SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brufen Akut Duo 200 mg/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 and muscular pain, cold and flu symptoms, sore throat and fever. This medicinal product is especially suitable for pain which has not been relieved by ibuprofen or paracetamol alone.

Brufen Akut Duo is indicated in adults aged 18 years and older.

4.2 Posology and method of administration

Posology
For short term-use only (not more than 3 days).

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

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

This medicinal product is for short-term use and is not recommended for use beyond 3 days.

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 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 (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.

Hepatic impairment
In patients with mild to moderate hepatic impairment the dose should be reduced or the dosing interval prolonged. Paracetamol containing medicinal products should not be used in severe hepatocellular impairment (see sections 4.3 and 4.4).

The daily effective dose should not exceed 60 mg/kg/day (up to a maximum 2 g/day) in the following situations:

- adults weighing less than 50 kg
- mild to moderate hepatic insufficiency
- Gilbert's syndrome (familial nonhaemolytic jaundice)
- dehydration
- chronic malnutrition
- chronic alcoholism

Renal impairment
In patients with mild to moderate renal impairment, the dose should be reduced or the dosing interval prolonged. A dosing interval of at least 6 hours should be observed. Paracetamol containing medicinal products should not be used in severe renal impairment (see sections 4.3 and 4.4).

Method of administration
Oral use.
To minimise side effects, it is recommended that patients take this medicinal product 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 concomitant use with other paracetamol-containing medicinal products – increased risk of serious adverse effects (see section 4.5).
- 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).
- 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

This medicinal product is for short-term use and is not recommended for use beyond 3 days.

Paracetamol:
Caution is advised if paracetamol is administered to patients with:
- mild to moderate renal impairment,
- mild to moderate hepatic impairment,
- Gilbert's syndrome,
- acute hepatitis,
- glucose-6-phosphate dehydrogenase deficiency,
- alcohol abuse/chronic alcoholism,
- chronic malnutrition, low body mass index, anorexia,
- dehydration,
- concomitant administration of medicinal products which affect liver function.

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Do not take with any other paracetamol-containing products. 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 (see section 4.9).

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.

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).

Masking of symptoms of underlying infections
Brufen Akut Duo 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 Brufen Akut Duo 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.

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.

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

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

Clinical studies 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.

- *Cardiovascular, renal and hepatic impairment:*

The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate 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. Treatment should be stopped in those patients who develop severe renal failure (see section 4.3).

Dose reduction is recommended in patients showing signs of worsening hepatic function. Treatment should be stopped in those patients who develop severe liver failure (see section 4.3).

- *Gastrointestinal effects*

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).

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.

Severe skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Use of this medicinal product should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may impair female fertility by an effect on ovulation and is not recommended in women attempting to conceive. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the medicinal product should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product should not be taken with other medicinal products containing paracetamol, ibuprofen, acetylsalicylic acid, salicylates or with any other anti-inflammatory drugs (NSAIDs) unless under a doctor's instruction.

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).

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

- Acetylsalicylic acid, unless low dose acetylsalicyclic acid (not above 75 mg daily) has been advised by a doctor as this may increase the risk of adverse reactions (see section 4.4). 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 the 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 use (see section 5.1).

- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see section 4.3).

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

- 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.
- 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).

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

- 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 coxib 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).
- 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.

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.

Paracetamol
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol 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

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 ibuprofen for several days from gestational week 20 onward. Brufen Akut Duo 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.

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

Breast-feeding
Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast-feeding.

Therefore it is not necessary to interrupt breast-feeding 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 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 (≥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	Haematopoietic disorders[1]
Immune system disorders	Uncommon	Hypersensitivity with urticaria and pruritus[2].

	Very rare	Severe hypersensitivity reactions. Symptoms can include: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)[2].
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[3]
Psychiatric disorders	Very rare	Confusion, depression and hallucinations.
Nervous system disorders	Uncommon	Headache and dizziness.
	Rare	Paraesthesia.
	Very rare	Aseptic meningitis[4], optic neuritis and somnolence.
Eye disorders	Very rare	Visual disturbance.
Ear and labyrinth disorders	Very rare	Tinnitus and vertigo.
Cardiac disorders	Common	Oedema.
	Very rare	Cardiac failure[5].
Vascular disorders	Very rare	Hypertension[5].
Respiratory, thoracic and mediastinal disorders	Very rare	Respiratory tract reactivity including asthma, exacerbation of asthma, bronchospasm and dyspnoea[2].
Gastrointestinal disorders	Common	Abdominal pain, vomiting, diarrhoea, dyspepsia, nausea and abdominal discomfort[6].
	Uncommon	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena haematemesis[7], mouth ulceration, exacerbation of ulcerative colitis and Crohn's disease[8] gastritis, pancreatitis, flatulence and constipation.
Hepatobiliary disorders	Very rare	Abnormal liver function, hepatitis and jaundice[9].
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Various skin rashes.
	Very rare	Bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis[2]. Exfoliative dermatoses, purpura.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions.
Renal and urinary disorders	Very rare	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure[10].
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

[1]Examples include 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.

[2]Hypersensitivity 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, including rashes of various types, pruritus, urticaria, pupura, angioedema and, more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).

[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. Very rare cases of high anion gap metabolic acidosis, when paracetamol is used concomitantly with flucloxacillin, generally in the presence of risk factors (see section 4.4).

[4]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, 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).

[5]Clinical studies suggest that use of ibuprofen, particularly at high doses (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).

[6]The adverse events observed most often are gastrointestinal in nature.

[7]Sometimes fatal, particularly in the elderly (see section 4.4).

[8]See section 4.4.

[9]In overdose Paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see section 4.9).

[10]Especially in long-term use, associated with increased serum urea and oedema.
Also, includes papillary necrosis.

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.

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 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 severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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 seek medical advice from a poisoning specialist and 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. Prolonged use at higher doses than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia. Acute renal failure 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: Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations, ATC code: M01AE51

Mechanism of action
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.

Pharmacodynamic effects
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 12yclooxygenase-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 competitively inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were 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. 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 4.5).

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.

Clinical efficacy and safety

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 backache.

Ibuprofen/paracetamol is especially suitable for pain which has not been relieved by 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 ibuprofen 400 mg ($P<0.05$) and paracetamol 1000 mg ($p<0.0001$) which are clinically and statistically significant.
- 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).

A 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 (1tablet 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 ibuprofen 400 mg ($p< 0.05$) and paracetamol 1000 mg ($p<0.0001$).
- 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

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.

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.

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.

Biotransformation and elimination
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.

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.

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

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

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

4 years

6.4 Special precautions for storage

Stored in the original blisters in order to protect from light.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blisters in cartons of 10, 12, 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

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN

8. MARKETING AUTHORISATION NUMBER(S)

HR-H-355286054

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first approval: 14 January 2020.
Date of renewal of approval: 26 November 2024.

10. DATE OF REVISION OF THE TEXT

20 March 2025