Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BENYLIN Day & Night Tablets, 500mg/60mg tablets and 500/25mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white (day) tablet contains Paracetamol 500 mg
Pseudoephedrine Hydrochloride 60 mg

Each blue (night) tablet contains Paracetamol 500 mg
Diphenhydramine Hydrochloride 25 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Day Tablet
White biconvex tablet in oblong form, 15.8-16.1mm long, 8.4-8.7mm wide and 6.5-6.8mm thick with dissecting score on one side; 'A7C' engraved on both sides of the score. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Night Tablet
Film-Coated Tablet (Tablet).
Blue, odourless, round and biconvex tablets, 12.6-13mm in diameter and 5.6mm thick.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BENYLIN Day & Night is indicated for the short-term symptomatic treatment of nasal and sinus congestion associated with daytime symptoms of cold and flu such as pain, headache and/or fever when in combination with bedtime symptoms which are causing difficulty in getting to sleep.

BENYLIN Day & Night is indicated in adult and adolescents aged 15 to 17 years.

4.2 Posology and method of administration

Adults and Adolescents over 15 years:

Four tablets should be taken daily.

One white tablet (paracetamol and pseudoephedrine) to be taken every 4 to 6 hours during the day (one tablet in the morning, at midday and in the afternoon). Do not take more than 3 white day-time tablets in 24 hours.
One blue tablet (paracetamol and diphenhydramine) to be taken at night.
Do not take the night-time tablets during the day.

Patients should consult their doctor or pharmacist if symptoms persist for more than 3 days or worsen (see section 4.4).

Method of administration

For oral use.

Children and adolescents under 15 years

Not recommended for children and adolescents under 15 years

Elderly:

Experience has indicated that normal adult dosage is usually appropriate. However, in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

The maximum daily dose should not exceed 60mg/kg/day (up to a maximum of 2g paracetamol per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Hepatic impairment

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged.

The daily dose should not exceed 2g paracetamol/day unless directed by a physician.

Renal impairment

Caution should be exercised when administering Benylin Day & Night to patients with mild to moderate renal impairment (see section 4.4).

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

4.3 Contraindications

BENYLIN Day & Night is contraindicated in patients with:

- Hypersensitivity to paracetamol, pseudoephedrine, diphenhydramine or 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
- Phaeocromocytoma
- Hyperthyroidism
- Closed angle glaucoma
- Severe renal impairment
- Urinary retention in patients at risk of developing respiratory failure.

4.4 Special warnings and precautions for use

Paracetamol should be administered with caution under the following circumstances (see section 4.2)

- Hepatic impairment
- Chronic alcoholism

- Renal impairment (GFR ≤ 50ml/min)
- Gilberts syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly patients

Hepatotoxicity at therapeutic dose of paracetamol

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9).

Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

Prolonged or frequent use is discouraged.

Paracetamol overdose warning: Taking more than the recommended dose (overdose) may result in severe liver damage. In case of overdose, medical help should be sought immediately. Urgent medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

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

Taking multiple daily doses in one administration can severely damage the liver. In such cases, medical assistance should be sought immediately.

Caution should be exercised when using the product in the presence of severe hepatic impairment or moderate to severe renal impairment (particularly if accompanied by cardiovascular disease). The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Patients with hepatic disease should consult a doctor before use.

Alcohol Warning: Chronic alcohol users should ask their physician whether they should take paracetamol (see section 4.5).

In general, medicinal products contains paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Hypersensitivity reactions, including skin rashes, angioedema and anaphylaxis have been reported very rarely with paracetamol (see Section 4.8).

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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.

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 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.

Although pseudoephedrine has virtually no pressor effects in normotensive patients, this medicine should be used with caution in patients taking antihypertensive agents, tricyclic antidepressants or other sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants). The effects of a single dose on the blood pressure of these patients should be observed before recommending repeated or unsupervised treatment.

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.

This product is contraindicated for use in patients with pre-existing cardiovascular disease, particularly those with coronary heart disease and hypertension (see section 4.3).

