

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ilvico Cold and Flu film-coated tablets Paracetamol 325 mg Caffeine 30 mg Brompheniramine maleate 3 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Paracetamol 325mg

Caffeine 30mg

Brompheniramine maleate 3mg

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, biconvex round, smooth on both sides, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms associated with the common cold, influenza, and upper respiratory tract infections.

4.2 Posology and method of administration

For oral use.

Adults and children older than 12 years

One or two tablets taken orally with water three times daily and the maximum dose of 6 tablets daily should not be exceeded.

Not for use in children under the age of 12 years (see sections 4.3 and 4.4).

Renal impairment:

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. The table below is provided for guidance only, noting that a 500mg dose cannot be achieved with this product:

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

Hepatic impairment:

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

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

The 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 (see section 4.4).

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

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Ilvico must not be used in the presence of narrow-angle glaucoma.
- Ilvico must not be used in patients who have brain damage or epilepsy.
- Use in children less than 12 years old.
- Use in patients with tachyarrhythmias.
- Use in patients with peptic ulcers.
- Use in patients with severe renal impairment.
- Use in patients with severe hepatic impairment (including viral hepatitis).
- Use in patients with haemophilia.
- Ilvico film-coated tablets contain brompheniramine, which should not be administered in patients with vesical neck obstruction, symptomatic prostatic hypertrophy, or urinary retention (the anti-cholinergic effects of brompheniramine may precipitate it or aggravate it).
- Administration of monoamine oxidase inhibitors (MAOIs) concomitantly or in the last 14 days (see section 4.5).

4.4 Special warnings and precautions for use

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

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR \leq 50ml/min)
- Gilbert's 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, as they may be more likely to get side effects, including confusion

This product should only be used when clearly necessary. In general, medicinal products containing 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.

Immediate medical advice should be sought in the event of overdose even if patient feels well due to the risk of irreversible liver damage.

Prolonged or frequent use is discouraged. In order to avoid the risk of an overdose, patients should be advised not to take other paracetamol containing products or other cough and cold medicines concurrently. Exceeding the recommended dose,

e.g., taking multiple paracetamol doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

Paracetamol must be administered with caution, avoiding prolonged treatment in patients with anaemia, cardiac or pulmonary afflictions or renal dysfunction (in the latter case, occasional use is acceptable, but the prolonged administration of high doses may increase the risk of adverse renal effects).

Concomitant use of alcohol should be avoided. The use of paracetamol in patients who habitually consume alcohol (three or more alcoholic beverages (e.g., beer, wine, liquor) per day) may cause hepatic damage. In chronic alcoholics, no more than 2g/day must be administered of paracetamol.

Caution is advised for patients with impaired glucose-6-phosphate dehydrogenase due to paracetamol content.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe with severe illness such as 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 underlying cause of HAGMA in patients with multiple risk factors.

Caution is advised in patients with phaeochromocytoma and in patients with hyperthyroidism due to the content of brompheniramine and caffeine which could impact on the catecholamine pathway leading to hypertension.

Caution is advised with asthmatic patients.

The hazards of overdose are greater in those with non-cirrhotic liver disease. The stated dose should not be exceeded.

Rarely, paracetamol can cause serious, potentially fatal skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN). See also section 4.8 Undesirable effects.

Brompheniramine should be administered with caution in children, who are more susceptible to the effects of antihistamines; brompheniramine may cause paradoxical excitation, and it may act as a cerebral stimulant in children and occasionally in adults giving rise to insomnia, nervousness, hyperpyrexia, tremors, and epileptiform convulsions.

Prolonged use of caffeine may result in withdrawal and rebound effects.

It is advisable to limit the intake of caffeine-containing medicines, food, and drinks while taking this product.

Excipients with known effect:

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

Interactions related to paracetamol

- Liver damage may be caused with paracetamol at doses which would otherwise not be harmful if the product is taken by patients who habitually consume alcohol or in chronic alcoholics (see section 4.4).
- Paracetamol is metabolised at the hepatic level, giving rise to hepatotoxic metabolites and thus may interact with the following products which utilise the metabolic pathways:
 - *Oral Anticoagulants (Coumarol, warfarin)*: The regular administration of paracetamol during prolonged periods at doses higher than 2 g/day with these types of products may provoke an increase of the anti-coagulant effect, possibly due to a diminution of the hepatic synthesis of the factors favouring coagulation. Patients undergoing treatment with oral anticoagulants should, therefore, only receive paracetamol over long periods under medical supervision.
 - *Anticonvulsants (phenytoin, phenobarbital, methylphenobarbital, primidone)*: Diminution of the bioavailability of the paracetamol as well as potentiation of the hepatic toxicity in overdosage, due to the induction of hepatic metabolism.

