# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Benylin Four Flu Film-Coated Tablets. Paracetamol 500mg Diphenhydramine hydrochloride 12.5mg Pseudoephedrine hydrochloride 22.5mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Diphenhydramine hydrochloride 12.5 mg
Paracetamol 500 mg
Pseudoephedrine hydrochloride 22.5 mg

Also contains:

Sunset yellow E110
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Orange, oval, biconvex, film coated tablets (tablets)

## 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 16 years and over:**
Two tablets, up to four times daily, as required. Do not take more frequently than every four hours.

**Children 10 to 15 years**
One tablet, up to four times daily, as required. Do not take more frequently than every four hours. Not to be used for more than five days without the advice of a doctor. Parents or carers should seek medical attention if the child's condition deteriorates during treatment.

**Children under 10 years**
Benylin Four Flu Tablets are contraindicated in children under the age of 10 years (see section 4.3).
Do not exceed the stated dose.

**Hepatic Dysfunction**
Caution should be exercised when administrating this medicine to patients with severe hepatic impairment.

**Renal Dysfunction**
Caution should be exercised when administering this medicine to patients with moderate to severe renal impairment.

### 4.3 Contraindications

Known hypersensitivity to diphenhydramine, paracetamol, pseudoephedrine or to any of the excipients listed in section 6.1.

Concomitant use of other sympathomimetic decongestants, beta-blockers (see section 4.5) or monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOI treatment (see section 4.5). The concomitant use of MAOIs may cause a rise in blood pressure and/or hypertensive crisis.

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

Not to be used in children under the age of 10 years.

**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.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, opioid analgesics, antipsychotics and tranquilizers. Alcoholic beverages should be avoided while taking this product.

If any of the following occur, Benylin Four Flu Tablets should be stopped

- Hallucinations
- Restlessness
- Sleep disturbances

Severe Skin reactions: Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of this medicine should be discontinued, and appropriate measures taken if needed.

Ischaemic colitis: Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy: Cases of ischaemic optic neuropathy have been reported with pseudoephedrine. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) / reversible cerebral vasoconstriction syndrome (RCVS) reported with sympathomimetic drugs, including pseudoephedrine. Symptoms reported include sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment. Pseudoephedrine should be discontinued, and medical advice sought immediately if signs or symptoms of PRES/RCVS develop.

Patients with the following conditions should be advised to consult a physician before using this product:

- Acute or chronic asthma, a persistent or chronic cough such as occurs with chronic bronchitis or emphysema or where cough is accompanied by excessive secretions
- Difficulty in urination,  urinary retention and/or prostatic hyperplasia.
- Patients with thyroid disease who are receiving thyroid hormones

Use with caution in patients with susceptibility to angle-closure, severe hepatic impairment, moderate to severe renal impairment, (particularly if accompanied by cardiovascular disease) or occlusive vascular disease. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not use with any other product containing diphenhydramine, including topical formulations used on large areas of skin.

Taking this product with other paracetamol-containing products could lead to overdose and should therefore be avoided.

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.

May cause drowsiness. This product should not be used to sedate a child.

This medicine contains Sunset yellow (E110). This may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

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

- Antimuscarinic drugs: Diphenhydramine may have an additive muscarinic action with other drugs, such as atropine and tricyclic antidepressants. This may result in tachycardia, mouth dryness, gastrointestinal disturbances (e.g., colic), urinary retention and headache.

- MAOIs (see section 4.3) and/or RIMAs: Pseudoephedrine exerts its vasoconstricting properties by stimulating α -adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since monoamine oxidase inhibitors (MAOIs) impede the metabolism of sympathomimetic amines and increase the store of releasable noradrenaline in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine. This product should 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 because of its pseudoephedrine content, this product may partially reverse the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, betanidine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers and beta-blockers
- Cardiac glycosides: increased risk of dysrhythmias
- Ergot alkaloids (ergotamine & methysergide): increased risk of ergotism
- Appetite suppressants and amphetamine-like psychostimulants: Concomitant use of this product with sympathomimetic agents, such as decongestants, tricyclic antidepressants, appetite suppressants and amphetamine-like psychostimulants, may cause a rise in blood pressure.
- Oxytocin – risk of hypertension
- Anaesthetic agents: Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

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

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular 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.

