SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen & Paracetamol 200 mg/500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg ibuprofen and 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (tablets)

White to off white, oblong, biconvex film-coated tablets with dimensions of (21 mm x 10.5 mm) ± 0.5 mm and marked with double circle mark on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The medicinal product is used for temporary relief of mild to moderate pain which has not been relieved by ibuprofen or paracetamol individually, such as migraine, headache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms, sore throat and fever.

Ibuprofen/Paracetamol is intended for adults from 18 years of age.

4.2 Posology and method of administration

Posology

For short term-use only.

The patient should try ibuprofen or paracetamol alone first.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

The patient should consult a doctor if the symptoms persist or worsen or if it is necessary to use this medicine for more than 3 days.

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

If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day. Leave at least six hours between doses.

Do not take more than six tablets (3000 mg Paracetamol, 1200 mg Ibuprofen) within 24 hours period.

Adverse reactions can be reduced by using the lowest effective dose for the shortest period necessary to relieve symptoms (see section 4.4).

To minimise side effects, it is recommended that patients take Ibuprofen/Paracetamol with food.

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 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 under 18 years.

Method of administration

For oral administration

4.3 Contraindications

- Hypersensitivity to ibuprofen, paracetamol or 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).

- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients with coagulation disorders.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see section 4.4).
- In concomitant use with other NSAID containing products, including selective cyclo-oxygenase-2 (COX-2) inhibitors and doses of acetylsalicylic acid above 75 mg daily – an increased risk of adverse reactions (see section 4.5).
- In concomitant use with other paracetamol-containing products – an 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).

4.4 Special warnings and precautions for use

Do not use until first trying ibuprofen or paracetamol individually to relieve your pain according to the pack instructions.

Consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

The risk associated with overdose of paracetamol is higher in patients with alcohol-induced liver failure without symptoms of cirrhosis. In the event of overdose, immediately contact a doctor even if the patient feels well because there is a risk of delayed, serious liver damage.

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 and 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.

To reduce the risk of adverse reactions, use the lowest effective dose for the shortest time duration necessary to control the symptoms (see section 4.2, and gastrointestinal and cardiovascular disorders below) and take the medicinal product with food (see section 4.2).

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.

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 nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

Elderly people:

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, cases of sudden bronchoconstriction after treatment with NSAIDs have been reported.

- *Cardiovascular, renal and hepatic impairment:*

  The administration of NSAIDs may cause a dose dependent suppression of prostaglandin synthesis and accelerate the occurrence of renal failure. 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).

- *Cardiovascular and cerebrovascular effects*:

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

  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 thromboembolic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g.≤1200mg/day) is associated with an increased risk of arterial thromboembolic 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 also be exercised before initiating long-term treatment in 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. 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 or perforation, which can be fatal, have 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 peptic 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 drugs likely to increase gastrointestinal risk (see below and section 4.5).

  Patients with a history of GI toxicity, particularly when 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 medicinal products that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or anti-aggregation agents such as acetylsalicylic acid (see section 4.5).

  When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn. NSAIDs should be used with caution in patients with a history of gastrointestinal diseases (ulcerative colitis, Crohn's disease), because these conditions may be exacerbated (see section 4.8).

- *SLE and mixed connective tissue diseases*:

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

- *Dermatological*:

  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).

- *Impaired female fertility*:

  The use of this medicinal product may impair fertility in women, therefore it is not recommended for women planning pregnancy. In women who have difficulties

conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

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

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

This medicinal product (like any other ibuprofen containing 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 selective cyclo-oxygenase-2 inhibitors as these may increase the risk of adverse effects (see section 4.3).

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

- Chloramphenicol: increased plasma concentration of chloramphenicol.
- Flucloxacillin: 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).

- 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 should 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.

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

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

- Antihypertensives: NSAIDs may reduce the effects of these drugs.

- 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.

- Cyclosporine: Increased risk of nephrotoxicity.

- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

- Diuretics: Reduced effect of diuretics. Diuretics may increase the risk for 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: Data from animal studies indicate that NSAIDs may increase the risk of seizures associated with the use of 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 concomitantly with tacrolimus.