This product is contraindicated for use in patients with thyroid disease, diabetes, glaucoma and, severe renal impairment (see Section 4.3).

Patients with difficulty in urination and/or enlargement of the prostate, should be advised to consult a physician before using pseudoephedrine.

This product may act as a cerebral stimulant giving rise to hyperpyrexia, tremor and epileptiform convulsions. Care should be taken when used in epileptic patients

If any of the following occur, this product should be stopped:

- Hallucinations
- Restlessness
- Sleep disturbances

Use with caution in occlusive vascular disease.

Pseudoephedrine may induce positive results in certain anti-doping tests.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, and tranquilizers. While taking this product, avoid alcoholic beverages and consult a healthcare professional prior to taking with central nervous system depressants. (see section 4.5).

Patients with the following conditions should be advised to consult a physician before using diphenhydramine: a respiratory condition such as emphysema, chronic bronchitis, or acute or chronic bronchial asthma; prostate hyperplasia with urinary

retention (see section 4.3).

Concomitant use of other products containing paracetamol or decongestants with Benylin Day & Night could lead to overdosage and should, therefore, be avoided.

Night time tablets only: May cause drowsiness. Patients should be advised not to drive or operate machinery if affected (see section 4.7 and 4.8). Alcoholic drink should be avoided.

Night time tablets only: Patients should be advised not to use with any other product containing Diphenhydramine.

The stated dose should not be exceeded.

Use in patients with congenital long QT-syndrome should be avoided.

The concurrent use of medicinal products, which also prolong the QT interval or result in hypokalemia should be avoided (see also section 4.5, 4.9 and 5.3).

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.

Immediate medical advice should be sought in an event of an overdose, even if you feel well. Please read the enclosed leaflet carefully (label).

Immediate medical advice should be sought in an event of an overdose, because of the risk of irreversible liver damage (leaflet).

Do not take with any other paracetamol containing products.

Do not use with any other product containing diphenhydramine, even one used on skin.

Use when only clearly necessary.

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

If symptoms persist or get worse, or if new symptoms occur, patients should stop use and consult a physician.

4.5 Interaction with other medicinal products and other forms of interaction

Pseudoephedrine
MAOIs and/or RIMAs:
Pseudoephedrine exerts its vasoconstricting properties by stimulating α-adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since 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. Acute hypertensive crises have been reported in the medical literature with the concomitant use of MAOIs and sympathomimetic amines therefore their concomitant use is contraindicated (see section 4.3).

This medicine should not be given to patients taking monoamine inhibitors or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis (see section 4.3).

Sympathomimetic agents: Concomitant use of Benylin Day & Night with tricyclic antidepressants or sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like stimulants), which interfere with the catabolism of sympathomimetic amines, may occasionally cause a rise in blood pressure.

Antihypertensives: Because of the pseudoephedrine contents, this medicine may antagonise the hypotensive action action of antihypertensive drugs which interfere with sympathetic activity including bretylium bethanide, guanethidine, reserpine, debrisoquine, adrenergic neurone blockers and beta blockers.

Moclobemide: risk of hypertensive crisis.

Because of its pseudoephedrine content, concomitant use of this medicine with oxytocin or cardiac glycosides may cause of a risk of hypertension or an increased risk of dysrhythmias, respectively.

When used concurrently with ergot alkaloids (ergotamine & methysergide), this product can increase the risk of ergotism.

Anticholinergic drugs: The effects of anti-cholinergics e.g., some psychotropic drugs (such as tricyclic antidepressants) and atropine, may be potentiated by this product giving rise to tachycardia, mouth dryness, gastrointestinal disturbances, e.g., colic, urinary retention and headache.

Anaesthetic agents: Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

Paracetamol
Chronic alcohol use can increase the hepatotoxicity of paracetamol overdosage 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 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 paracetamol and a faster elimination rate.

The speed of absorption of paracetamol may be increased by drugs that stimulate gastrointestinal motility such as metoclopramide or domperidone, and absorption reduced by drugs that delay gastric emptying and 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.

