Acamol Tsinun and Shapaat Night Summary of Product Characteristics

1. Name of the medicinal product

Acamol Tsinun and Shapaat Night Caplets

2. Qualitative and quantitative composition

Acamol Tsinun and Shapaat Night caplets contain Paracetamol 500 mg, Pseudoephedrine hydrochloride 30mg Dextromethorphan hydrobromide 15 mg and Chlorpheniramine maleate 2 mg.

Excipients with known effect:

Each caplet contains Sodium 0.588-0.882 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Purple, capsule shaped biconvex film coated tablet, plain on one side and scored on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Acamol Tsinun and Shapaat Night is indicated for a relief of cold, cough and nasal congestion associated with fever and pain, for Night care.

4.2 Posology and method of administration

Posology

Adults and children aged 12 years and over:

1-2 caplets before bedtime.

Children under 12 years:

Acamol Tsinun and Shapaat Night is contraindicated in children under the age of 12 years (see section 4.3).

The Elderly:

In the elderly the rate and extent of paracetamol absorption is normal but plasma half life is longer and paracetamol clearance is lower than in young adults.

When used in combination with Acamol Tsinun and Shapaat Day do not take more than a total of 8 caplets a day. (when using in parallel Acamol Tsinun and Shapaat Day, one dose of Acamol Tsinun and Shapaat Day should be replaced with one dose of Acamol Tsinun and shapaat Night, do not take it in addition to the maximum recommended dosage mentioned above)

Consult with your doctor before using this product.

Hepatic dysfunction

Caution should be exercised when administering Acamol Tsinun and Shapaat Night to patients with hepatic impairment.

Renal dysfunction:

Caution should be exercised when administering Acamol Tsinun and Shapaat Night to patients with moderate renal impairment.

Method of administration

For oral use

4.3 Contraindications

Acamol Tsinun and Shapaat Night is contraindicated in individuals with known hypersensitivity to paracetamol, pseudoephedrine,Dextromethorphan, chlorpheniramine 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. The anticolinergic properties of chlorpheniramine are intensified by monoamine oxidase inhibitors (MAOIs)

Taking selective serotonin reuptake inhibitor (SSRI), or other medications for depression, psychiatric or emotional conditions, or Parkinson's disease, or for 2 weeks after stopping the medication. If you are not sure if your prescription medications contains one of these medicines, ask a doctor or pharmacist before taking this product.

Cardiovascular disease

Severe hypertension or uncontrolled hypertension

Diabetes mellitus

Phaeochromocytoma

Hyperthyroidism

Closed angle glaucoma

Severe acute or chronic kidney disease/renal failure

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

Patients with, or at risk of developing, respiratory failure (e.g. those with chronic obstructive airways disease or pneumonia, or during an asthma attack or an exacerbation of asthma).

4.4 Special warnings and precautions for use

Patients experiencing difficulty in urination and/or enlargement of the prostate, or patients with thyroid disease who are receiving thyroid hormones should not take pseudoephedrine unless directed by a physician.

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), or in occlusive vascular disease. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

If any of the following occur, this product 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.

Posterior reversible encephalopathy syndrome (PRES) and reversable cerebral vasoconstriction syndrome (RCVS)

Cases of PRES and RCVS have been reported with the use of pseudoephedrine containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).
Pseudoephedrine should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism), who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as an underlying cause of HAGMA in patients with multiple risk factors.

Patients suffering from chronic cough as occurs with smoking, asthma or patients suffering from an acute asthma attack, chronic bronchitis, and emphysema, or where cough is accompanied by excessive secretions should be advised to consult a Healthcare Professional before use.

Causes of chronic cough should be excluded if symptoms are persistent. Any accompanying symptoms should be actively sought and appropriately investigated/ treated. Stop use and ask your healthcare professional if your cough lasts more than 7 days, comes back or is accompanied by a fever, rash or persistent headache. These could be signs of serious conditions.

Medical advice should be sought before taking **dextromethorphan** in patients with: severe renal impairment.

Concomitant use of other cough and cold medicines should be avoided.

Concomitant use of alcohol should be avoided.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

Serotonin syndrome

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, treatment should be discontinued

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

For Paracetamol

Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.

Anyone who develops a skin rash or reaction while using paracetamol should stop the drug and seek medical attention right away. Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

Paracetamol can cause accidental poisoning in toddlers and infants. Paracetamol-containing products should be kept well out of reach of children.

