya oil)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

A clear orange to brown oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of symptoms associated with colds and flu; including relief of nasal congestion and congestion of mucous membranes of the upper respiratory tract, sneezing, runny nose, coughing, fever, headache, muscular aches and pains.

4.2 Posology and method of administration

For oral use

Adults, the elderly and children aged 12 years and over:

One 20 ml dose up to four times daily, as required. Do not take more frequently than every four hours.

Children under 12 years:

Benylin Four Flu Oral Solution is not recommended for use in children under the age of 12 years (see section 4.4).

Do not exceed the stated dose.

4.3 Contraindications

Known hypersensitivity to diphenhydramine, paracetamol, pseudoephedrine or to any of the excipients.

Concomitant use of other sympathomimetic agents including those given by other routes, beta-blockers (see section 4.5) and monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOI treatment (see section 4.5).

Cardiovascular disease including hypertension
Diabetes mellitus
Phaeochromocytoma
Hyperthyroidism
Closed angle glaucoma
Severe renal impairment

4.4 Special warnings and precautions for use

As both diphenhydramine and pseudoephedrine have been associated with central nervous system adverse events (see section 4.8), there is a possibility that the risk of experiencing such adverse events may be increased by use of the combination.

If any of the following occur, Benylin Four Flu Oral Solution should be stopped
- Hallucinations
- Restlessness
- Sleep disturbances

Use with caution in prostatic hypertrophy, urinary retention, susceptibility to angle-closure glaucoma, moderate renal impairment, hepatic disease or occlusive vascular disease.

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

Benylin Four Flu Oral Solution is not recommended for use in children under the age of 12 years (see section 4.2).

The product labelling will contain the following advice:-

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.

Do not take with any other paracetamol-containing products.

If symptoms persist, consult your doctor or pharmacist.

Keep out of the reach and sight of children.

Ask a doctor before use if you suffer from a chronic or persistent cough, if you have asthma, are suffering from an acute asthma attack or where cough is accompanied by excessive secretions.

4.5 Interaction with other medicinal products and other forms of interaction

CNS depressants: may enhance the sedative effects of CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics and alcohol.

Antimuscarinic drugs: may have an additive muscarinic action with other drugs, such as atropine and some antidepressants.

- MAOIs (see section 4.3) and/or RIMAs: Not to be used in patients taking MAOIs or within 14 days of

stopping treatment as there is a risk of serotonin syndrome (diphenhydramine) or hypertensive crisis (pseudoephedrine).

- Moclobemide: risk of hypertensive crisis.
- Antihypertensives (including adrenergic neurone blockers & beta-blockers - see section 4.3): Benylin Four Flu Oral Solution may block the hypotensive effects.
- Cardiac glycosides: increased risk of dysrhythmias
- Ergot alkaloids (ergotamine & methysergide): increased risk of ergotism
- Appetite suppressants and amphetamine-like psychostimulants: risk of hypertension
- Oxytocin – risk of hypertension
- Enhances effects of anticholinergic drugs (such as TCAs)

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

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

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

4.6 Fertility, pregnancy and lactation

The active ingredients in Benylin Four Flu have not been conclusively associated with adverse effects on the developing foetus; but as with all drugs, care should be exercised in use of the product, particularly during the first trimester.

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.

All of the actives are excreted into breast milk, although few adverse effects have been reported as a result of ingestion, cautious use of Benylin Four Flu is advised during 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

Benylin Four Flu may cause drowsiness. If patients are affected they should not drive or use machinery.

4.8 Undesirable effects

System Organ Class	Adverse Event
Blood and the lymphatic system disorders	Blood disorders; blood dyscrasias such as thrombocytopenia and agranulocytosis have been reported following paracetamol use, but were not necessarily causally related to the drug
Immune system disorders	Hypersensitivity reactions, including skin rash and cross-sensitivity with other sympathomimetics
Psychiatric disorders	Confusion; depression; sleep disturbances; irritability; anxiety; restlessness; excitability; insomnia; hallucinations and paranoid

	delusions
Nervous system disorders	Drowsiness (usually diminishes within a few days); paradoxical stimulation; headache; psychomotor impairment; extrapyramidal effects; dizziness; tremor; convulsions
Eye disorders	Blurred vision
Cardiac disorders	Palpitations; tachycardia; arrhythmia; other cardiac dysrhythmias
Vascular disorders	Hypotension; hypertension
Respiratory, thoracic and mediastinal disorders	Thickened respiratory tract secretions
Gastrointestinal disorders	Gastrointestinal disturbances; dry mouth; nausea and/or vomiting
Hepato-biliary disorders	Liver dysfunction
Skin and subcutaneous tissue disorders	Rash
Renal and urinary disorders	Urinary retention