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)

Diphenhydramine
Diphenhydramine may potentiate the effects of CNS depressants, including alcohol, sedatives, and tranquilizers (see section 4.4).

The concurrent use of medicinal products, which also prolong the QT interval (e.g. class IA and III anti-arrhythmic drugs, some antibiotics, anti-malaria drugs, neuroleptics) or result in hypokalemia (e.g. certain diuretics) should be avoided (see also section 4.4, 4.9 and 5.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of a combination of diphenhydramine, paracetamol, and pseudoephedrine in pregnant women.
BENYLIN Day & Night Tablets should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs any possible risk to the developing fetus.

Paracetamol:
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.

When given to the mother in labelled doses, paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is effectively metabolised by foetal sulfate conjugation.

Pseudoephedrine:
There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The use of pseudoephedrine hydrochloride decreases maternal uterine blood flow but clinical data are insufficient with respect to effects on pregnancy.

Diphenhydramine:
There are no adequate and well-controlled clinical studies of diphenhydramine in pregnant women. Based on animal studies diphenhydramine is not expected to increase the risk of congenital anomalies (see section 5.3). However, there are no adequate and well-controlled studies in pregnant women. Diphenhydramine is known to cross the placenta. Use of sedating antihistamines during the third trimester may result in adverse reactions in the newborn.

Breastfeeding

Paracetamol
There are no adequate and well-controlled clinical studies of paracetemol in breast-feeding women. Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose).

Pseudoephedrine
There are no adequate and well-controlled clinical studies of pseudoephedrine in breast-feeding women. Pseudoephedrine distributes into and is concentrated in breast milk and can affect a breast-fed infant (irritability, excessive crying and altered sleeping patterns). Up to 0.7% of a single 60-mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3 fold higher than those in plasma. This milk/plasma drug concentration profile suggests low protein binding, although no protein plasma binding data in humans are available. 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.

Diphenhydramine
There are no adequate and well-controlled clinical studies of diphenhydramine breast-feeding women. Diphenhydramine crosses the placenta and is excreted into 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. New-born or premature infants show increased sensitivity to antihistamines.

This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus or breastfeeding infant.

Fertility

There is no information on the effects of this medicine on human fertility.

4.7 Effects on ability to drive and use machines

Benylin Day & Night has a major influence on the ability to drive and use machines. Benylin Day & Night may cause drowsiness. If affected do not drive or operate machinery.

4.8 Undesirable effects

Clinical Trials
Placebo-controlled studies with sufficient adverse event data were not available for the combination of diphenhydramine, paracetamol, and pseudoephedrine. The following adverse events were reported by ≥ 1% of subjects in randomized, placebo-controlled trials with single-ingredient diphenhydramine, single ingredient pseudoephedrine, diphenhydramine/paracetamol, or paracetamol/pseudoephedrine and are included as undesirable effects in their respective safety information: dizziness, somnolence, dry mouth, nausea, asthenia, insomnia, and nervousness.

Post-marketing Data:
Adverse drug reactions identified during post-marketing experience with diphenhydramine, paracetamol, pseudoephedrine or the combination are included below. The frequencies are provided 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)

System Organ Class	Adverse Event	Frequency
Immune system disorders	Anaphylactic reaction, hypersensitivity	Not known
Investigations	Blood pressure increased; transaminases increased†	Not known
Psychiatric disorders	Anxiety, confusional state, euphoric mood, hallucination, hallucination visual, restlessness, irritability	Not known
Nervous system disorders	Agitation, coordination abnormal, convulsion, headache, paraesthesia, psychomotor hyperactivity, sedation, sleep disturbances, tremor, somnolence, cerebrovascular accident†, Posterior Reversible Encephalopathy Syndrome, Reversible Cerebral Vasoconstriction Syndrome	Not known
Eye disorders	Blurred vision, Ischaemic optic neuropathy	Not known
Ear and labyrinth disorders	Tinnitus	Not known
Cardiac disorders	Palpitations, tachycardia, arrhythmia, mycocardial infarction †	Not known
Vascular disorders	Hypotension	Not known
Respiratory, thoracic and mediastinal disorders	Chest discomfort, dry throat, nasal dryness, dyspnoea	Not known
Gastrointestinal disorders	Abdominal pain, constipation, diarrhoea, dyspepsia, vomiting, Ischaemic colitis	Not known
Skin and subcutaneous tissue disorders	Rash, pruritus, rash pruritic, urticaria, Angiodema, Serious skin reactions, including acute generalised exanthematous pustulosis (AGEP), fixed eruption	Not known
Renal and urinary disorders	Urinary retention, dysuria	Not known
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	Not known
Hepato-biliary disorders	Liver dysfunction	Not known