Potentially fatal hepatotoxicity can result from paracetamol overdosage. However, in rare cases, hepatotoxicity has occurred in patients receiving high or excessive doses within therapeutic doses. Certain patients may be more susceptible to paracetamol hepatotoxicity, e.g., chronic alcoholics, patients with liver disease, or those who are malnourished or taking other drugs that induce hepatic enzymes.

Because of the risk of heptotoxicity, patients should be cautioned against the inadvertent administration of excessive doses of paracetamol by using multiple paracetamol-containing products at once, such as cough and cold remedies, analgesics or arthritic formulations, antipyretics or products for relief of menstrual symptoms or muscle spasm. Administration of paracetamol to children may be especially prone to error due to the many concentrations and strengths of products available. To avoid dosing errors, all product labels should be checked carefully to ensure calculation of the amount of paracetamol to be given.

Chlorphenamine in common with other drugs having anticholinergic effects, should be used with caution in epilepsy,raised intra-ocular pressure including glaucoma, prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment; renal impairment. Children and the elderly are more likely toexperience the neurological anticholinergic effects and paradoxical excitation (eg. increased energy, restlessness,nervousness). Avoid use in elderly patients with confusion.

The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.
Concurrent use with drugs which cause sedation such as anxiolytics and hypnotics may cause an increase in sedative effects, therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines.

The effects of alcohol may be increased and therefore concurrent use should be avoided.
Should not be used with other antihistamine containing products, including antihistamine containing cough cold medicines.

Risks of abuse

Pseudoephedrine carries the risk of abuse. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. The recommended maximum dose and treatment duration should not be exceeded (see section 4.2).

Keep out of the sight and reach of children.

Do not exceed recommended dose.

Excipients:

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, 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 a- 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 monoamine inhibitors or within 14 days of stopping treatment as there is a risk of hypertensive crisis.

Do not use if you are now taking a prescription a selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressants (TCAs) or other medications for depression, psychiatric, or emotional conditions, or Parkinson's disease, or for 2 weeks after stopping the medication

Moclobemide: Risk of hypertensive crisis

Sympathomimetic agents: Concomitant use of this product with tricyclic antidepressants or sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) or with monoamine oxidase inhibitors may cause a rise in blood pressure.

Antihypertensives: Because of the pseudoephedrine content, this product may partially reverse the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, betanidine, guanethedine, 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

Anticholinergic drugs: Enhances effects of anticholinergic drugs (such as tricyclic antidepressants)

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 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.

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.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Concurrent use of **chlorphenamine** and hypnotics or anxiolytics may cause an increase in sedative effects, therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines.
Chlorphenamine inhibits phenytoin metabolism and can lead to phenytoin toxicity.

The anticholinergic effects of chlorphenamine are intensified by MAOIs (see section 4.3).

4.6 Fertility, pregnancy and lactation

Paracetamol and Pseudoephedrine There are no adequate and well-controlled clinical studies in pregnant or breast-feeding women for the combination of paracetamol, and pseudoephedrine**.**

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 foetus or breastfeeding infant.

Pregnancy

The safety of **pseudoephedrine** in pregnancy has not been established.

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.

There is no adequate data from the use of **chlorphenamine maleate** in pregnant women. The potential risk for humans is unknown. Use during the third trimester may result in reactions in the newborn or premature neonates. Not to be used during pregnancy unless considered essentially by a physician.

Breastfeeding

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 60 mg 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 650 mg 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.

Chlorphenamine maleate and other antihistamine may inhibit lactation and may be secreted in breast milk.

Not to be used during lactation unless considered essential by a physician.

Fertility

No studies have been conducted in animals to determine whether pseudoephedrine has the potential to impair fertility. There is no information of the effect of this medicine on fertility.

Dextromethorphan

Fertility

There are no relevant clinical data available regarding effects on fertility from patients taking dextromethorphan. Studies in rats have demonstrated a lack of adverse effect on fertility (see section 5.3). Therefore, no adverse effects on human fertility are expected at therapeutically relevant doses.

Pregnancy

There are no relevant clinical data available regarding effects on pregnancy from patients taking dextromethorphan. Animal studies do not indicate embryofetal toxicity (see section 5.3). Dextromethorphan should not be used during pregnancy without medical advice.

Breastfeeding

Avoid the use of the product during lactation, unless the benefits to the mother outweigh the risks to the infant. If used, the lowest effective dose and shortest duration of treatment should be considered.