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 medicine, like most medicines should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs any possible risk to the developing foetus.

Paracetamol, pseudoephedrine and diphenhydramine have been in widespread use for many years without any apparent ill consequence. 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. The safety of pseudoephedrine in pregnancy has not been established. Diphenhydramine is known to cross the placenta and, therefore should only be used during pregnancy if considered essential by a doctor.

Breast-feeding
Pseudoephedrine is excreted in breast milk in small amounts, but the effect of this on breast-fed infants is not known. It has been estimated that approximately 0.4 to 0.7% of a single 60mg dose of pseudoephedrine ingested by a nursing mother will be excreted in the breast milk over 24 hours.
Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2.2 to 6.7% of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding. A pharmacokinetic study of paracetamol in 12 nursing mothers revealed that less than 1% of a 650mg oral dose of paracetamol appeared in the breast-milk. Similar findings have been reported in other studies, therefore maternal ingestion of therapeutic doses of paracetamol does not appear to present a risk to the infant.

Diphenhydramine is excreted into human breast milk, but levels have not been reported. Although the levels are not thought to be sufficiently high enough after therapeutic doses to affect the infant, the use of diphenhydramine during breast-feeding is not recommended.

**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**

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with diphenhydramine, paracetamol, pseudoephedrine or the combination are included below by System Organ Class (SOC).

The frequencies are defined according to the following convention:

Very common ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

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'.

| System Organ Class (SOC) | Frequency | Adverse Drug Reaction (Preferred Term) |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Blood disorders, blood dyscrasias (including thrombocytopenia and agranulocytosis) have been reported following paracetamol use, but were not necessarily causally related to the drug |
| Immune system disorders | Rare | Hypersensitivity (cross-sensitivity may occur with other sympathomimetics) |
| Psychiatric disorders | Common | Insomnia<br>Nervousness |
| | Uncommon | Confusional state<br>Irritability |
| | Rare | Depression<br>Sleep disorder |
| | Not known | Anxiety<br>Euphoric mood<br>Excitability<br>Hallucinations<br>Paranoid delusions<br>Restlessness |
| Nervous system disorders | Very common | Headache<br>Somnolence<br>Sedation |
| | Common | Dizziness<br>Paradoxical stimulation Psychomotor impairment |
| | Rare | Extrapyramidal disorder<br>Seizure<br>Tremor |
| | Not known | Cerebrovascular accident<br>Paraesthesia<br>Posterior reversible encephalopathy syndrome (PRES)/reversible cerebral vasoconstriction syndrome (RCVS)<br>Psychomotor hyperactivity |
| Eye disorders | Common<br>Not known | Vision blurred<br>Ischaemicoptic neuropathy |
| Ear and labyrinth disorders | Uncommon | Tinnitus |
| Cardiac disorders | Rare | Palpitations |
| | Not known | Dysrhythmias<br>Myocardial infarction/myocardial ischaemia<br>Tachycardia |
| Vascular disorders | Rare | Hypotension |
| | Not known | Hypertension |
| Respiratory, thoracic and mediastinal disorders | Common | Increased viscosity of bronchial secretions |
| | Not known | Dyspnoea<br>Nasal dryness |
| Gastrointestinal disorders | Common | Dry mouth<br>Gastrointestinal disorder<br>Nausea |
| | Not known | Ischaemic colitis<br>Vomiting |
| Hepato-biliary disorders | Rare | Liver disorder |
| Skin and subcutaneous tissue disorders | Uncommon | Rash |
| | Not known | Angioedema<br>Erythema<br>Fixed eruption<br>Pruritus<br>Rash pruritic<br>Serious skin reactions, including acute generalised |

| | | |
|---|---|---|
| | | exanthematous pustulosis (AGEP)<br>Urticaria |
| Renal and urinary disorders | Common | Urinary retention (in men in whom prostatic enlargement could have been an important predisposing factor) |
| | Not known | Dysuria |
| General disorders and administration site conditions | Common | Asthenia |
| | Not known | Chest discomfort |

Very rare cases of serious skin reactions have been reported with paracetamol

*Metabolism and nutrition disorders:* Post marketing experience - Very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorization of themedicinal product is important. It allows continued monitoring of thebenefit/risk balance of the medicinal product. Healthcare professionals areasked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

**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

1. Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. Or
2. Regularly consumes ethanol in excess of recommended amounts. Or
3. Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
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.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

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 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.