No differences between adult and paediatric safety profiles have been identified.

†These events have been reported very rarely in post-marketing safety. A recent post-authorisation safety study (PASS) did not provide any evidence of increased risk of myocardial infarction or cerebrovascular accident associated with the use of vasoconstrictors for nasal decongestion, including pseudoephedrine.

†Low level transaminase elevations may occur in some patients taking labeled doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

Reporting of suspected adverse reactions
Reporting of 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

No adverse events associated with overdose have been identified for the combination product from the review of postmarketing data and the literature. The information presented below describes overdose with the single active ingredients.

Paracetamol

Please refer to local guidance for the treatment of paracetamol overdose.

Paracetamol overdose can result in liver damage which may be fatal.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults and adolescents who have taken more than the recommended amount of paracetamol. It is considered that excess quantities of a toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include:
Patients with liver disease
Elderly patients
Young children
Patients receiving long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Patients who regularly consume ethanol in excess of recommended amounts.
Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdose generally appear within the first 24 hours and may comprise pallor, hyperhidrosis, general malaise, decreased appetite, nausea, vomiting, anorexia and abdominal pain or patients may be asymptomatic.

Clinical and laboratory evidence of hepatic toxicity may not become apparent until 48 to 72 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased. These clinical events associated with paracetamol overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

They following sequelae to acute hepatic failure associated with paracetamol overdose (adults and adolescents: ≥ 12 years of age: > 7.5g within 8 hours) are considered expected and may be fatal.

Expected Sequelae to Acute Hepatic Failure Associated with Paracetamol Overdose:

System Organ Class (SOC)	**Adverse event**
Infections and infestations	Bacterial infection Fungal infection Sepsis
Blood and lymphatic system disorders	Coagulopathy Disseminated intravascular coagulation Thrombocytopenia
Metabolism and nutrition disorders	Hypoglycaemia Hypophosphatemia Lactic acidosis Metabolic acidosis
Nervous system disorders	Cerebral oedema Coma (with massive paracetamol overdose or multiple drug overdose) Encephalopathy
Cardiac disorders	Cardiomyopathy Cardiac arrhythmias
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Respiratory failure
Gastrointestinal disorders	Gastrointestinal haemorrhage Pancreatitis
Renal and urinary disorders	Acute renal failure*
General disorders and administration site conditions	Multi-organ failure

*Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Blood and Lymphatic Disorders
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 transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

Pseudoephedrine

Symptoms
Overdosage may result in:
Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia

Psychiatric disorders: CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses

Nervous system disorders: seizures, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children

Eye disorders: mydriasis

Cardiac disorders: palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction

Vascular disorders: hypertension, hypertensive crisis

Gastrointestinal disorders: nausea, vomiting, ischaemic bowel infarction

Musculoskeletal and connective tissue disorders: rhabdomyolysis

Renal and urinary disorders: acute renal failure, difficulty in micturition

Management
Measures should be taken to maintain and support respiration andcontrol 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.

Diphenhydramine

Mild to Moderate Symptoms - Somnolence, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, mild hypertension, nausea and vomiting are common after overdose. Agitation, confusion and hallucinations may develop with moderate poisoning.

Severe Symptoms - Effects 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.

