Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500.0mg and diphenhydramine hydrochloride 25.0mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet
Blue/light blue film coated capsule shaped tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the short term treatment of bedtime symptoms of pain, for example arising from colds and flu, rheumatic and muscle pain, backache, toothache, headache and period pain which is causing difficulty in getting to sleep.

4.2 Posology and method of administration

Oral administration only.
Adults (including the elderly) and adolescents 16 years and over:
2 tablets to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4000 mg (including this product) in any 24 hour period. Allow at least four hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets:
Two tablets (1000mg paracetamol, 50mg diphenhydramine) in 24 hours.

Adolescents 12 to 15 years:
1 tablet to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 3000 mg (including this product) in any 24 hour period. Allow at least four to six hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets:
One tablet (500mg paracetamol, 25mg diphenhydramine) in 24 hours.

The maximum daily dose of paracetamol should not exceed 2000 mg in the following situations, unless directed by a physician:
- Adults or adolescents weighing less than 50 Kg
- Hepatic impairment
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Do not take Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film -coated Tablets for more than 7 consecutive nights without consulting your doctor.
Do not exceed the stated dose.

The elderly:
Should not be taken by elderly with confusion. Sedating antihistamines may cause confusion and paradoxical excitation in the elderly. Experience has indicated that normal adult dosage with paracetamol is appropriate. However in frail, immobile, elderly subjects, a reduction in the amount or frequency of dosing of paracetamol may be appropriate.

Children under 12 years:
Not recommended for children under 12 years of age except on medical advice.

Hepatic Impairment:
Patients with hepatic impairment should seek the advice of a doctor before taking this product. When giving paracetamol to patients with impaired hepatic function or Gilbert's Syndrome, the dose may need to be reduced or the dosing interval prolonged. (See section 4.4)

Renal Impairment:
Patients with renal impairment should seek the advice of a doctor before taking this product.

It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.

Adults:

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

4.3 Contraindications

· Hypersensitivity to paracetamol ,diphenhydramine hydrochloride or any of the excipients listed in section 6.1.
· closed angle glaucoma
· Porphyria.
· Concomitant use with other with other antihistamine-containing preparations, including topical antihistamines and cough and cold medicine

Antihistamines are contraindicated in premature infants or neonates who have increased susceptibility to antimuscarinic effects.

4.4 Special warnings and precautions for use

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
Caution should be exercised in patients with epilepsy or seizure disorders, myasthenia gravis, narrow-angle glaucoma prostatic hypertrophy, urinary retention, pyloroduodenal obstruction, asthma, bronchitis and chronic obstructive pulmonary disease (COPD). The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
Do not take for more than 7 days without consulting a doctor. If symptoms persist, medical advice must be sought.
Patients should be advised to consult their doctor if their headaches become persistent.
May increase the effects of alcohol therefore, alcohol should be avoided (see Interactions). Concurrent use of drugs which cause sedation such as tranquillizers, hypnotics and anxiolytics may cause an increase in sedative effects therefore medical advice should be sought before taking diphenhydramine with such medicines (see Interactions).
Avoid use with other antihistamine-containing preparations, including topical antihistamines and cough and cold medicines.
Use with caution with monoamine oxidase inhibitors (MAOIs) or within 2 weeks of stopping an MAOI (see Interactions).
Use with caution with other drugs with antimuscarinic properties (e.g. atropine, tricyclic antidepressants (see Interactions).
Use with caution in the elderly, who are more likely to experience adverse effects. Avoid use in elderly patients with confusion.
May cause drowsiness.
Keep out of sight and reach of children.
Prolonged or frequent use is discouraged. . Allow at least four hours between taking any paracetamol-containing product and this product. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4000 mg (including this product) in any 24 hour period. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.
Immediate medical advice should be sought in the event of an overdose, even if you feel well (see section 4.9).
Paracetamol should be administered only with particular caution under the following circumstances (see section 4.2 where relevant):
• Hepatic Impairment

• Chronic alcoholism
• Renal failure (GFR≤50ml/min)
• Gilbert's Syndrome (familial non-haemolytic jaundice)
• Concomitant treatment with medicinal products affecting hepatic function
• Glucose-6-phosphatedehydrogenase deficiency
• Haemolytic anaemia
• Glutathione deficiency
• Dehydration
• Chronic malnutrition
• Weight less than 50kg
• Elderly

Use in patients with congenital long QT-syndrome or other clinically relevant cardiac disorders (in particular coronary heart disease, cardiac conduction disorders, arrhythmias) should be avoided.
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 hypokalaemia (see also section 4.5, 4.9 and 5.3) should be avoided.
Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

4.5 Interaction with other medicinal products and other forms of interactions

The absorption of paracetamol may be increased by metoclopramide and domperidone and reduced by cholestyramine. However, the interactions are not considered to be clinically significant for over-the-counter products intended for short term use.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Diphenhydramine may potentiate the sedative effects of alcohol and other CNS depressants (e.g. tranquillizers, hypnotics, opioid analgesics, and anxiolytics).
Monoamine oxidase inhibitors may prolong and intensify the anticholinergic effects of diphenhydramine.
As diphenhydramine has some anticholinergic activity, the effects of some anticholinergic drugs (e.g. atropine, tricyclic antidepressants) may be potentiated.
Diphenhydramine is an inhibitor of the cytochrome p450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with drugs which are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.
The concurrent use of medicinal products, which also prolong the QT interval (e.g. class IA and III anti-arrythmic 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).
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity of paracetamol.
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
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. Use of sedating antihistamines during the third trimester may result in adverse reactions in the newborn. Antihistamines are contraindicated in premature infants (see section 4.3).
Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets, 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.
Lactation
Paracetamol is excreted in breast milk, but not in clinically significant amounts. To date no undesirable effects on breast-fed infants have been reported.
Diphenhydramine has been detected in breast milk, but this has not been quantified.
The effects of diphenhydramine on breast-fed infants are unknown. New-born or premature infants show increased sensitivity to antihistamines.

Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets is not recommended for use in nursing mothers.

Fertility:

There is no information of the effect of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film -coated Tablets on fertility.

4.7 Effects on ability to drive and use machines

May cause drowsiness, dizziness, blurred vision, cognitive and psychomotor impairment, which can seriously affect the patient's ability to drive or operate machinery. If affected, do not drive or operate machinery.

4.8 Undesirable effects

Undesirable effects are listed below by System Organ Class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Paracetamol

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency. As the adverse reactions identified from post-marketing use are reported voluntarily from a population of uncertain size, the frequency is not known but likely to be very rare (<1/10,000).

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopaenia
Immune System disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angioedema, and Stevens Johnson syndrome. Very rare cases of serious skin reactions have been reported.
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs.
Hepatobiliary disorders	Hepatic dysfunction.

Diphenhydramine

Adverse reactions which have been observed in clinical trials and which are considered to be common or very common are listed below by MedDRA System Organ Class. The frequency of other adverse reactions identified during postmarketing use is not known, but these reactions are likely to be uncommon or rare.

Body System	**Undesirable effect**
General disorders and administration site conditions	Common: Fatigue
Immune system disorders	Not known: Hypersensitivity reactions including rash, urticaria, dyspnoea and angioedema
Psychiatric disorders	Not known: Confusion*, paradoxical excitation* (e.g. increased energy, restlessness, nervousness) * The elderly are more prone to confusion and paradoxical excitation
Nervous system disorders	Common: Sedation, drowsiness, disturbance in attention, unsteadiness, dizziness Not known: Convulsions, headache, paraesthesia, dyskinesias
Eye disorders	Not known: Blurred vision
Cardiac disorders	Not known: Tachycardia, palpitations
Respiratory, thoracic & mediastinal disorders	Not known: Thickening of bronchial secretions
Gastrointestinal disorders	Common: Dry mouth. Not known: Gastrointestinal disturbance including nausea, vomiting.
Musculoskeletal and connective tissue disorders	Not known: Muscle twitching
Renal and urinary disorders	Not known: Urinary difficulty, urinary retention

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. Healthcare professionals are asked to report any suspected

adverse reactions via the HPRA Pharmacovigilance, Earlsfort Terrace , IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol

Symptoms and Signs

There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol in a single administration in adults or in children 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.

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.

Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

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

Risk Factors include:

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.

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 >150mg/kg paracetamol has been taken within 1 hour.

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

Symptomatic treatment should be implemented.

Diphenhydramine Hydrochloride

Symptoms and Signs

Diphenhydramine overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation tremor, dystonic reactions, hallucinations and ECG changes. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse.

Treatment

Treatment should be supportive and directed towards specific symptoms. The stomach should be emptied by aspiration and gastric lavage. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol:
ATC code: N02BE51 Analgesics and antipyretics
Paracetamol has analgesic and antipyretic effects. It is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its ability to reduce fever (a central action) and to induce analgesia.
Diphenhydramine:
ATC code: R06AA02 Antihistamines for systemic use
Diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of antihistamine at the H1 receptor sites. However, like most H1 antihistamines it has additional sedative anticholinergic (muscarinic) and local anaesthetic properties.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration in plasma generally reaches a peak in 30-120 minutes; plasma half-life is 1-4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids. Plasma binding is variable. Excretion is almost exclusively renal in the form of conjugates.
In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with renal failure (GFR≤50ml/min), to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.
Diphenhydramine is well absorbed from the gastrointestinal tract following oral administration. Peak, plasma concentrations are achieved in 2 to 3 hours and the effects usually last 4 to 6 hours. Diphenhydramine is extensively metabolised mainly in the liver, and excreted usually as metabolites in the urine.

5.3 Preclinical safety data

Diphenhydramine:
In electrophysiological in vitro studies, diphenhydramine blocked the rapid delayed rectifier potassium channel and increased action potential duration in concentrations exceeding the therapeutic concentrations by a factor of about 40. Therefore, diphenhydramine may have the potential to elicit Torsades de Pointes arrythmias in the presence of additional contributing factors (see 4.5 and 4.9). This concern is supported by individual case reports.
The mutagenic potential of diphenhydramine has been investigated in *in vitro* investigations. The tests did not show relevant mutagenic effects.
Longterm investigations in rats and mice did not provide evidence for a tumorgenic potential.
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.
Paracetamol:
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Table core
Maize starch
Pregelatinised maize starch
Povidone K30
Talc
Stearic acid

Film coat
Hypromellose (E464),
Talc
Titanium dioxide (E171),
Macrogol 400,
Indigo Carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVDC/PVC/aluminium blister packed into outer cardboard cartons.
Pack sizes: 4, 10, 12, 20, 24 and 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical
Dublin Road
Loughrea
Co. Galway
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0688/039/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2022