Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Combileve 500 mg/200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated 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

For the short-term symptomatic treatment of mild to moderate pain.
Combileve 500 mg/200 mg film-coated tablets are especially useful for pain that cannot be relieved by the use of ibuprofen or paracetamol alone.
Combileve 500 mg/200 mg film-coated tablets are indicated in adults aged 18 years and over.

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 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. 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 (equivalent to 3000 mg Paracetamol, 1200 mg Ibuprofen a day) within 24 hour 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.

Renal impairment
In case of renal impairment (glomerular filtration rate 10-50 mL/min), the single dose should not exceed 500 mg of paracetamol (one tablet) and the interval between single doses should be at least six hours. For patients with severe renal impairment, see section 4.3.

Hepatic impairment
In patients with impaired hepatic function or Gilbert's syndrome, the dose should be reduced or the dose interval prolonged. The daily dose should not exceed 2 g of paracetamol (4 tablets). For patients with severe hepatic impairment, see section 4.3.

The daily dose should also not exceed 2 g of paracetamol/day (4 tablets) in the following clinical situations:

- adults weighing less than 50 kg
- chronic alcoholism
- dehydration
- chronic malnutrition

Method of administration

For oral use.

The tablet(s) should be taken with a glass of water.

To minimise side effects, it is recommended that patients take Combileve 500 mg/200 mg film-coated tablets with food.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- In concomitant use with other paracetamol-containing products – an 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).
- 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 cerebrovascular or other active hemorrhages
- In patients with unexplained hematopoietic disorders.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see section 4.4).
- In patients with severe dehydration (e.g. caused by vomiting, diarrhoea or insufficient fluid intake).
- During the third 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 medicine is for short-term use and is not recommended for use more than 3 days.
Paracetamol:
Caution is advised if paracetamol is used by

- elderly
- adults weighing under 50 kg

and in patients with:

- renal impairment
- hepatic impairment
- Gilbert's syndrome
- acute hepatitis
- glucose-6-phosphate dehydrogenase deficiency
- haemolytic anaemia
- alcohol abuse/chronic alcoholism
- chronic malnutrition, low body mass index, anorexia
- dehydration
- concomitant administration of medicinal products which affect liver function (see section 4.5)

There is a risk of severe liver damage in case of overdose. The risk associated with overdose of paracetamol is higher in patients with non-cirrhotic alcoholic liver disease. 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. In case of chronic alcoholism, caution is advised (see also section 4.2). During treatment with paracetamol, alcohol should not be used.

Patients should be warned not to take other products containing paracetamol concurrently due to the risk of severe liver damage in case of overdose (see sections 4.3 and 4.9).

Single administration of several times the maximum daily paracetamol dose may severely damage the liver. In such cases, unconsciousness does not occur. However, 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).

Underlying liver diseases increase the risk of paracetamol-related liver damage. Patients who have experienced impaired liver or kidney function should seek medical advice before using this medicinal product.

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).

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.

Potential laboratory test interferences

The intake of paracetamol can influence the uric acid determination by phosphotungstic acid as well as the blood sugar determination by glucose oxidase peroxydase.

Urine tests

Paracetamol in therapeutic doses may interfere with the determination of

5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Ibuprofen:

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

The concomitant use with NSAIDs, including cyclo-oxygenase-2 specific inhibitors, increases the risk of adverse reactions (see section 4.5) and should be avoided.

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:

- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- Dehydration
- Directly after major surgery

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking/administering ibuprofen therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

In patients with asthma, seasonal allergic rhinitis, swelling of nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary disease or chronic infection of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to NSAIDs such as asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's edema or urticaria are more frequent than in other patients. Special precaution is recommended in such patients (readiness for emergency). This is also applicable to patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Respiratory disorders:

In patients suffering from, or with a history of, bronchial asthma, cases of sudden bronchoconstriction after treatment with NSAIDs have been reported.

SLE and mixed connective tissue disease:

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

Masking of symptoms of underlying infections:

Combileve 500 mg/200 mg film-coated tablets 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 Combileve 500 mg/200 mg film-coated tablets is administered for 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.

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 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), diagnosed 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 reactionassociated with constriction of coronary arteries and potentially leading to myocardial infarction.
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). Treatment should be stopped in those patients who develop severe renal failure. 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 gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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.

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).

Coagulation defects
Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Patients with coagulation disturbances should therefore be monitored carefully.

Medication overuse headache
Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Impaired female fertility:
Please see section 4.6.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, 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 medicinal products –increased risk of serious adverse effects (see section 4.3).

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

Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
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)

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.

Active substances that increase gastric emptying, e.g. metoclopramide and domperidone: The absorption of paracetamol is increased.

Active substances that decrease gastric emptying: Paracetamol absorption can be decreased by active substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.