Treatment of overdosage should be symptomatic and supportive. Measures to promote rapid gastric emptying (such as induced emesis or gastric lavage), and in cases of acute poisoning activated charcoal, may be useful. The intravenous use of physostigmine may be efficacious in antagonising severe life-threatening anticholinergic symptoms, but its use is controversial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02BE51

The single actives; paracetamol, pseudoephedrine and diphenhydramine; are all well-established monotherapies for relief of pain and fever and symptoms of cold and flu.

Paracetamol: Paracetamol is a well-established efficacious analgesic and antipyretic that is used for the reduction of pain and fever associated, including colds and influenza. 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. Paracetamol is a very well tolerated drug at therapeutic doses of up to 4 g/day in adults. adverse events with paracetamol are rare and usually mild. The main safety concern related to paracetamol use is its hepatic toxicity, especially after overdosage.
The use of paracetamol at therapeutic doses is considered to be generally safe, with no specific paediatric hazards.
Paracetamol is preferred over salicylates for the treatment of pain and fever in children, as its use is not associated with development of Reye's syndrome.

Pseudoephedrine: Pseudoephedrine is an effective decongestant frequently used in cold and flu medications.
Pseudoephedrine is a sympathomimetic drug that has weak direct agonist activity at α- and β-adrenergic receptors. Its principal mechanism is indirect action on the adrenergic receptor system in which pseudoephedrine displaces norepinephrine from storage vesicles in presynaptic neurons. The displaced norepinephrine is released into the neuronal synapse where it is free to activate the postsynaptic α-adrenergic receptors. Stimulation of α1-adrenergic receptors located on capacitance blood vessels of the nasal mucosa (postcapillary venules) results in vasoconstriction, decreased blood volume and a decrease in the volume of the nasal mucosa (nasal decongestion). Constricted blood vessels allow less fluid to enter the nose, throat, and sinus linings, which result in decreased inflammation of nasal membranes as well as decreased mucous production. Thus, by constriction of blood vessels, mainly those located in the nasal passages, pseudoephedrine causes a decrease in nasal congestion. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system. Pseudoephedrine is a very well-tolerated drug at therapeutic doses of up to 240 mg/day in adults. Potentially life-threatening effects are very rare at normal doses and no severe or irreversible adverse events have been reported. The most common AEs include tachycardia, anxiety, restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred.
The clearance of pseudoephedrine is more rapid in children, reflecting a smaller volume of distribution and a more rapid intrinsic clearance.

Diphenhydramine hydrochloride:
Diphenhydramine is an ethanolamine and a first-generation H1 antagonist. It is a reversible, competitive inhibitor of histamine and binds to the H1 receptor. H1 antagonists, especially ethanolamines, have significant antihistaminic activity and antimuscarinic activity and concurrent sedative properties.
The sedative mechanism for diphenhydramine is thought to result from antagonism of central histamine and cholinergic receptors by intact diphenhydramine. The time course for sedation following a 50-mg oral dose was associated with higher plasma concentrations, and was significantly different from placebo during the first three hours following administration. The pharmacodynamics of sedation was correlated with peak concentrations of drug occurring during absorption and the alpha distribution phase. In addition to being H1 selective antihistamine, diphenhydramine is a potent muscarinic antagonist. The sedative effects as well as the antimuscarinic properties of diphenhydramine, which may be responsible for altering the secretions in the airways, may result in cough suppression.
The antitussive property of diphenhydramine is thought to involve a central mechanism involving the medullary cough center. However, the onset of statistically significant antitussive activity not later than 15 minutes after diphenhydramine ingestion suggests that a peripheral mechanism of action may also contribute to the effectiveness of diphenhydramine.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption:
Oral paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract, primarily in the small intestine. The relative bioavailability ranges from 85% to 99%. Peak plasma concentrations are usually attained about 30–60 minutes after oral dosing. For individual adults, maximum plasma concentrations occur within 1 hour following ingestion, and range from 14.8 to 17.6 µg/mL for a single 1000 mg dose. Although maximum concentrations of paracetamol are delayed when administered with food, the extent of absorption is not affected. Paracetamol can be taken independently of meal times.

