1 NAME OF THE MEDICINAL PRODUCT

Benylin Day and Night Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BLUE (NIGHT) TABLETS

Paracetamol	500.0mg
Diphenhydramine Hydrochloride	25.0mg

WHITE (DAY) TABLET

Paracetamol	500.0mg
Pseudoephedrine Hydrochloride	60.0mg

3 PHARMACEUTICAL FORM

Tablet
White, biconvex oblong tablet with bisecting score on one side and “AC7” engraved on both sides of the score.

Film-coated Tablet
Blue, round, biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of the symptoms associated with colds and influenza

4.2 Posology and method of administration

Posology
Adults and Children over 12 years

Four tablets should be taken daily:

One white tablet to be taken every 4 to 6 hours during the day (no more than three white tablets a day).

One blue tablet to be taken at night.

Take only one tablet at a time and only at the times of day indicated on the pack. Do not take the nighttime tablets during the day.

Elderly

As for adults (see Pharmacokinetics).

Children

Not recommended for children under 12 years of age.

Method of Administration
For oral use

Hepatic Dysfunction
Caution should be exercised when administering 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

Use in individuals with 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 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
Phaeochromocytoma
Hyperthyroidism
Closed angle glaucoma
Severe renal impairment

4.4. Special warnings and precautions for use

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 Day and Night 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.

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

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 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.

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.

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.

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

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.

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.

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 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.

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 contra-indicate 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

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

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with diphenhydramine, paracetamol, or pseudoephedrine (single ingredients) or combinations of diphenhydramine + paracetamol or pseudoephedrine + paracetamol, are listed 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 disorder	Rare	Hypersensitivity (cross-sensitivity may occur with other sympathomimetics)
Psychiatric disorders	Common	Insomnia Nervousness
	Uncommon	Confusional state Irritability
	Rare	Depression Sleep disorder
	Not known	Anxiety Euphoric mood Excitability Hallucinations Paranoid delusions Restlessness
Nervous system disorders	Very common	Headache Somnolence Sedation
	Common	Dizziness Paradoxical stimulation Psychomotor impairment
	Rare	Extrapyramidal disorder Seizure Tremor
	Not known	Cerebrovascular accident Paraesthesia Posterior reversible encephalopathy syndrome (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) Psychomotor hyperactivity
Eye disorders	Common	Vision blurred
	Not known	Ischaemic optic neuropathy
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Rare	Palpitations

	Not known	Dysrhythmias Myocardial infarction/myocardial ischaemia Tachycardia
Vascular disorders	Rare	Hypotension
	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Increased viscosity of bronchial secretion
	Not known	Dyspnoea Nasal dryness
Gastrointestinal disorders	Common	Dry mouth Gastrointestinal disorder Nausea
	Not known	Ischaemic colitis Vomiting
Hepatobiliary disorders	Rare	Liver disorder
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Not known	Angioedema Erythema Fixed eruption Pruritus Rash pruritic Serious skin reactions, including acute generalised exanthematous pustulosis (AGEP) 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:

If the patient

- Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

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

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.

Pseudoephedrine:
Overdose may result in:
Hyperglycaemia, hypokalaemia, CNS stimulation, 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.

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 pointes, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol:

Paracetamol is an analgesic and antipyretic. The therapeutic effects of paracetamol are thought to be related to inhibition of prostaglandin synthesis, as a result of the inhibition of cyclo-oxygenase. There is some evidence that it is a more effective inhibitor of central as opposed to peripheral cyclo-oxygenase. Paracetamol has only weak anti-inflammatory properties. The antipyretic action of paracetamol appears to stem from a direct action on the hypothalamic heat-regulating centres, producing peripheral vasodilation, and consequent loss of heat.

Pseudoephedrine:

Pseudoephedrine has direct and indirect sympathomimetic activity and is an orally effective upper respiratory tract decongestant. Pseudoephedrine is less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and less potent in causing stimulation of the central nervous system.

Diphenhydramine:

Diphenhydramine is an antihistamine that competes with histamine for receptor sites on effector cells. The compound also possesses antispasmodic, antitussive, antiemetic, sedative and secretolytic effects.

5.2. Pharmacokinetic properties

Paracetamol:
Paracetamol is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring approximately 30 to 90 minutes following oral administration. Paracetamol is incompletely available to the systemic circulation after oral administration since a variable proportion is lost through first pass metabolism. Oral bioavailability in adults appears to depend on the amount of paracetamol administered, increasing from 63% following a 500mg dose, to nearly 90% after 1 or 2 g. Effects are apparent within 30 minutes and last for between 4 and 8 hours. Less than 25% is protein bound. The compound is extensively metabolised in the liver to inactive conjugates of glucuronic and sulphonic acids (saturable) and to a hepatotoxic intermediate metabolite (first order) by P450 mixed function oxidase. The intermediate is detoxified by glutathione (saturable). Less than 4% is excreted unchanged in the urine.

The elimination half-life for the drug usually lies in the range 1-3.5 hours although this may be mildly increased in chronic liver disease, or extended in acute paracetamol poisoning.

There is some evidence to suggest that serum half-life is markedly increased, and clearance of paracetamol is decreased in frail, immobile, elderly subjects when compared to fit young individuals. However, differences in pharmacokinetic parameters observed between fit young and fit elderly subjects are not thought to be of clinical significance.

Pseudoephedrine:
Pseudoephedrine is rapidly and completely absorbed after oral administration. After the administration of an oral dose of 60mg to healthy adults, a peak plasma concentration of 180ng/ml was obtained approximately 2 hours post dose. The plasma half-life is approximately 5.5 hours. Urinary elimination is accelerated, and half-life consequently decreased, when the urine is acidified. Conversely, as the urine pH increases, the urinary elimination is reduced and half-life is increased. Pseudoephedrine is partly metabolised in the liver by N-demethylation to an active metabolite. Excretion of pseudoephedrine and its metabolite is mainly in the urine.

Diphenhydramine:
Diphenhydramine is well absorbed from the gastrointestinal tract. Peak serum levels are reached between 2 and 2.5 hours after an oral dose. Duration of activity is between 4 and 8 hours. The drug is widely distributed throughout the body, including the CNS and some 78% is bound to plasma proteins. Estimates of the volume of distribution lie in the range 3.3-6.8L/kg.

Diphenhydramine experiences extensive first-pass metabolism, two successive N-demethylations, and the resultant amine is then oxidised to a carboxylic acid. Values for plasma clearance lie in the range 600-1300ml/min and the terminal elimination half-life lies in the range 3.4-9.3 hours. Little unchanged drug is excreted in the urine.

5.3. Preclinical safety data

Preclinical data, where available, reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

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

Each white (DAY) tablet is formulated to contain:
Pregelatinised maize starch
Povidone
Crospovidone
Stearic acid
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Each blue (NIGHT) tablet is formulated to contain:
Core
Microcrystalline cellulose
Maize starch
Sodium starch glycollate
Hydroxypropylcellulose
Pregelatinised maize starch
Croscarmellose sodium
Stearic acid (powder)
Magnesium stearate

Film coating:
Hypromellose
Indigo carmine (E132)
Titanium dioxide (E171)
Propylene glycol

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.

6.5 Nature and contents of container

Carton containing 16 tablets (12 'DAY' tablets and 4 'NIGHT' tablets).

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

McNeil Products Limited
50 – 100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0108

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/01/2009

10 DATE OF REVISION OF THE TEXT

28/03/2022