

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen/Paracetamol 200/500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen and 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White to off-white, oval shaped, film-coated tablets, with dimensions 19.7 mm x 9.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This medicinal product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

Ibuprofen/Paracetamol is indicated in adults aged 18 years and older.

4.2 Posology and method of administration

Posology

For short term-use only.

The patient should consult a doctor if the symptoms persist or worsen or if the medicinal product is required for more than 3 days.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to relieve symptoms (see section 4.4).

Adults: One tablet to be taken up to three times per day with water. The interval between single doses should be at least six hours.

If single doses of one tablet do not control symptoms, a maximum of two tablets may be taken up to three times a day. The interval between single doses should be at least six hours.

The maximum dose is six tablets (1200 mg ibuprofen, 3000 mg paracetamol) in any 24 hours period.

Elderly: No special dosage modifications are required (see section 4.4).

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Paediatric population

Not for use by children and adolescents under 18 years.

Method of administration

Oral use.

To minimise side effects, patients should take Ibuprofen/Paracetamol with food.

4.3 Contraindications

This medicinal product is contraindicated:

- In patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic impairment, severe renal impairment or severe heart failure (NYHA Class IV) (see section 4.4).

- In concomitant use with other NSAID-containing medicinal products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see section 4.5).
- In concomitant use with other paracetamol-containing medicinal products – increased risk of serious adverse effects (see section 4.5).
- During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see section 4.6)

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.4 Special warnings and precautions for use

Paracetamol:

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 underlying cause of HAGMA in patients with multiple risk factors.

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Ibuprofen:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see section 4.2).

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Caution is required in patients with certain conditions:

- *Respiratory disorders:*

In patients suffering from, or with a history of, bronchial asthma or allergic disease, NSAIDs have been reported to precipitate bronchospasm.

- *Cardiovascular, renal and hepatic impairment:*

The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal impairment. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3).

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

- *Cardiovascular and cerebrovascular effects:*

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial data suggest that use of ibuprofen, particularly at high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided. Careful consideration should be exercised before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) particularly if high doses of ibuprofen (2400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with Ibuprofen/Paracetamol 200/500 mg film-coated tablets. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

- *Gastrointestinal bleeding, ulceration and perforation:*

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen-containing medicinal products, the treatment should be withdrawn.

NSAIDS should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

- *SLE and mixed connective tissue disease:*

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease, there may be an increased risk of aseptic meningitis (see section 4.8).

- *Severe cutaneous adverse reactions (SCARs):*

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

- *Masking of symptoms of underlying infections:*

Ibuprofen/Paracetamol can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Ibuprofen/Paracetamol is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

- *Impaired female fertility:*

See section 4.6.

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product (like any other paracetamol-containing medicinal products) is contraindicated in combination with other paracetamol containing medicinal products – increased risk of serious adverse effects (see section 4.3).

This medicinal product (like any other ibuprofen-containing medicinal products and NSAIDs) is contraindicated in combination with:

- Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see section 4.3).

This medicinal product (like any other paracetamol-containing medicinal products) should be used with caution in combination with:

- Chloramphenicol: Increased plasma concentration of chloramphenicol.
- Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin: 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).

This medicinal product (like any other ibuprofen-containing medicinal products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin (see section 4.4).
- Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: NSAIDs may reduce the effects of these medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a NSAID concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Acetylsalicylic acid: Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

- Ciclosporin: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Lithium: Decreased elimination of lithium.
- Methotrexate: Decreased elimination of methotrexate.
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risk of haematological toxicity with NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

SUMMARY OF PRODUCT CHARACTERISTICS

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of use of ibuprofen/paracetamol 200 mg/500mg film-coated tablets in humans during pregnancy.

Due to the presence of ibuprofen:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short

as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to <x> for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen/paracetamol 200 mg/500mg film-coated tablets is contraindicated during the third trimester of pregnancy.

Due to the presence of paracetamol:

A large amount of data on pregnant women indicate neither malformative, nor fetoneonatal 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.

Breast-feeding

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, paracetamol may be used in breast-feeding.

Ibuprofen and its metabolites can pass in very small amounts into the breast milk. As a precaution, the administration of ibuprofen to the breast-feeding woman should be avoided.

Fertility

The use of the medicinal product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the medicinal product should be considered.

4.7 Effects on ability to drive and use machines

Ibuprofen/Paracetamol has minor influence on the ability to drive and use machines. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. Patients experiencing these adverse reactions should not drive or use machines.

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.8 Undesirable effects

Clinical trials with ibuprofen/paracetamol have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

Tabulated list of adverse reactions

The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use, tabulated by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leucopenia, neutropenia, pancytopenia and thrombocytopenia). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeding.
Immune system disorders	Very rare	Hypersensitivity reactions ¹ have been reported. These may consist of non-specific allergic reactions and anaphylaxis. Severe hypersensitivity reactions. Symptoms can include: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
Psychiatric disorders	Very rare	Confusion, depression and hallucinations
Nervous system disorders	Uncommon	Headache and dizziness
	Very rare	Paraesthesia, optic neuritis and

		<p>somnolence.</p> <p>Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with symptoms such as: stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).</p>
Eye disorders	Very rare	Visual disturbance
Ear and labyrinth disorders	Very rare	Tinnitus and vertigo
Cardiac disorders	Very rare	<p>Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).</p>
	Not known	Kounis syndrome
Respiratory, thoracic and mediastinal disorders	Very rare	Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting
	Uncommon	<p>Flatulence and constipation</p> <p>Peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly (see section 4.4).</p> <p>Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease following administration (see section 4.4).</p> <p>Less frequently gastritis has been observed and pancreatitis reported.</p>
Hepatobiliary disorders	Very rare	Abnormal liver function, hepatitis and

		jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic impairment, hepatic necrosis and liver injury (see Section 4.9).
Skin and subcutaneous tissue disorders	Uncommon	Rashes of various types including pruritis and urticaria. Angioedema and swelling face.
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP)
Metabolism and Nutrition Disorders	Not known	Decreased Appetite
	Not known	Hypokalaemia ²
	Not known	High anion gap metabolic acidosis ³
Renal and urinary disorders	Very rare	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.
	Not known	Ureteric colic, dysuria
	Not known	Renal tubular acidosis ²
General disorders and administration site conditions	Very rare	Fatigue and malaise.
Investigations	Common	Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased, blood urea increased
	Uncommon	Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, haemoglobin decreased and platelet count increased.