- *Oestrogens*: Diminution of the plasmatic levels of paracetamol, with possible inhibition of its effects, through possible induction of its metabolism.
- *Loopdiuretics*: Paracetamol may reduce renal excretion of prostaglandins and the activity of the plasmatic rennin, reducing diuretics effects.
- *Isoniazid*: Diminution of the paracetamol clearance, with possible potentiation of its action and / or toxicity, through inhibition of its hepatic metabolism.
- *Lamotrigine*: Diminution of the area under the curve (20%) and of the half-life (15% of lamotrigine), with possible inhibition of its effect, through possible induction of its hepatic metabolism.
- *Probenecid*: Decreases the renal clearance of paracetamol and may slightly increase the paracetamol half-life.
- *Propranolol*: Inhibits the enzymatic system responsible for the glucuronidation and oxidation of paracetamol, which may strengthen the action of paracetamol.
- *Rifampicin*: Increases the clearance of paracetamol through possible induction of its hepatic metabolism, which may increase hepatotoxicity.
- *Chloramphenicol*: Prolongation of its half-life, increasing the risk of chloramphenicol toxicity.
- *Anti-cholinergics(glycopyrrone,propantheline)*: Slow gastric emptying which may reduce the rate of paracetamol absorption and result in later onset action.
- *Metoclopramide*: Accelerates gastric emptying which may increase the rate of paracetamol absorption.
- *Cholestyramine and activated charcoal*: Diminution in the absorption of paracetamol with possible inhibition of its effect, through fixation of paracetamol in the intestine.
- *Zidovudine*: Paracetamol may provoke a diminution of the pharmacological effects of zidovudine through an increase in the clearing of this substance. Concomitant use can also enhance the tendency to develop neutropenia. Ilvico should be only taken simultaneously if recommended by a physician.
- *Flucloxacillin*: Caution should be taken when paracetamol is used concomitantly, as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk factors (see section 4.4).
- *EthylAlcohol*: Potentiates paracetamol hepatotoxicity toxicity, through possible induction of the hepatic metabolites of paracetamol.

Interactions related to brompheniramine

- Monoamine oxidase inhibitors (MAOIs): Concomitant MAOI therapy increases the risk of serotonin syndrome. Furthermore, MAOIs enhance the anticholinergic effects of antihistamines such as brompheniramine. Consequently, administration of monoamine oxidase inhibitors (MAOIs) concomitantly or in the last 14 days is contraindicated (see section 4.3).
- Concomitant use of brompheniramine may interact with other medicines with anti-cholinergic properties (such as other antihistamine: e.g., doxylamine, diphenhydramine, and anti-cholinergics: e.g., glycopyrrone, propantheline, ipratropium) leading to increased anti-cholinergic effects such as sedation and urinary retention.
- Brompheniramine may increase the effects of other CNS depressors, such as alcohol, hypnotics, anxiolytics monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, barbiturates, anaesthetics, maybe provoking overdose symptoms. Ilvico may potentiate the effect of agents with central depressant action, e.g., analgesics and tranquillisers, alcohol and vice versa.
- Plasma concentrations of H1 antihistamines such as brompheniramine may be decreased by concomitant administration with inducers of CYP P450 activity such as benzodiazepines, macrolides, antifungal drugs, and calcium channel antagonists.
- In common with other first-generation antihistamines, brompheniramine affects the serotonergic neurotransmitter systems and may potentially interact with pro-serotonergic drugs leading to serotonin syndrome: amphetamines, antidepressants/mood stabilisers, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonin 2A receptor blocker, St. John's wort, tricyclic antidepressants, and antimigraine drugs.
- First generation antihistamines such as brompheniramine may re-enforce the negative effects of alcohol upon oculomotor coordination, cognitive function and driving.

Interactions related to caffeine

- Concomitant use of phenylpropanolamine and caffeine enhances absorption or inhibits elimination of caffeine and results in an additive increase in blood pressure.
- Caffeine may significantly inhibit the metabolism of clozapine and thereby increases risk of clozapine toxicity.