Dextromethorphan is excreted in breast milk in minor quantities. There is a lack of data available on the effect of infant exposure through breast milk.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

The anticholinergic properties of **chlorphenamine** may cause drowsiness, dizziness, blurred vision and psychomotor impairment which can seriously hamper the patient's ability to drive and use machinery

When taking this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

Adverse drug reactions identified during clinical trials and post-marketing experience with paracetamol, pseudoephedrine, dextromethorphan, chlorpheniramine or the combination 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, including isolated reports

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	Not known	Blood disorders, blood dyscrasias (including agranulocytosis and thrombocytopenia) have been reported following paracetamol use but were not necessarily causally related to the drug haemolytic anaemia, blood dyscrasias
Immune system disorders	Rare	Hypersensitivity (cross-sensitivity may occur with other sympathomimetics)
	Unknown:	allergic reaction, angioedema, anaphylactic reactions
Psychiatric disorders	Common	Insomnia Nervousness

	Not known	Anxiety Euphoric mood Excitability Hallucinations Irritability Paranoid delusions Restlessness Sleep disorder confusion*, excitation*, irritability*, nightmares*, depression
Nervous system disorders	Very common	Headache sedation, somnolence
	Common	Dizziness disturbance in attention, abnormal coordination, headache
	Not known	Cerebrovascular accident Paraesthesia Posterior reversible encephalopathy syndrome (PRES)(see section 4.4)/Reversible cerebral vasoconstriction syndrome (RCVS)(see section 4.4) Psychomotor hyperactivity Somnolence Tremor
Eye Disorders	Common:	blurred vision
	Not known	Ischaemic optic neuropathy
Ear and labyrinth disorders	Unknown:	tinnitus
Cardiac disorders	Not known	Dysrhythmias Myocardial infarction/myocardial ischaemia Palpitations Tachycardia arrhythmias
Vascular disorders	Not known	Hypertension Hypotension
Gastrointestinal disorders	Common	Dry mouth Nausea
	Not known	Abdominal pain Diarrhoea Ischaemic colitis Vomiting dyspepsia
Hepatobiliary disorders	Rare	Hepatic necrosis
	Unknown:	hepatitis, jaundice
Skin and subcutaneous tissue disorders	Rare	Rash

	Not known	Angioedema Fixed eruption Pruritus Rash pruritic Severe skin reactions, including Acute generalised exanthematous pustulosis (AGEP) Urticaria exfoliative dermatitis, rash, photosensitivity
General disorders and administration site conditions	Common:	fatigue
	unknown	chest tightness
Metabolism and nutritional disorders	Unknown:	anorexia
Respiratory, thoracic and mediastinal disorders:	Unknown:	thickening of bronchial secretions
Musculoskeletal and connective tissue disorders	Unknown:	muscle twitching, muscle weakness

Renal and urinary disorders	Uncommon	Nephropathy toxic
	Not known	Dysuria Renal papillary necrosis (after prolonged administration) Urinary retention (in men whom prostatic enlargement could have been an important predisposing factor)
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis

*(Chlorpheniramine) Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation(e.g. increased energy, restlessness, nervousness).

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic dosages of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of their disease improved after paracetamol withdrawal.

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

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4).

Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Dextromethorphan

The following adverse events have been observed in clinical trials with dextromethorphan.

Gastrointestinal Disorders:

Gastrointestinal upset, nausea, vomiting, abdominal discomfort

Nervous System Disorders:

Dizziness, drowsiness, mental confusion

Adverse reactions identified during post-marketing use are listed below. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown.

Immune System Disorders:

Hypersensitivity

Psychiatric Disorders:

Frequency unknown: Drug dependence (see section 4.4)

Skin and Subcutaneous Disorders

Allergic reactions (e.g. rash, urticaria, angioedema)

General Disorders and Administration Site Conditions:

Frequency unknown: drug withdrawal syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Signs and symptoms

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

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

Or

B. Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms

Symptoms of paracetamol 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, coma and death.

Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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 are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Pseudoephedrine

Symptoms

8/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.

Dextromethorphan hydrobromide

Symptoms and signs:

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.

In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Management:

-Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

-For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

Chlorpheniramine maleate

Symptoms and signs

The estimated lethal dose of chlorphenamine is 25 to 50mg per kg body weight. Symptoms and signs include sedation,paradoxical excitation of the CNS, toxic psychosis, apnoea, convulsions, anticholinergic effects, dystonic reactions andcardiovascular collapse including arrhythmias.