Distribution:
Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is 0.7 to 1 L/kg in children and adults. A relatively small proportion (10% to 25%) of paracetamol is bound to plasma protein.

Biotransformation:
Paracetamol is primarily metabolized in the liver and involves three main pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via cytochrome P450 enzyme pathway. The principal cytochrome P450 isoenzyme involved in vivo appears to be CYP2E1.

Elimination:
The elimination half-life of paracetamol is about 1 to 3.5 hours. It is approximately one hour longer in cirrhotic patients. Paracetamol is eliminated from the body as glucuronide (45-60%) and sulfate (25-35%) conjugates, thiols (5-10%) as cysteine and mercapturate metabolites, and catechols (3-6%) that are excreted in the urine. Renal clearance of unchanged paracetamol is about 3.5% of the dose.
There is some evidence to suggest that serum half-life is increased and clearance of paracetamol is decreased in frail, immobile, elderly subjects when compared to mobile, elderly subjects. However the clinical significance of these differences is unclear. Differences in pharmacokinetic parameters observed between fit young and fit elderly subjects are not thought to be of clinical significance.

Linearity/non-linearity:
Oral bioavailability in adults appears to depend on the amount of paracetamol administered, increasing from 63% following a 500 mg dose, to nearly 90% after 1 or 2 g.

PKPD relationship:
Effects are apparent within 30 minutes and last for between 4 and 6 hours.

Pseudoephedrine:

Absorption:
Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract after oral administration. The oral bioavailability of pseudoephedrine is high, as determined by urine collections greater than 96% of administered doses. When pseudoephedrine is taken after a high-fat meal, the absorption rate is decreased, resulting in about an hour delay in attaining maximum concentrations. Food does not affect the rate or extent of pseudoephedrine absorption from various extended-release formulations. Following oral administration of a single 30 mg tablet, a mean maximum plasma concentration of 104 ± 19 ng/mL is attained in 1.46 ± 0.55 hours. Following oral administration of a single 60 mg dose as tablets, mean maximum plasma concentrations of 180 ± 30 and 232 ± 30 ng/mL are attained at 1.94 ± 0.86 and 1.96 ± 0.62 hours, respectively.

Distribution:
The apparent volume of distribution for pseudoephedrine ranges from 2.3 to 3.3 L/kg. Up to 0.7% of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3-fold higher than those in plasma. This milk/plasma drug concentration profile suggests low protein binding although no protein plasma binding data in humans are available. 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.

Biotransformation:
In adults, only a minor fraction of pseudoephedrine is metabolized in the liver. About 1% to 6.2% of a dose undergoes N-demethylation to the metabolite, norpseudoephedrine, which is excreted in the urine.

Elimination:
Pseudoephedrine is mainly eliminated by renal excretion as unchanged drug. Most of an oral dose (43% to 96%) is excreted unchanged in the urine within 24 hours. In adults, the elimination half-life (t½) for both immediate- and extended-release pseudoephedrine ranges from 5.5 to 7.0 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.

Linearity/non-linearity:
Following oral administration of a single 30 mg tablet, a mean maximum plasma concentration of 104 ± 19 ng/mL is attained in 1.46 ± 0.55 hours. Following oral administration of a single 60 mg dose as tablets, mean maximum plasma concentrations of 180 ± 30 and 232 ± 30 ng/mL are attained at 1.94 ± 0.86 and 1.96 ± 0.62 hours, respectively, in two separate studies.

PKPD relationship:
Symptoms of congestion improve significantly following a single dose of oral pseudoephedrine (60 mg capsule) compared with placebo at 60, 90, 120 and 150 minutes after the dose.

Diphenhydramine Hydrochloride:

Absorption:
Diphenhydramine is well absorbed from the gastrointestinal tract. Peak serum levels are reached at between 2 – 2.5 hours after an oral dose. After multiple oral doses of 50 mg diphenhydramine four times during each day to four subjects, minimum diphenhydramine plasma concentrations at steady state on the third day ranged from 57-150 ng/mL.