Interactions with Diagnostic Tests

- Paracetamol may alter the values of the following diagnostic tests:

- a. Blood(biological) increase of transaminases (ALT and AST), alkaline phosphatase, ammonium, bilirubin, creatinine, lactate dehydrogenase (LDH) and urea.
- b. Increase (analytical interference) of glucose, theophylline, and uric acid.
- c. Increase of the prothrombin time (in patients with warfarin maintenance dosages, although without clinical significance).
- d. Reduction (analytical interference) of glucose when oxidase-peroxidase method used.

- *Urine test*: falsely increased values of metadrenaline and uric acid may appear.
- *Pancreatic function tests with bentiromide*: paracetamol, as does bentiromide, metabolises in the form of arylamine, thus increasing the apparent recovered quantity of Para-Amino Benzoic Acid (PABA). **It is recommended to interrupt treatment with paracetamol for at least three days before the administration of bentiromide.**
- *5-hydroxyindoleacetic acid (5-HIAA) determination in urine*: in qualitative diagnostic detection tests that use nitrosonaphthol as reagent, paracetamol may produce falsely positive results. The quantitative tests are not altered.
- *Cutaneous tests*: antihistamines like brompheniramine may interfere in cutaneous tests made with allergenic extracts. It is recommended to suspend the medication for at least 3 days prior to the commencement of cutaneous allergenic testing.

Myocardial imaging: adenosine receptor agonists like caffeine can reduce the vasodilating effect of substances used for myocardial imaging. Caffeine should be avoided for 24 hours before myocardial imaging.

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol crosses the placental barrier.

A large amount of data on the use of paracetamol in pregnancy 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 may 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 are no adequate data from the use of brompheniramine 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 essential by a doctor. Care should be taken with concomitant ingestion of dietary sources of caffeine. Pregnant women are advised to restrict their caffeine intake to no more than 200 mg per day (the approximate amount provided by two cups of instant coffee).

As a precautionary measure, this product should not be used in pregnancy unless advised by a doctor.

Breast-feeding

H1 antihistamines may inhibit lactation and have been reported to be excreted in breast milk, leading to sedation and other adverse effects in these breastfed infants. Not to be used during lactation unless considered essential by a doctor.

Paracetamol may be found in maternal milk in quantities similar to those of maternal plasma. The latter concentration does not appear to result in a pharmacologically significant dose to the breastfeeding infant.

Caffeine appears in breast milk. Maternal caffeine consumption in moderate amounts during breastfeeding is not associated with any side effects in breastfeeding infants. Maternal consumption of large amounts of caffeine has been associated with infant irritability and poor sleeping patterns.

As a precautionary measure, this product should not be used when breast-feeding unless advised by a doctor.

Fertility

In clinical studies caffeine has been shown to be associated with a delay in conception among fertile women when consumed in high levels and associated with enhancement of the negative effect of alcohol on ability to conceive.

There are no clinical studies on the effect of brompheniramine or paracetamol on human fertility.

4.7 Effects on ability to drive and use machines

This product may cause drowsiness, dizziness, or blurred vision, therefore, if affected, patients should refrain from driving or operating machinery.

Furthermore, antihistamines may re-enforce the negative effects of alcohol upon oculomotor coordination and cognitive function and this combination may further increase the risk of accidents.

4.8 Undesirable effects

The most serious adverse reactions which may occur are due to paracetamol and are blood dyscrasias: agranulocytosis, leucopenia, neutropenia, pancytopenia, thrombocytopenia, and haemolytic anaemia, all of which are very rare adverse reactions, with an estimated frequency of less than 1 case in every 10,000 patients.

Hepatic effects (e.g., increased level of aminotransferase, jaundice) can also occur in predisposed patients.

The most frequently occurring adverse reactions are: sedation, drowsiness, dizziness, headache and dry mouth, which are due to the brompheniramine; ataxia and hypertension, neither of which can be specifically attributed to any particular active ingredient.

Rarely allergic or hypersensitivity reactions may occur after administration of drugs containing paracetamol, including anaphylaxis. Very rare serious skin reactions have been reported with paracetamol. Bronchospasms have been triggered in predisposed persons (analgesic asthma). Quinke's oedema, dyspnoea, sweating, nausea, and a drop in blood pressure to the point of shock have also been described for the active constituent paracetamol.