Treatment

Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions, and fluid and electrolyte balance.

If overdosage is by the oral route, treatment with activated charcoal should be considered provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion).

Hypotension and arrhythmias should be treated vigorously; CNS convulsions may be treated with I.V. diazepam.Haemoperfusion may be used in severe cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Expectorants, ATC code: N02B E51

Pseudoephedrine

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

Paracetamol

Paracetamol has analgesic and antipyretic actions but only weak anti-inflammatory properties. This may be explained by presence of cellular peroxides at sites of inflammation which prevent inhibition of cyclo-oxygenase by paracetamol. At other sites associated with low levels of cellular perioxides, e.g. pain, fever, paracetamol can successfully inhibit prostaglandin biosynthesis.

Dextromethorphan hydrobromide

ATC code: R05DA09

Dextromethorphan Hydrobromide is a cough suppressant which has a central action on the cough center in the medulla. It has no analgesic properties.

Dextromethorphan

Pharmacotherapeutic group: Cough suppressant

Chlorphenamine

ATC code R06AB04

Chlorpheniramine is a potent antihistamine (H1-antagoonist)..

Antihistamines diminish or abolish the actions of histamine in the body by competitive reversible blockade of histamineH1-receptor sites on tissues. Chlorphenamine also has anticholinergic activity.

Antihistamines act to prevent the release of histamine, prostaglandins and leukotrienes and have been shown to prevent the migration of inflammatory mediators. The actions of chlorphenamine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

5.2 Pharmacokinetic properties

Pseudoephedrine

Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine: 55% to 75% of a dose is excreted unchanged. The rate of urinary excretion of pseudoephedrine is accelerated when the urine is acidified. Conversely as the urine pH increases, the rate of urinary excretion is slowed.

Paracetamol

Peak plasma paracetamol concentration usually occurs between 30 and 90 minutes after oral ingestion. Paracetamol is distributed uniformly throughout most body fluids and is only 15 to 25 per cent bound to plasma proteins. The plasma half life of paracetamol after therapeutic doses is in the range of 1 to 3 hours.

Dextromethorphan hydrobromide

Dextromethorphan hydrobromide is well absorbed from the gastrointestinal tract.

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

Chlorphenamine is well absorbed from the GI tract, following oral administration. The effects develop within 30minutes, are maximal within 1 to 2 hours and last 4 to 6 hours. The plasma half-life is estimated to be 12 – 15 hours.
There is significant plasma protein binding. The drug is largely inactivated in the liver and excreted as metabolites in the urine. Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivative. About 22% of an oral dose is excreted unchanged in the urine. Only trace amounts have been found in the faeces.

5.3 Preclinical safety data

Paracetamol and Pseudoephedrine are well known constituents of medicinal products and their safety profile is well documented. The results of pre-clinical 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.

Dextromethorphan

Non-clinical safety data on dextromethorphan obtained from the literature and in-house have not revealed findings which are of relevance to the recommended dosage and use of the product.

Reproductive and developmental toxicity

No adverse effects on male and female fertility or postnatal development were observed rats following oral administration of up to 50 mg/kg/day dextromethorphan. No effects on embryofetal development were observed in both rats and rabbits following oral administration of up to 50 mg/kg/day dextromethorphan during pregnancy. A 50 mg/kg/day dose in rats and rabbits is approximately 5- and 11-times the maximum human equivalent therapeutic dose (based on the body weight of 12-year-old child of 40 kg), respectively.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, sodium starch glycolate, hypromellose, silicon dioxide, stearic acid, magnesium stearate, polyvinyl alcohol, macrogol 3350 (polyethylene glycol), talc, titanium dioxide, erythrosine aluminum lake, FD&C blue #1/brilliant blue FCF aluminum lake.

6.2 Incompatibilities None known

6.3 Shelf life: 36 months

6.4 Special precaution for storage: Store in a dry place below 25°C. Keep out of the reach and sight of children.

6.5 Nature and content of container: Carton containing 14 caplets, Blister PVDC/Aluminium

6.6 Special precautions for disposal and other handling:

Medicines should not be disposed of via wastewater or household waste. Ask a pharmacist how to dispose of medicines no longer required. These measures will help to
protect the environment.

7 LICENCE HOLDER AND MANUFACTURER

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REGISTRATION NUMBERS

136-48-31129

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