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, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

B. Regularly consumes ethanol in excess of recommended amounts.

Or

C. Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdose 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, 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.

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.

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 local centres and/or experts that provide advice on poisons and overdoses or a liver unit.

Diphenhydramine

Symptoms of overdose may include drowsiness, hyperpyrexia and anticholinergic effects. With higher doses, and particularly in children, symptoms of CNS excitation include insomnia, nervousness, tremors and epileptiform convulsions. With massive overdose, coma or cardiovascular collapse may follow.

Treatment of overdose should be symptomatic and supportive. Measures to promote gastric emptying (such as induced emesis or gastric lavage), and in cases of acute poisoning activated charcoal, may be useful.

Pseudoephedrine

As with other sympathomimetic agents, symptoms of overdose include irritability, restlessness, tremor, convulsions, palpitations, hypertension and difficulty in micturition.

Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed if indicated. Catheterisation of the bladder may be necessary. If desired, the elimination of

pseudoephedrine can be accelerated by acid diuresis or by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02BE51.

Diphenhydramine has a potent antihistaminic action although the actions most beneficial in influenza are its antitussive and to a lesser extent anticholinergic properties, which may alleviate mucus hypersecretion.

Paracetamol has central analgesic and antipyretic actions and pseudoephedrine is an indirectly acting sympathomimetic which has vasoconstrictor, bronchodilator and decongestant effects.

5.2 Pharmacokinetic properties

Diphenhydramine is well absorbed after oral administration with peak plasma levels at 2.5 hours and is subject to extensive first pass metabolism. The drug is 75% bound to plasma proteins, but binding decreases with chronic liver disease. Metabolism is by 2 successive N-demethylations followed by oxidation to a carboxylic acid. The terminal half life lies between 3.4 and 9.3 hours.

Paracetamol is rapidly and completely absorbed with peak plasma levels seen within 30 to 60 minutes. Less than 50% is protein bound and the drug is uniformly distributed throughout the body fluids. Paracetamol is eliminated by metabolism to inactive conjugates followed by urinary excretion. The half life is 2.75- 3.25 hours.

Pseudoephedrine is rapidly absorbed, with peak serum levels after approximately 2.6 hours and onset of effect within about 30 minutes. It is well distributed throughout body fluids and tissues. Approximately 50% of the drug is excreted unchanged, the remainder undergoes metabolism to inactive metabolites. About 6% is converted to the active metabolite norpseudoephedrine.

5.3 Preclinical safety data

The active ingredients of Benylin Four Flu Oral Solution are well known constituents of medicinal products and their safety profile is well documented. The results of preclinical studies do not therefore add anything of relevance for therapeutic purposes.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene glycol
Glycerol
Propylene glycol
Saccharin sodium
Citric acid monohydrate
Sodium benzoate
Eucalyptol
Menthol
Carmellose sodium
Sodium citrate
Ethanol 96% v/v

Colourings:
Quinoline Yellow E 104

Ponceau 4R (E 124)
Patent Blue V (E 131)

Flavourings:
Honey
Lemon and cream
Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30^{o}C. Keep container in the outer carton.

6.5 Nature and contents of container

30 ml and 200 ml round amber glass bottles with aluminium screw cap.

30 ml and 200 ml round amber glass bottles with a plastic child resistant, tamper evident closure fitted with a polyester faced wad or polyethylene/expanded polyethylene laminated wad.

A polypropylene measuring cup is supplied with each 200 ml bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Keep bottle tightly closed.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Limited
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 823/34/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 1998

Date of last renewal: 1 June 2008

10 DATE OF REVISION OF THE TEXT

November 2010