**Diphenhydramine:**
Following overdose in adults, moderate symptoms have been associated with ingestions of greater than 300-500 mg and serious symptoms associated with doses greater than 1 g diphenhydramine.
Young children may be more sensitive to the effects of overdose.
Mild to moderate symptoms of overdose may include drowsiness, hyperpyrexia, anticholinergic effects (mydriasis, dry mouth and flushing), tachycardia, hypertension, nausea and vomiting. Agitation, confusion and hallucinations may develop with moderate poisoning. With higher doses, and particularly in children, symptoms of CNS excitation include insomnia, nervousness, tremors and epileptiform convulsions.
Severe symptoms may include delirium, psychosis, seizures, coma, hypotension, QRS widening, and ventricular dysrhythmias, including torsades de pointe but are generally only reported in adults after large ingestions. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizures. Death may occur as a result of respiratory failure or circulatory collapse.

Management
Treatment of overdosage should be symptomatic and supportive. The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) only if the patient presents within 1 hour of ingestions of a potentially toxic amount. The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms.

Pseudoephedrine:
Overdose may result in: Hyperglycaemia, hypokalaemia, CNS stimulations, insomnia, irritability, restlessness, anxiety, agitation, confusion, delirium, hallucinations, psychoses, seizures, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children, mydriasis, palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction, hypertension, vomiting, ischaemic bowel infarction, acute renal failure, difficulty in micturition.

Management
Necessary measures should be taken to maintain and support respiration and control convulsions. 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 2.3 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 elimination half life lies between 8.5 and 11.5 hours in adults.

Paracetamol is rapidly and completely absorbed from the gastrointestinal tract with peak plasma levels seen within 30 to 60 minutes. Less than 25% is protein bound and the drug is widely distributed throughout the body tissues. Paracetamol is eliminated by metabolism to inactive conjugates followed by urinary excretion. The elimination half-life is 1 - 3.5 hours.

Pseudoephedrine is rapidly absorbed from the gastrointestinal tract, with peak serum levels after approximately 1.5 hours and onset of effect within about 30 minutes. It is well distributed throughout body fluids and tissues. Most of an oral dose (43 to 96%) of the drug is excreted unchanged, the remainder undergoes metabolism to inactive metabolites. About 1 to 6% is converted to the active metabolite norpseudoephedrine, which is excreted in the urine.

**5.3 Preclinical safety data**

The active ingredients of Benylin Four Flu tablets are well known constituents of medicinal products and their safety profile is well documented. The results of preclinical studies do not add anything of relevance for therapeutic purposes. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available for paracetamol.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Pregelatinized maize starch
Povidone
Crospovidone
Stearic acid
Cellulose microcrystalline
Pregelatinised maize starch
Croscarmellose Sodium
Magnesium stearate

Film-coating material

Hypromellose
Macrogol 6000
Talc
Titanium dioxide
Quinoline yellow lake
Sunset yellow E110
Quinoline yellow

**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.
Keep container in the outer carton.

**6.5 Nature and contents of container**

Blister pack containing 24 tablets

Each blister strip consists of a white, opaque PVC/PVdC film and either:

Aluminium foil blister lidding
Or
Paper/aluminium foil child resistant blister lidding

**6.6 Special precautions for disposal**

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

## 7 MARKETING AUTHORISATION HOLDER

JNTL Consumer Health I (Ireland) Limited
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Block 5
High Street
Tallaght
Dublin 24
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## 8 MARKETING AUTHORISATION NUMBER

PA23490/013/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd June 1998

Date of last renewal: 1st June 2008

## 10 DATE OF REVISION OF THE TEXT

March 2024