PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

EMPAPED PLUS SUSPENSION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains: paracetamol 160 mg

ibuprofen 48 mg

Preservative (sodium benzoate 0,1 % *m/v*)

Contains sugar (maltitol 1250 mg/5 ml) and sweetener (sucralose 7 mg/5 ml)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suspension

Viscous pink suspension, free from foreign matters with characteristic strawberry flavouring.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EMPAPED PLUS SUSPENSION is indicated for the short-term treatment of mild to moderate pain and the reduction of fever in children 2 to 12 years of age.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

EMPAPED PLUS SUSPENSION is for short term use and is not recommended for use beyond two days. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.8).

Doses should be given every 4-6 hours as necessary, with no more than 4 doses in 24 hours.

Age*	Average body weight	Dose (ml)
2 to 3 years	12 - 14 kg	5 ml
3 to 4 years	14 - 16 kg	5 - 6 ml
4 to 5 years	16 - 18 kg	6 - 7 ml
6 to 7 years	18 - 20 kg	7 - 8 ml
7 to 8 years	20 - 22 kg	8 ml
8 to 9 years	22 - 25 kg	8 - 9 ml
9 to 10 years	28 - 32 kg	9 - 11 ml
10 to 11 years	32 - 36 kg	12 - 14 ml
11 to 12 years	36 - 41 kg	14 - 15 ml

* If the child's weight is less than the weight corresponding to their age in the table, select the dose for their weight. Do not exceed a dose of 31 ml, regardless of the weight of the child.

Paediatric population

Children under 2 years of age: EMPAPED PLUS is not recommended for children under 2 years of age.

Method of administration

The bottle should be shaken well before use. The graduated syringe should be used to draw up the correct volume in millilitres.

Directions for using the syringe:

1. Shake the bottle for at least 10 seconds before use.
2. Push the syringe firmly into the plug (hole) in the opening of the bottle.
3. To fill the syringe, turn the bottle upside down. Whilst holding the syringe in place, gently pull the plunger down drawing the medicine to the correct mark on the syringe.
4. Turn the bottle the right way up, and then gently twist the syringe to remove from the bottle plug.
5. Place the end of the syringe into the child's mouth, normally to the side of the mouth between the

gums and cheek. Press the plunger down to slowly and gently release the medicine.

6. If the dosing table above recommends a dose of more than 5 ml, repeat steps 2 to 5 to administer the correct amount of medicine.
7. After use replace the cap on the top of the bottle tightly. Store all medicines out of the sight and reach of children.
8. Wash the syringe in warm water and allow to dry.

4.3 Contraindications

- Hypersensitivity reaction to paracetamol, ibuprofen, other NSAIDs or to any of the excipients (see section 6.1)
- Heart failure, cardiovascular disease, renal and hepatic impairment
- A history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including EMPAPED PLUS SUSPENSION
- Active or history of recurrent ulcer/haemorrhage/perforations.
- A history of asthma, urticaria, or other allergic-type reactions after taking aspirin, ibuprofen or other NSAIDs
- Uncontrolled asthma and bronchospasm
- Children under the age of 6 months
- In patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

4.4 Special warnings and precautions for use

This product contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

EMPAPED PLUS should not be taken with other products containing ibuprofen, paracetamol, or with any other anti-inflammatory medicines unless under a medical practitioner's instruction (see section 4.5).

Hepatic effects

Dosages in excess of those recommended may cause severe liver damage.

Elevations of one or more liver function tests may occur. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in less than 1 % of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and flu-like symptoms). Excessive use can be harmful and increase the risk of liver damage.

Cardiovascular effects

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, history of atherosclerotic cardiovascular disease, diabetes mellitus) and should only be treated with EMPAPED PLUS SUSPENSION after careful consideration. EMPAPED PLUS SUSPENSION is contraindicated in patients with heart problems.

Hypertension and heart failure

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with EMPAPED PLUS SUSPENSION therapy. In view of the EMPAPED PLUS SUSPENSION inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Gastrointestinal events

The risk of gastrointestinal perforation, ulceration, or bleeding (PUBs) is higher with increasing doses of EMPAPED PLUS SUSPENSION, in patients with a history of ulcers. When gastrointestinal bleeding or ulceration occurs in patients receiving EMPAPED PLUS SUSPENSION, treatment with EMPAPED PLUS SUSPENSION should be stopped. EMPAPED PLUS SUSPENSION should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn’s disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Combination use of ACE inhibitors or angiotensin receptor antagonists, NSAID’s, thiazide diuretics

The use of an ACE inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment (see also section 4.3). This includes use in fixed-combination products containing more than one class of medicine. Combined use of these medicines should be accompanied by increased

monitoring of serum creatinine, particularly at the institution of the combination. The combination of medicines from these three classes should be used with caution.

