SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panacombo Dual Action Pain Relief 200 mg/500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White or almost white film-coated oval tablets Size of the film-coated tablet: length: 18.9-19.4 mm, width: 8.9-9.3 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, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

4.2 Posology and method of administration

Posology

For short term-use only.
Before this medicine is taken, the patient should first try ibuprofen or paracetamol for pain relief in accordance with the product instructions, for the first day of treatment.
If the pain has not been relieved by ibuprofen or paracetamol during the first day of treatment, then the next day this medicine can be taken.
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms and minimise undesirable effects (see section 4.4).
The patient should consult a doctor if the symptoms persist or worsen or if the product is required 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) in any 24 hours period. To minimise side effects, it is recommended that patients take this medicine 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 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 under 18 years.

Method of administration
Oral use.

4.3 Contraindications

This product is contraindicated:

- In patients with a known hypersensitivity to active substances - ibuprofen, paracetamol 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 failure, severe renal failure or severe heart failure (NYHA Class IV) (see section 4.4).
- In concomitant use with other NSAID containing 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 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).

4.4 Special warnings and precautions for use

Do not exceed the recommended dose.

Do not use until first trying ibuprofen or paracetamol individually to relieve your pain according to the pack instructions.
Consult a doctor to see if the symptoms persist or worsen or if the product is required for more than 3 days. Keep out of the sight and reach of children.

Paracetamol:
The hazards of paracetamol overdose are 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.

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 concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis (refer also to section 4.9).

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.
- 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
  Cases of Kounis syndrome have been reported in patients treated with this medicine. 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.

  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 a high dose (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 (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.

- Gastrointestinal effects:
  NSAIDs should be given with care to patients with a history of gastrointestinal 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 drugs 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 products, the treatment should be withdrawn.

Severe cutaneous adverse reactions 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
This medicinal product 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 this medicine 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:
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 product should be considered.

Excipients
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 product (like any other paracetamol containing products) is contraindicated in

combination with other paracetamol containing products – increased risk of serious adverse effects (see section 4.3).

This 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, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor (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 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).
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see section 4.3).

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

- 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 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, i.e. warfarin (see section 4.4).
- Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: NSAIDs may reduce the effects of these drugs. 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).
- 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 using this product in humans during pregnancy.

From the 20th week of pregnancy onward, this medicine 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, this medicine should not be given unless clearly necessary. If this medicine 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 This medicine for several days from gestational week 20 onward. This medicine 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 function disorders (see above).

The mother and the neonate, at the end of the 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, this medicine is contraindicated during the 3rd trimester of pregnancy (see section 4.3 and 5.3).

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.

Congenital abnormalities have been reported in association with NSAID

administration in man; 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 foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed, and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). 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.

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).

Lactation
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 breastfeeding.

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

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.

Adverse events which have been associated with Ibuprofen alone or Paracetamol alone are given below, 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 Event
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

		throat swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)[2]
Psychiatric Disorders	Very rare	Confusion, depression and hallucinations
Nervous System Disorders	Uncommon	Headache and dizziness
	Very rare	Aseptic meningitis[3], paraesthesia optic neuritis and somnolence
Eye Disorders	Very rare	Visual disturbance
Ear and Labyrinth Disorders	Very rare	Tinnitus and vertigo
Cardiac Disorders	Very rare	Cardiac failure and oedema[4]
	Not known	Kounis syndrome
Vascular Disorders	Very rare	Hypertension[4]
Respiratory and Thoracic and Mediastinal Disorders	Very rare	Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea[2]
Gastrointestinal Disorders	Common	Abdominal pain, vomiting, diarrhoea, nausea, dyspepsia, and abdominal discomfort[5]
	Uncommon	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis[6], mouth ulceration, exacerbation of colitis and Crohn's disease[7] gastritis, pancreatitis, flatulence and constipation
Hepatobiliary Disorders	Very rare	Abnormal liver function, hepatitis and jaundice[8]
Skin and Subcutaneous Tissue Disorders	Common	Hyperhidrosis
	Uncommon	Various skin rashes[2]
	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)

		Photosensitivity reactions
Metabolism and Nutrition Disorders	Not known Not known Not known	Decreased Appetite Hypokalaemia* High anion gap metabolic acidosis[10]
Renal and Urinary Disorders	Very rare	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure[9]
	Not known	Ureteric colic, dysuria
	Not known	Renal tubular acidosis*
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 phosphokinease increased, blood Creatinine 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, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).

[3]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).

[4]Clinical studies suggest that use of ibuprofen particularly at high a 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).

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

[6]Sometimes fatal, particularly in the elderly.

[7] See section 4.4.

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

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

[10] 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.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the 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 Yellow Card Scheme at 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 drugs 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.

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

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 is not a problem, 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 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. Consider oral administration of activated charcoal 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. 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 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 cycloxygenase-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 platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (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.

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.

This product 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.

Summary of 2 tablet clinical data

A 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:

- This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$) and ibuprofen 400 mg ($p<0.05$) which are clinically and statistically significant.
- This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 18.3 minutes. The onset of action was significantly more rapid than for ibuprofen 400 mg (23.8 minutes, $p=0.0015$). 'Meaningful pain relief' for this product was achieved in a median of 44.6 minutes, which was significantly faster than for ibuprofen 400 mg (70.5 minutes, $p<0.0001$). 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 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 ($p<0.0001$).

A randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:

- The product provides 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 the product 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. The product performed significantly better than paracetamol 1000 mg ($p<0.001$).

5.2 Pharmacokinetic properties

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 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.

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 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.

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 product are not altered when taken in combination as a single or repeat dose.

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

Croscarmellose sodium
Hydroxypropylcellulose
Microcrystalline cellulose
Silica, colloidal anhydrous
Stearic acid
Magnesium stearate

Film-coating:

Polyvinyl alcohol
Calcium Carbonate(E170)
Carmellose sodium
Microcrystalline cellulose
Stearic acid

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

Child-resistant blister packs of 10, 16 film-coated tablets.

Aluminium/PVC/PVDC blisters in outer packaging.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Haleon UK Trading Limited,
The Heights,
Weybridge,
Surrey,
KT13 0NY,
U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/11/2024

10 DATE OF REVISION OF THE TEXT

21/10/2025