Distribution:
Diphenhydramine is widely distributed throughout the body, including the central nervous system. Diphenhydramine is highly protein bound, with free drug concentrations of 24.0 ± 1.9% and 14.8 ± 1.5% measured in Asian and Caucasian plasma. In adults with liver disease, protein binding is lower, although the volume of distribution is comparable to healthy adults.

Biotransformation:
Diphenhydramine undergoes first-pass metabolism with an absolute bioavailability of 72% ± 8%. It is extensively metabolized in the liver by demethylation to N-demethyl diphenhydramine (DMDP), clinical pharmacokinetics data suggest that diphenhydramine may be an inhibitor of CYP2D6 without being extensively metabolized by this cytochrome P450 isozyme.

Elimination:
For diphenhydramine, mean beta elimination half-lives from 8.5 and 11.5 hours in adults have been reported in studies in which blood is sampled up to 24 to 72 hours. The half-life is increased to 13.6 ± 4.2 h in the elderly and to 15.2 ± 1.5 h in adults with liver cirrhosis. Little unchanged drug is excreted in the urine.
In elderly adults, the mean clearance rate was 11.7 ± 3.1 mL/min/kg, on the other hand it is 23.3 ± 9.4 mL in young adults, while in children, it is 49.2 ± 22.8 mL/min/kg.

Linearity/non-linearity:
N/A.

PKPD relationship:
The antitussive property of diphenhydramine is thought to involve a central mechanism involving the medullary cough center. However, the onset of statistically significant antitussive activity not later than 15 minutes after diphenhydramine ingestion suggests that a peripheral mechanism of action may also contribute to the effectiveness of diphenhydramine. Duration of activity is between 4 – 8 hours.

5.3 Preclinical safety data

Nonclinical data for each component reveal no special hazard for humans based on available studies of repeat dose toxicity and genotoxicity. No data is available on the use of paracetamol, pseudoephedrine and diphenhydramine in combination.

In electrophysiological studies, diphenhydramine blocked the rapid delayed rectifier potassium channel and increased action potential duration. Diphenhydramine may have the potential to elicit arrhythmias in the presence of additional contributing factors (see section 4.4, 4.5 and 4.9).
There are no known reports of animal carcinogenicity studies for pseudoephedrine.

Reproductive toxicity

Paracetamol
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Pseudoephedrine
Reproductive toxicity studies in mice and rats with pseudoephedrine hydrochloride (15 mg/kg) revealed no indication of maternal or fetal toxicity or teratogenicity. At a maternally toxic dose, pseudoephedrine hydrochloride induced fetotoxicity (reduced fetal weight and delayed ossification) in rats.

Diphenhydramine
Embryotoxic effects were observed in rabbits and mice for daily doses of more than 15 – 50 mg/kg body weight; however, there was no evidence for teratogenic effects.

Fertility

Paracetamol
The doses at which effects on fertility are seen are much higher than the recommended doses in humans.

Diphenhydramine
There is insufficient information to determine whether diphenhydramine hydrochloride has the potential to impair fertility in animals. A reproductive risk to humans has not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each white (day) tablet contains:
Pregelatinised maize starch
Povidone K30
Crospovidone
Stearic acid
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Each blue (night) tablet contains:
Microcrystalline cellulose
Maize starch
Sodium starch glycollate
Hydroxypropylcellulose
Pregelatinised maize starch
Croscarmellose sodium
Stearic acid
Magnesium stearate

Film coating (blue tablet only):
Opadry blue 02H205000
Containing:
Hydroxypropylmethyl cellulose
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 container.

6.5 Nature and contents of container

Container:
16 tablet carton containing 12 white oblong PVC/PVDC/Aluminium foil blister-packed 'DAY' tablets and 4 blue round PVC**/**PVDC/Aluminium blister-packed 'NIGHT' tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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