Warfarin/anticoagulants: 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.

Zidovudine: increased frequency of neutropenia. Therefore, paracetamol and zidovudine should only be administered concomitantly on medical advice.

Probenecid: The conjugation of paracetamol with glucuronic acid is inhibited, leading to a reduction in paracetamol clearance by approximately 50%. In patients concurrently taking probenecid, a reduction of the paracetamol dose should be considered.

Hepatotoxic active substances (see section 4.4) or medicinal products that induce liver microsomal enzymes (see section 4.9): The hepatotoxicity of paracetamol may be potentiated by concomitant administration of medicinal products that affect the liver, such as barbiturates, tricyclic antidepressants, and alcohol.

Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other medicinal products for tuberculosis.

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: (ACE inhibitors, beta-blockers 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, beta-blocker or Angiotensin II antagonist and active substances that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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. The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).

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. The concomitant use of ibuprofen with digoxin may increase the serum level of digoxin. A check of serum-digoxin is not as a rule required on correct use (maximum over 3 days).

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Cyclosporine: Increased risk of nephrotoxicity.

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

Lithium: Decreased elimination of lithium. A check of serum-lithium is not as a rule required on correct use (maximum over 3 days).

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate. The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Phenytoin: The concomitant use of ibuprofen with phenytoin may increase the serum level of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 3 days).

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.

Sulfonylureas: Clinical investigations have shown interactions between NSAIDs and antidiabetics (sulphonylureas). Rare cases of hypoglycemia were reported in patients with concomitant administration of sulfonylurea and ibuprofen. A check of blood-glucose values is recommended as a precaution on concomitant intake.

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.

Aminoglycosides: NSAIDs may reduce the excretion of aminoglycosides.

Probenecid and sulfinpyrazone: Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

CYP2C9 inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased (S)-(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

4.6 Fertility, pregnancy and lactation

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

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

A large amount of data in pregnant women does not indicate the occurrence of malformations or feto/neonatal toxicity effect. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.
In case of clinical need, paracetamol can be administered during pregnancy, but the lowest effective dose should be used with the shortest possible duration of treatment and the lowest possible dosing 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 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. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin 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 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, ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3).

Therefore, the use of this medicinal product should be avoided if possible in the first 6 months of pregnancy and this medicinal product is contraindicated in the last 3 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
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.

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive anduse machines. Undesirable effects such as dizziness, drowsiness, fatigue andvisual disturbances are possible after taking NSAIDs. Patients experiencingthese adverse reactions should not drive or use machines

4.8 Undesirable effects

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

With the following adverse reactions, it must be accounted for that they are predominantly dose-dependent and vary interindividually.

The most commonly observed adverse reactions are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg daily), may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Tabulated list of adverse reactions
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 Events**
Infections and infestations	Very rare	Exacerbation of infection-related inflammation (e.g. development of necrotizing fasciitis); Severe skin infections and soft-tissue complications during a varicella infection (in exceptional cases)
Blood and Lymphatic System Disorders	Very rare	Hematopoietic system disorders[1]
Immune System Disorders		Hypersensitivity reactions[2] have been reported. These may consist of non-specific allergic reactions and anaphylaxis.
	Uncommon	Urticaria, pruritus
	Very rare	Severe hypersensitivity reactions. Symptoms may include: swelling of the face, tongue and larynx, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or vascular or life-threatening shock)[2].
Psychiatric Disorders	Very rare	Confusion, depression psychotic reactions, hallucinations.
Nervous System Disorders	Uncommon	Headache, dizziness, sleeplessness, agitation, irritability, tiredness.
	Rare	Paraesthesia, dream abnormalities
	Very rare	Aseptic meningitis[3], optic neuritis, somnolence
Eye Disorders	Very rare	Visual disturbance. Any patient with eye complaints should have an ophthalmological examination.
Ear and Labyrinth Disorders	Very rare	Tinnitus, vertigo, hearing loss.
Cardiac Disorders	Common	Oedema
	Very rare	Heart failure, palpitations, myocardial infarction.
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	Very rare	Respiratory tract activity including asthma, exacerbation of asthma, bronchospasm and dyspnoea[2].
Gastrointestinal disorders	Common	Gastrointestinal complaints such as abdominal pain, vomiting, diarrhoea, dyspepsia, nausea, flatulence, constipation, heartburn and slight gastrointestinal blood losses that may cause anaemia in exceptional cases.
	Uncommon	Gastrointestinal ulcers, potentially with bleeding and perforation or gastrointestinal haemorrhage, melaena, haematemesis[4], ulcerative stomatitis, exacerbation of colitis and Crohn's disease[5], gastritis.
	Very rare	Oesophagitis, pancreatitis, formation of intestinal, diaphragmatic strictures.