After the administration of Ilvico the following adverse reactions may occur: frequent (estimated frequency $>1/100$, $<1/10$); rare (estimated frequency $>1 / 10,000$, $<1/1,000$); very rare, including isolated notifications (estimated frequency $<1/10,000$).

MedDRA System Organ Class	Active Ingredient	Adverse Reactions	Frequency
Blood and lymphatic system disorders	Paracetamol Brompheniramine Maleate	Thrombocytopenia Leucopenia Agranulocytosis Pancytopenia Haemolytic-anaemia Neutropenia	Very rare Very rare Very rare Very rare Very rare Very rare
Immune system disorders	Brompheniramine Maleate Paracetamol	Hypersensitivity Anaphylaxis	Rare
Psychiatric disorders	Caffeine	Nervousness	Frequency not known
	Brompheniramine Maleate	Confusional state Euphoric mood	Frequency not known
Cardiac disorders	Caffeine Brompheniramine Maleate	Palpitations Arrhythmia Ventricular depression Bradycardia	Frequency not known
	Caffeine	Tachycardia	Frequency not known
Vascular disorders	Brompheniramine Maleate	Hypotension	Frequency not known
	Not attributable to a specific active or excipient	Hypertension	Common
		Transient vasodepression	Rare
Nervous system disorders	Caffeine	Agitation Insomnia Restlessness	Common
	Brompheniramine Maleate	Sedation Dizziness Headache	Frequency not known Frequency

			not known Frequency not known
	Not attributable to a specific active or excipient	Ataxia	Common
	Brompheniramine Maleate	Somnolence Impairment of cognition Tremor Depressed level of consciousness Agitation Coordination abnormal Seizure Extrapyramidal disorder	Frequency not known
Eye disorders	Brompheniramine Maleate	Mydriasis (dilation of pupils) Blurred vision Dry eyes	Frequency not known
Respiratory, thoracic and mediastinal disorders	Paracetamol	Bronchospasms Dyspnoea	Very rare
Gastrointestinal disorders	Caffeine	Gastrointestinal irritation	Common
	Paracetamol	Abdominal pain Vomiting Nausea	Common Common Rare
	Brompheniramine Maleate	Dry mouth Constipation Nausea Vomiting	Common Frequency not known Frequency not known Frequency not known
General disorders and administration site conditions	Paracetamol Caffeine Brompheniramine Maleate	Fatigue	Frequency not known
Hepatobiliary disorders	Paracetamol	Increased level of Aminotransferase Jaundice	Frequency not known
Renal and urinary tract disorders	Brompheniramine Maleate	Urinary retention Urinary hesitation Erectile dysfunction Dysuria	Frequency not known
Skin and subcutaneous tissue disorders	Paracetamol	Skin rash Urticaria Skin reactions Quinke's oedema Sweating Paracetamol can cause serious, potentially fatal skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).	Rare Rare Very rare Very rare Very rare Very rare
	Brompheniramine Maleate	Allergic dermatitis	Frequency not known
Metabolism and nutrition disorders	Paracetamol	High anion gap metabolic acidosis	Frequency not known

Description of selected adverse reactions

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.

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: HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose**Paracetamol**

Immediate medical attention must be sought in the event of an overdose as there is a risk of permanent and irrevocable liver damage, which may be fatal.

Acute symptoms and signs and potential sequelae:

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

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, hypoglycaemia, haemorrhage, abnormalities of glucose, metabolism, metabolic acidosis, and encephalopathy, which may lead to coma and death. Simultaneously, Liver damage may become apparent with increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 72 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of 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.
- Pregnant patients.
- Patients taking isoniazid.
- Patients with prolonged fasting.

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 also been reported.

Other symptoms may include CNS depression, cardiovascular effects, and renal damage.

Overdose of antihistamines may lead to death resulting from adverse reactions such as convulsions, coma, cardiorespiratory depression, cerebral oedema, acute renal failure, or bone marrow depression. Paradoxical CNS excitation with irritability, hyper alertness, insomnia, hallucinations, and seizures might precede drowsiness and other CNS symptoms in infants and young children

The estimated acute lethal dose of caffeine in adults is 5 to 10g. The earliest symptoms of acute caffeine poisoning include vomiting, abdominal pain, and central nervous system symptoms, such as agitation, altered conscious state, rigidity, and seizures. The cardiovascular effects include supraventricular and ventricular tachyarrhythmia.

Emergency Procedure for Management of Overdose:

Immediate transfer to hospital.