Severe cutaneous adverse reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. EMPAPED PLUS SUSPENSION should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with EMPAPED PLUS SUSPENSION must immediately be discontinued and appropriate treatment instituted.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as EMPAPED PLUS SUSPENSION Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis,_or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue EMPAPED PLUS SUSPENSION and evaluate the patient immediately.

Patients appear to be at highest risk for these reactions early in the course of therapy. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Coagulation defects

Ibuprofen, as in EMPAPED PLUS SUSPENSION, can inhibit platelet aggregation and it has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, products containing ibuprofen,

as in EMPAPED PLUS SUSPENSION, should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Pre-existing asthma

Products containing ibuprofen, as in EMPAPED PLUS SUSPENSION, should not be administered to patients with aspirin sensitive asthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with products containing ibuprofen, as in EMPAPED PLUS SUSPENSION, should have an ophthalmological examination.

Aseptic meningitis

For products containing ibuprofen, as in EMPAPED PLUS SUSPENSION, aseptic meningitis has been reported only less frequently in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Masking signs of infection

Medicines containing ibuprofen, as in EMPAPED PLUS SUSPENSION, by reducing fever it may mask the usual signs of infection.

Renal effects

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses (see section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Special precautions

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when products containing ibuprofen, as in EMPAPED PLUS SUSPENSION, are added to the treatment program.

Effects on laboratory tests

Urine tests

Paracetamol, as in EMPAPED PLUS SUSPENSION, in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding EMPAPED PLUS SUSPENSION ingestion several hours before and during the collection of the urine specimen.

Special precaution necessary relating to excipients

EMPAPED PLUS SUSPENSION contains maltitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

- Do not use EMPAPED PLUS SUSPENSION with products containing paracetamol. The combination can result in an overdose of paracetamol, causing severe liver damage (see section 4.4).
- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs)
- Anti-coagulants: EMPAPED PLUS SUSPENSION may enhance the effects of anti-coagulants such as warfarin. Ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract.
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.
- ACE inhibitors, beta-blockers and diuretics: ibuprofen may reduce the anti- hypertensive effect of these medicines and may cause natriuresis and hyperkalaemia.
- Cardiac glycosides: ibuprofen may increase the plasma levels of these medicines.
- Lithium: ibuprofen may decrease renal clearance and increase plasma concentration of lithium.
- Methotrexate: There is potential for an increase in plasma methotrexate.
- Zidovudine: Severe hepatotoxicity has occurred after concomitant use with paracetamol. Ibuprofen may prolong bleeding time in patients treated with this zidovudine.
- Metoclopramide: Paracetamol absorption is increased by medicines that increase gastric emptying.
- Propantheline, antidepressants with anticholinergic properties, and narcotic analgesics: Paracetamol absorption is decreased by substances that decrease gastric emptying.
- Hepatotoxic medicines or medicines that induce liver microsomal enzymes such as alcohol and anticonvulsant medicines: The risk of paracetamol toxicity may be increased.
- Probenecid: Paracetamol excretion may be affected, and plasma concentrations altered.
- Cholestyramine: Reduces the absorption of paracetamol if given within 1 hour of paracetamol.

- Isoniazid alone or with other medicines for tuberculosis: Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported.
- Co-trimoxazole: paracetamol may increase chloramphenicol plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate information regarding the use of EMPAPED PLUS SUSPENSION in pregnancy. Therefore, EMPAPED PLUS SUSPENSION should not be used during pregnancy or in patients planning to become pregnant.

Breastfeeding

EMPAPED PLUS SUSPENSION is not recommended for nursing mothers.