Hepatobiliary disorders	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis, jaundice[6]
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Various types of rashes[2]
	Very rare	Purpura, exfoliatve dermatoses, alopecia. Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)[2].
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and urinary disorders	Rare	Kidney-tissue damage (papillary necrosis)
	Very rare	Various forms of nephrotoxicity, including interstitial nephritis, nephrotic syndrome, and acute or chronic renal failure.
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[7].
General disorders and administration site conditions	Very rare	Fatigue, malaise.
Investigations	Common	Increased alanine aminotransferase, increased gamma-glutamyltransferase and liver function tests abnormal with paracetamol. 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, increased platelet count.
	Rare	Elevated uric acid concentrations in the blood

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 e.g. 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 medicinal product 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]Sometimes fatal, particularly in the elderly.

[5]See section 4.4.

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

[7] 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Paracetamol
Paracetamol overdose can result in liver damage which may be fatal. Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include:
- Patients with liver disease
- Elderly patients
- Young children
- Adults weighing under 50 kg
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion 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 or patients may be asymptomatic. Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
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
Emergency Procedure: Immediate transfer to hospital.
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.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Treatment with activated charcoal should be considered if the overdose occurred within 1 hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. 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.

Symptomatic treatment should be implemented.

Ibuprofen
In adults the dose response effect is not clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms
Most patients who have ingested clinically significant amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia. 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. 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: Other analgesics and antipyretics; Paracetamol, combinations excluding psycholeptics
ATC Code: N02BE51

Mechanism of action
The pharmacological effects 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 active substances alone.

Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.
Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and antipyretic activity. The drug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis.

Pharmacodynamics
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 were taken within 8 hours before or within 30 minutes 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 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).

Clinical efficacy and safety
The clinical efficacy of paracetamol 500 mg/ ibuprofen 200 mg combination product was investigated in studies of acute and chronic pain.

In a randomized, double-blind placebo-controlled trial, 735 patients with post-operative dental pain were treated with ½, 1 or 2 tablets of the combination product, or paracetamol or ibuprofen monotherapy, or placebo.
- Efficacy of a single dose was assessed with the SPRID 0-8 (difference in sum of pain relief and pain intensity from 0 to 8 hours). Results indicate that a single 1-tablet dose of the combination was more effective than placebo, 500 and 1000 mg paracetamol ($p<0.0001$) and 200 mg ibuprofen ($p=0.0001$). Similarly, a single 2-tablet dose of the combination was more effective than placebo, 1000 mg paracetamol ($p<0.0001$) and 400 mg ibuprofen ($p=0.0221$). One tablet of the combination product was more effective than ½ tablet ($p=0.0189$), but did not significantly differ from 2 tablets of the combination product.

• Efficacy of multiple doses of the combination product (taken at least 8 hours apart) was assessed as the 'number of completed 24-hours with ≤ 1 rescue medication' (0, 1, 2, 3 periods) 72 hours post-surgery, with patients' well-being of at least 'good'. Results indicate that multiple doses of the combination product (½, 1 and 2 tablets) were more effective than placebo (all $p<0.0001$).

5.2 Pharmacokinetic properties

Ibuprofen

Absorption
Ibuprofen is well absorbed from the gastrointestinal tract and strongly binds to plasma proteins. Ibuprofen passes into the synovial fluid. Ibuprofen, which is a component of this medicinal product, is detected in plasma after 5 minutes and reaches its maximum plasma concentration 1-2 hours after administration on an empty stomach. If the medicinal product was administered with food, ibuprofen plasma concentrations were lower and delayed by a median of 25 minutes, but the extent of absorption was similar.

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.
The ability to bind to plasma proteins appears to be negligible when used at therapeutic doses, although this is a dose-dependent phenomenon. Paracetamol, which is a component of this medicinal product, is detected in plasma after 5 minutes and reaches its maximum plasma concentration 0.5-0.67 hours after administration on an empty stomach. If the medicinal product was administered
with food, the plasma concentration of paracetamol was lower and delayed by a median of 55 minutes, but the extent of absorption was similar.

Distribution
Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent.

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.

Combination of paracetamol and ibuprofen
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.

Ibuprofen poses a risk to the aquatic environment (see section 6.6).

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
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 conditions.

6.5 Nature and contents of container

PVDC/PVC//Alu blisters of 10 film-coated tablets.
or
PVDC/PVC//Alu /PET child-resistant blisters of 10 film-coated tablets.
Cardboard box with 1 blister (10 tablets) or 2 blisters (20 tablets) and package leaflet inside. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product poses a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs
Suite 12, Bunkilla Plaza
Bracetown Business Park

Clonee
Co. Meath.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1113/032/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2025

10 DATE OF REVISION OF THE TEXT

September 2025