- **Monitoring**

If an overdose has been ingested the patient must be treated immediately at a medical centre even if there are no symptoms or significant signs because, even though they may be fatal, often they are not manifested immediately after ingestion, but rather from the third day onwards. Death may occur through hepatic necrosis. Likewise, acute renal failure may occur. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

- **Use of agonist / antagonist / antidote**

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. Binding of the cytotoxic metabolite can be achieved by intravenous administration of SH donors such as cysteamine or N-acetylcysteine, if possible, within 8 hours after intoxication. 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. Where there is doubt over the timing of paracetamol ingestion, N-acetylcysteine should be given without delay.

General supportive measures must be available. Treatment of other symptoms is by symptomatic management.

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 24 hours from ingestions, should be discussed with a liver unit.

- **Method to increase elimination**

Treatment with activated charcoal should be considered if fewer than 2 hours have elapsed since the ingestion.

If paracetamol intoxication is suspected, gastric lavage is indicated in the first 6 hours after overdose. The paracetamol plasma concentration can be lowered by dialysis.

Caffeine

Management

In case of caffeine overdose patients should receive general supportive care (e.g., hydration and maintenance of vital signs).

In case of caffeine overdose the combination of phenylephrine and lidocaine should be considered in the treatment of cardiovascular collapse secondary to overdose of methylxanthines such as caffeine. Caffeine may be removed from the circulatory system by use of haemodialysis.

Brompheniramine

Management

Treatment following large doses of antihistamines may involve supportive measures such as evacuation of stomach contents, administration of anticonvulsants and haemodialysis.

While no specific antidotes are available, treatment with physostigmine under medical supervision may reverse the anticholinergic actions on the central nervous system. However, physostigmine is contraindicated in the presence of cardiovascular diseases and arrhythmias such as wide complex tachycardia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Other combined preparations for common cold

Code ATC: R05X

Paracetamol is an analgesic pharmacopoeia that also possesses antipyretic properties. The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly inhibiting the synthesis of prostaglandin at the central nervous system level and to a lower degree blocking the generation of the pain impulse at peripheral level. The peripheral action may also be due to the inhibition of the prostaglandin synthesis or to the inhibition of the synthesis, or of the action, of other substances that sensitise the nociceptors to mechanical or chemical stimulations.

Probably paracetamol produces the antipyretic effect acting at central level over the hypothalamic centre regulating temperature, to produce a peripheral vasodilatation that gives place to an increase of perspiration and to flow of blood in the

skin and loss of heat. The action at central level probably is related with the inhibition of the prostaglandin synthesis in the hypothalamus.

Brompheniramine maleate: is a highly effective antagonist of the H1 receptors of histamines.

From the different studies in this field, it is known that the antihistaminic effect reduces capillary permeability and the permeability of cellular membranes producing a diminution of the secretion and congestion of the inflamed mucous membranes of the superior respiratory tract. This diminution of permeability, which appears to be independent of the histamine and the allergic process, appears independently of whatever is the cause of the increase of permeability. The experimental use of brompheniramine in animals has evidenced antitussive effects and stimulation of blood circulation. At the same time, it has a slight sedative effect.

Caffeine stimulates circulation and strengthens the analgesic and antipyretic effects of paracetamol.

5.2 Pharmacokinetic properties

It is quickly and completely absorbed after oral administration, reaching maximum plasmatic peak between 3-4 hours. Plasmatic bioavailability is 60-80%, linking with proteins at 10%. It metabolises mainly through the liver, being eliminated mainly through the kidney as inactive metabolites.

Average plasmatic life is between 1.5-2.5 hours, being completely eliminated after 24 hours. Maximum pharmacological effect is achieved at 4-6 hours.

5.3 Preclinical safety data

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

Studies of chronic toxicity in animals show that high Paracetamol doses produce testicular atrophy and inhibition of spermatogenesis; the importance of this fact in humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycolate Type A
Crospovidone
Hypromellose
Cellulose powder
Magnesium stearate
Titanium dioxide E171
Glycerol
Macrogol 4000
Macrogol 6000
Talc
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium package blisters containing 20 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

P&G Health Germany GmbH
Sulzbacher Strasse 40
Schwalbach Am Taunus
Hassia
65824
Germany

8 MARKETING AUTHORISATION NUMBER

PA22703/001/001

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Date of first authorisation: 5th November 2010

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10 DATE OF REVISION OF THE TEXT

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