- Zidovudine: Increased risk of haematological toxicity with NSAIDS in concomitant use with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in humans; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the development of foetal cardiovascular system (risk of premature constriction/closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and prolong its duration with an increased bleeding tendency in both mother and child (see section 4.3). 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, NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

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

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Therefore, if possible, the use of this product should be avoided in the first six months of pregnancy and is contraindicated in the last three months of pregnancy (see section 4.3).

Breastfeeding

Ibuprofen and its metabolites can penetrate at very low doses (0.0008% of the dose given to the mother) to breast milk. There are no known harmful effects in infants.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

Fertility

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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

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.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), 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 Events
Blood and Lymphatic System Disorders	Very rare	Hematopoietic system disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leucopenia, neutropenia, pancytopenia and thrombocytopenia). **The first symptoms 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 such as non-specific hypersensitivity reactions and anaphylactic reactions. Severe hypersensitivity reactions. **Symptoms may include**: swelling of the face, tongue and larynx, shortness of breath, tachycardia, hypotension, (anaphylactic reaction, angioedema or

		vascular or life-threatening shock).
Psychiatric Disorders	Very rare	Confusion, depression and hallucinations.
Nervous System Disorders	Uncommon	Headache and dizziness.
	Very rare	Paraesthesia, optic neuritis and somnolence Isolated 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).
Eye Disorders	Very rare	Visual disturbance.
Ear and Labyrinth Disorders	Very rare	Tinnitus and vertigo.
Cardiac and Vascular disorders	Very rare	Oedema, hypertension, cardiac failure and Kounis syndrome[1].
Respiratory, thoracic and mediastinal disorders	Very rare	Respiratory tract activity including asthma, aggravated asthma, bronchospasm and shortness of breath.
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea, abdominal discomfort, vomiting.
	Uncommon	Flatulence and constipation Gastrointestinal ulcers, perforation or gastrointestinal bleeding manifesting in melaena, or haematemesis, sometimes fatal especially in the elderly (see section 4.4). Ulcerative stomatitis, exacerbation of colitis and Crohn's disease after administration of the medicinal product (see section 4.4). Gastritis and pancreatitis have been reported less frequently.
Hepatobiliary disorders	Very rare	Hepatic impairment, hepatitis or jaundice. In the event of paracetamol overdose, acute liver failure, hepatic failure, hepatic necrosis and liver damage may occur (see section 4.9).
Skin and	Uncommon	Various types of rashes, including

subcutaneous tissue disorders		pruritus and urticaria. Angioedema and swelling of the face.
	Very rare	Hyperhydrosis, purpura and photosensitivity. 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).
Renal and urinary disorders	Very rare	Various forms of nephrotoxicity including interstitial nephritis, nephrotic syndrome and acute or 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	Increased alanine aminotransferase, increased gamma-glutamyltransferase activity and altered parameters of liver function after paracetamol administration. Blood creatinine increased and blood urea increased.
	Uncommon	Increased aspartate aminotransferase, increased alkaline phosphatase in the blood, increased creatinine phosphokinase in the blood, decreased haemoglobin, and increased platelet count.
Metabolism and Nutrition Disorders	Not known Not known	Decreased appetite Hypokalaemia[2] High anion gap metabolic acidosis[3]

Description of selected adverse reactions

[1]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).

[2]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.

[3]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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 medicines 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 of overdose

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 failure 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 renal damage. Cardiac arrhythmias and pancreatitis have been reported.

Management of overdose

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 occurred within 1 hour. Plasma concentration of paracetamol should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

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

Ibuprofen

Symptoms of overdose

Most patients who have ingested clinically significant 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 the effect on the activity of blood coagulation factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

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 failure and liver damage may occur.