4.7 Effects on ability to drive and use machines

EMPAPED PLUS SUSPENSION may be associated with dizziness, drowsiness, fatigue, and visual disturbances (see SECTION 4.8). Therefore, the ability to perform difficult tasks may be impaired.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: frequent, less frequent or frequency unknown (cannot be estimated from the available data)

MedDRA System Organ Class	**Frequency**	**Side Effects**
Infections and infestations	Less frequent	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis)
Blood and lymphatic system disorders	Less frequent	Decrease in haemoglobin and haematocrit and bleeding episodes, e.g. epistaxis and menorrhagia, haematopoietic disorders, such as agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leukopenia, neutropenia,

MedDRA System Organ Class	**Frequency**	**Side Effects**
		pancytopenia, thrombocytopenia with or without purpura
Immune system disorders	Less frequent	Hypersensitivity reactions including skin rash, cross-sensitivity with sympathomimetics, serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema
Metabolism and nutrition disorders	Less frequent	Gynaecomastia, hypoglycaemic reaction, , metabolic acidosis at very high doses
	Frequency unknown	Hypokalaemia*
Nervous system	Frequent	Dizziness, headache, nervousness

MedDRA System Organ Class	Frequency	Side Effects
disorders	Less frequent	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever, coma, paraesthesia, hallucinations, dream abnormalities, paradoxical stimulation, optic neuritis, somnolence, psychomotor impairment, extrapyramidal effects, tremor, convulsions
Eye disorders	Less frequent	Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision)
Ear and labyrinth disorders	Frequent	Tinnitus
	Less frequent	Vertigo
Cardiac disorders	Frequent	Oedema, fluid retention
	Less frequent	Tachycardia, palpitations, dysrhythmia
Respiratory, thoracic and mediastinal disorders	Less frequent	Thickened respiratory tract secretions, stridor, hypoxemia, respiratory reactivity including asthma, exacerbation of asthma, bronchospasm and dyspnoea
Gastrointestinal disorders	Frequent	Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort, vomiting, flatulence,

MedDRA System Organ Class	Frequency	Side Effects
		constipation, slight gastrointestinal blood loss that may cause anaemia
	Less frequent	Peptic/ gastrointestinal ulcers, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, dyspepsia, abdominal pain, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis, pancreatitis, acid peptic disease, oesophagitis, formation of intestinal diaphragm-like strictures
Hepatobiliary disorders	Less frequent	Hepatic damage, hepatic failure, abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic necrosis and liver injury
Skin and subcutaneous tissue disorders	Frequent	Rash (including maculopapular type), pruritus
	Less frequent	Alopecia, hyperhidrosis, purpura and photosensitivity, exfoliative dermatoses and bullous reactions including erythema multiform, Stevens Johnson syndrome and toxic epidermal necrolysis, severe skin infections and soft-tissue complications during varicella infection. Drug Reaction with

MedDRA System Organ Class	Frequency	Side Effects
		Eosinophilia and Systemic Symptoms (DRESS).
Renal and urinary disorders	Less frequent	Urinary retention, kidney tissue damage (papillary necrosis), nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure, acute tubular necrosis, risk of renal cell carcinoma with chronic paracetamol use.
	Frequency unknown	Renal tubular acidosis*.
General disorders and administration site conditions	Less frequent	Fatigue, malaise, pyrexia
Injury, poisoning and procedural complications	Less frequent	Post-operative haemorrhage following tonsillectomy
Investigations	Frequent	Increased alanine aminotransferase, increased gamma-glutamyl transferase, abnormal liver function tests with paracetamol, increased blood creatinine, increased blood urea
	Less frequent	Increased aspartate aminotransferase, increased blood alkaline phosphatase, increased blood

MedDRA System Organ Class	Frequency	Side Effects
		creatine phosphokinase, decreased haemoglobin, increased platelet count, elevated blood uric acid concentrations

Description of Selected Adverse Reactions

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to Acino Pharma via email on drugsafety_za@acino.swiss OR SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen, which may result, are depression of the central nervous system and the respiratory system. Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed. Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater

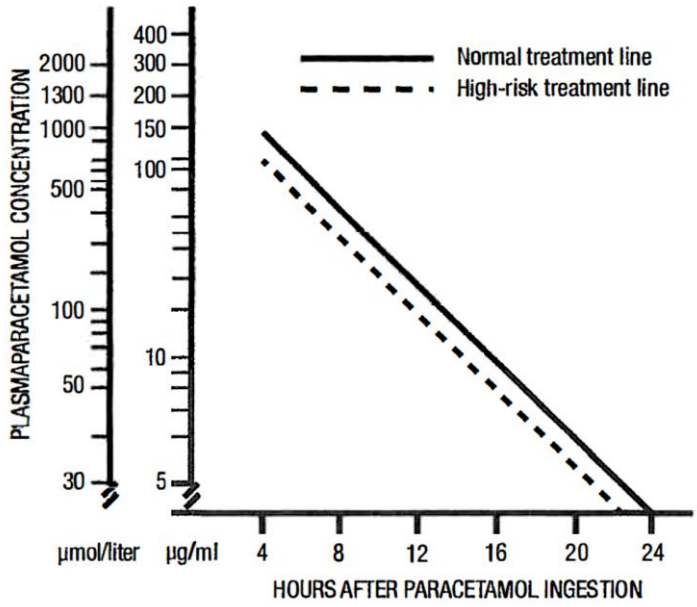
than 5 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have a single dose of 50 g activated charcoal given. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children. Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses. A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion. Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over

sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.



5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.8 Analgesic combinations

Pharmacotherapeutic group: Paracetamol, combinations excl. psycholeptics.

ATC code: N02BE51

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic, and anti-inflammatory activities. Like other NSAIDs, ibuprofen is believed to work by inhibiting cyclooxygenase (COX), thus inhibiting prostaglandin synthesis.

Paracetamol is an analgesic and antipyretic medicine that has little anti-inflammatory activity. The precise mechanism has not yet been established.

Combination of paracetamol and ibuprofen: The 3.3:1 ratio of paracetamol to ibuprofen in EMPAPED PLUS SUSPENSION show superior analgesia over mono-components and minimising the ibuprofen doses is important to avoid the risk of class-related adverse events.

5.2 Pharmacokinetic properties

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract following oral

administration. After oral administration of immediate release paracetamol preparations, paracetamol related plasma concentrations are attained within approximately 60 minutes.

The paracetamol half-life is ranging between 2 to 3 hours.

Ibuprofen is rapidly absorbed after oral administration. The ibuprofen half-life is short, about 2 hours. The rate and absorption of both paracetamol and ibuprofen from the combination product is slightly delayed following administration after food.

Distribution

Paracetamol is not extensively bound to plasma proteins and is distributed into most body tissues.

Ibuprofen is highly protein bound (90-99 %) and is distributed into most connective tissues.

Metabolism

Both paracetamol and ibuprofen are metabolised primarily by the liver. Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation Paracetamol metabolites include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage. Paracetamol is metabolised differently by premature infants, new-borns, and young children compared with adults, the sulphate conjugate being most predominant. This may contribute to the comparatively low susceptibility of young children to liver damage following paracetamol overdose.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways. In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen (as a fixed combination).

Excretion

The elimination half-life of paracetamol from plasma varies from about 1 to 3 hours. The main route of elimination from the body is in the urine, mainly as inactive glucuronide and sulphate conjugates. Less

than 5 % of a paracetamol dose is excreted unchanged. Clearance rates are relatively low in neonates but increase to reach 80 % of the rate observed in children aged 2-15 years by 6 months Ibuprofen is 90 % excreted in the urine.

The elimination half-life of ibuprofen from plasma is in the range of 1,9 to 2,2 hours. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95 % of the administered dose eliminated in the urine within 4 hours of ingestion. In infants up to the age of 0,5 years, there is a prolonged $T_{1/2}$, however beyond this age, $T_{1/2}$ falls within a similar range as observed in adults.

Combination

There is no pharmacokinetic interaction between paracetamol and ibuprofen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmine dye C1 175470, E122

Citric acid monohydrate, E330

Fantasy Fruit Masking Flavour PHL-203715

Glycerol, E422

Maltitol, E965

Polysorbate 80, E433

Purified water

Sodium benzoate, E211

Strawberry Flavour PHL-028584

Sucralose

Sweetie Flavour FD-221-141-8

Trisodium citrate dihydrate, E331

Vanilla Cream Flavour PHL-203716

Vivapur MCG 591P containing: Microcrystalline cellulose and Carmellose sodium

Xanthan gum, E415

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original packaging to protect from light.

6.5 Nature and contents of container

100 ml and 200 ml amber polyethylene terephthalate bottles with white child-proof caps.

The bottle and a 5 ml syringe are packed into an outer carton with the leaflet.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

Tel: 087 742 1860

8 REGISTRATION NUMBER

54/2.8/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 May 2024

10 DATE OF REVISION OF THE TEXT

21 November 2025