Description of selected adverse reactions

¹Hypersensitivity reactions have been reported. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity, e.g. asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin reactions, e.g. pruritus, urticaria, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis, and erythema multiforme).

²Renal 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.

³High 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 **the national reporting system listed in Appendix V.**

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

- a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other medicinal products that induce liver enzymes.
- b) Regularly consumes alcohol in excess of recommended amounts.
- c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic impairment may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema 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.

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).

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.

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 does not occur, oral methionine may be a suitable alternative for remote areas, outside hospital.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen

In children ingestion of more than 400 mg/kg of ibuprofen may cause symptoms. In adults the dose-response effect is less clear cut.

The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal impairment and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Oral administration of activated charcoal should be considered if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators for asthma should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations, ATC code: M01AE51

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cyclooxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

Ibuprofen/paracetamol is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets provide more effective pain relief than paracetamol 1000 mg ($p < 0.0001$).

Duration of analgesia was significantly longer for ibuprofen/paracetamol 200 mg/500 mg film-coated tablets (.8.4 hours) compared to paracetamol 500 mg (4 hours, $p < 0.0001$) or 1000 mg (5.2 hours, $p < 0.0001$). The global evaluation of the study medication by the subjects showed high levels of satisfaction with 88.0% rating ibuprofen/paracetamol 200 mg/500 mg film-coated tablets as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed

significantly better than *ibuprofen 200 mg, paracetamol 500 mg and 1000 mg* ($p < 0.0001$ in all cases).

An one tablet dose of ibuprofen/paracetamol 200 mg/500 mg film-coated tablets provides more effective pain relief than a combination of paracetamol 1000 mg / codeine phosphate 30 mg ($p = 0.0001$) and was shown to be noninferior to a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg.

Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets have a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 15.6 minutes (1 tablet dose) or 18.3 minutes (2 tablets dose), which is faster than for ibuprofen 200 mg (30.1 minutes, $p < 0.001$), ibuprofen 400 mg (23.8 minutes, $p = 0.0001$) and paracetamol 500 mg (23.7 minutes, $p = 0.0001$). 'Meaningful pain relief' for this product was achieved in a median of 39.3 minutes (1 tablet dose) or 44.6 minutes (2 tablets dose), which was significantly faster than for ibuprofen 200 mg (80.0 minutes, $p < 0.0001$), ibuprofen 400 mg (70.5 minutes, $p = 0.0001$), paracetamol 500 mg (50.4 minutes, $p = 0.001$) and paracetamol 1000 mg (45.6 minutes, $p < 0.05$).

Other randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets provide more effective pain relief than paracetamol 1000 mg ($p < 0.0001$) and ibuprofen 400 mg ($p < 0.05$).
- Duration of analgesia was significantly longer for ibuprofen/paracetamol 200 mg/500 mg film-coated tablets (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5.2 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg ($p < 0.0001$).

Another randomised, double-blind controlled clinical study was conducted with ibuprofen/paracetamol 200 mg/500 mg film-coated tablets in the treatment of chronic knee pain. The study showed that:

- Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets provide more effective pain relief than paracetamol 1000 mg in short-term treatment ($p < 0.01$) and long term treatment ($p < 0.01$).
- The global evaluation of ibuprofen/paracetamol 200 mg/500 mg film-coated tablets by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets performed significantly better than paracetamol 1000 mg ($p < 0.001$).

Ibuprofen/paracetamol 200 mg/500 mg film-coated tablets provide more effective pain relief than a combination of paracetamol 1000 mg /codeine phosphate 30 mg

($p < 0.0001$), and a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg ($p = 0.0001$).

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from ibuprofen/paracetamol 200 mg/500 mg tablets are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When ibuprofen/paracetamol 200 mg/500 mg tablets were taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Biotransformation

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from ibuprofen/paracetamol 200 mg/500 mg tablets are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When ibuprofen/paracetamol 200 mg/500 mg tablets were taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.

The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this medicinal product are not altered when taken in combination as a single or repeat dose.

This medicinal product is formulated using a technology which releases both ibuprofen and paracetamol simultaneously, so that the active ingredients deliver a combination effect.

5.3 Preclinical safety data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

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

Tablet core

Maize starch

Crospovidone (Type A) (E1202)

Silica, colloidal anhydrous (E551)

Povidone K-30 (E1201)

Starch, pregelatinized (maize)

Talc (E553b)

Stearic acid (50)

Film-coating

Poly(vinyl alcohol) (E1203)

Talc (E553b)

Macrogol 3350 (E1521)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blisters in cartons of 16 or 20 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

PharOS-Pharmaceutical Oriented Services Ltd
Lesvou str. (end), Thesi Loggos, Industrial Zone,
144 52 Metamorfossi Attikis,
Greece

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 23022/0152

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/01/2025

10 DATE OF REVISION OF THE TEXT

27/01/2025