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 of overdose

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. In case of frequent or prolonged convulsions intravenous diazepam or lorazepam should be given. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations

ATC Code: M01AE51

The pharmacological effects of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are also synergistic, which means that the product has stronger antinociceptive and antipyretic properties than its active ingredients used alone.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), whose efficacy of prostaglandin synthesis inhibition has been confirmed in conventional animal inflammation models. Prostaglandins sensitize nociceptive afferent nerve terminals to mediators such as bradykinin. The analgesic effect of ibuprofen is caused by peripheral inhibition of cyclooxygenase-2 (COX-2) isoenzyme and subsequent reduction in sensitivity of nociceptive nerve terminals. Ibuprofen also inhibits induced-leucocyte migration to sites of inflammation. Ibuprofen has a significant effect on the spinal cord, partly due to its ability to inhibit COX activity. The antipyretic effect of ibuprofen is due to the central inhibition of prostaglandin synthesis in the hypothalamus. Ibuprofen inhibits platelet aggregation in a reversible manner. In humans, ibuprofen reduces pain caused by inflammation, swelling and fever.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when a single dose of ibuprofen (400 mg) was taken within 8 hours before or within 30 minutes after immediate-release acetylsalicylic acid (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although it is uncertainies regarding extrapolation of these data to the clinical situations, 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 4.5).

The exact mechanism of action of paracetamol is still not fully understood, however, there is considerable evidence to support the hypothesis of its central antinociceptive effect. The results of various biochemical tests point to inhibition of central COX-2 enzyme activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways, that inhibit nociceptive signal transmission in the spinal cord. Studies have shown that paracetamol is a very weak inhibitor of peripheral COX-1 and COX-2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea and fever; furthermore efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and back pain.

This medicinal product is particularly suitable for treatment of pain which requires stronger pain relief than 400 mg of ibuprofen or 1000 mg of paracetamol used alone or as an analgesic to relieve pain faster than ibuprofen.

Clinical efficacy

Summary of clinical data after administration of 2 tablets

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

- The medicinal product provides more effective pain relief than paracetamol 1000 mg ($p < 0.0001$) and ibuprofen 400 mg ($p < 0.05$) which is clinically and statistically significant.

  The medicinal product has fast onset of action with "confirmed analgesic effect" - achieved in a median of 18.3 minutes. The onset of action was significantly faster than for ibuprofen 400 mg (23.8 minutes, $p = 0.0015$). The "stronger analgesic effect" for this medicinal product was achieved in a median of 44.6 minutes, which is significantly faster than for ibuprofen 400 mg (70.5 minutes, $p < 0.0001$).
- The duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5 hours).
- The global evaluation of the study medication by the subjects showed a high level of satisfaction with 93.2% of respondents rating the product as "good", "very good" or “excellent” in achieving pain relief. The fixed combination product has shown significantly better results than 1000 mg of paracetamol ($p<0.001$).

A randomized, double-blind controlled clinical study was conducted with the medicinal product to treat chronic knee pain. The study showed:

- The medicinal product provides more effective pain relief than paracetamol 1000 mg in short-term treatment ($p < 0.0001$) and long-term treatment used ($p < 0.01$).
- The global evaluation of the product by the subjects showed a high level of satisfaction with 60.2% of the respondents rating the product as "good" or "excellent" as long term treatment for a painful knee. The product had significantly better results than paracetamol 1000 mg ($p<0.001$).

5.2 Pharmacokinetic properties

Ibuprofen

Absorption

Ibuprofen is well absorbed from the gastrointestinal tract. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Distribution

Ibuprofen is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid.

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.

Elimination

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

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract.

Distribution

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

Biotransformation

Paracetamol is metabolised in the liver.

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.

Elimination

Paracetamol is 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.

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maize starch

Povidone K-30 (E1201)

Croscarmellose sodium (E468)

Cellulose, microcrystalline (E460)

Silica, colloidal anhydrous (E551)

Glycerol dibehenate (E471)

Film-coating

Opadry White

Polyvinyl alcohol-partially hydrolysed

Talc

Titanium dioxide (E171)

Glyceryl monocaprylocaprate

Sodium laurilsulfate

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 condition.

6.5 Nature and contents of container

The film-coated tablets are blister-packed in:

Blister: White PVC/PVDC/ Aluminium hard foil, each blister containing proper number of film-coated tablets

or

Child resistant blister: White PVC/PVDC/ Aluminium push through foil, fortified by polyester layer, each blister containing proper number of film-coated tablets.

Cardboard box with 1 blister (8 or 10 tablets) or 2 blisters (16 tablets) and instruction leaflet inside.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Galpharm Healthcare Limited,

Wrafton,

Braunton,

Devon,

EX33 2DL,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16028/0186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/06/2025

10 DATE OF REVISION OF THE TEXT

06/11/2025