1. NAME OF THE MEDICINAL PRODUCT

Parabufin 500 mg/200 mg, filmomhulde tabletten

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 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 short-term symptomatic treatment of mild to moderate pain.
[Product name] is especially suitable for pain which has not been relieved by ibuprofen or paracetamol alone.

[Product name] 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).

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.

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

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

The maximum dose is six tablets (1 200 mg ibuprofen, 3 000 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
[Product name] is contraindicated in children and adolescents under 18 years (see section 4.3).

Renal impairment
In case of mild to moderate renal impairment, the single dose should not exceed 500 mg of paracetamol (one tablet). The medicinal product is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment
In patients with mild to moderate hepatic impairment 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). The medicinal product is contraindicated in 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
- dehydration
- chronic malnutrition
- chronic alcoholism

Method of administration
Oral use.
The tablet(s) should be taken with a glass of water.
To minimise the risk of gastrointestinal effects, it is recommended that patients take [Product name] with food.

4.3 Contraindications

This medicinal product is contraindicated:

- In patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- In patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to hepatotoxicity (due to the paracetamol component).
- 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 gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- In patients with cerebrovascular or other active bleeding.
- In patients with severe hepatic impairment, severe renal impairment or severe heart failure (NYHA Class IV) (see section 4.4).
- In patients with unclarified blood-formation disturbances.
- In patients with severe dehydration (caused by e.g. vomiting, diarrhoea or insufficient fluid intake).
- During the last trimester of pregnancy (see section 4.6).
- In children and adolescents under 18 years.

4.4 Special warnings and precautions for use

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).

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

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
- In patients who have already reacted allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of ibuprofen.
- In patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma) Quincke's oedema or urticaria.

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

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

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

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

Clinical studies suggest that use of ibuprofen, particularly at high doses (2 400 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. ≤1 200 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 (2 400 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 (2 400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Haematological Effects

Blood dyscrasias have been very rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

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

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

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

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

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

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

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

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

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalised 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).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Ophthalmological effects
Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with products containing ibuprofen should have an ophthalmological examination.

Masking of Symptoms of underlying infections

Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When ibuprofen is administered for 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.

Paracetamol
Caution is advised if paracetamol is administered to patients with:

- renal impairment
- hepatic impairment
- Gilbert's syndrome
- acute hepatitis
- glucose-6-phosphate dehydrogenase deficiency
- haemolytic anaemia
- 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 of paracetamol overdose is increased in patients with non-cirrhotic alcoholic liver disease. Single administration of several times the maximum daily paracetamol dose may severely damage the liver. In such cases, unconsciousness does not occur. 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). 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).

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).

In patients with glutathione depletion, the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

High anion gap metabolic acidosis (HAGMA)
Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

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.

Other notes
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.

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.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore, it should be avoided.

The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. Also, patients with impaired liver function or a history of liver disease, or who are on long term ibuprofen therapy or paracetamol treatment should have hepatic function monitored at regular intervals, as ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though very rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued. Both active substances have been reported to cause hepatotoxicity and even hepatic failure, especially paracetamol.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product should be avoided in combination with:
– other medicinal products, containing paracetamol, ibuprofen, acetylsalicylic acid, salicylates or with any other anti-inflammatory drugs (NSAIDs) unless under a doctor's instruction as these may increase the risk of adverse effects (see section 4.4).

This medicinal product (like any other ibuprofen-containing medicinal products) 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, 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 agents 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 use of ibuprofen with potassium-sparing diuretics may lead to hyperkalaemia.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

- 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).
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. The concomitant use of ibuprofen with digoxin preparations 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 retards and reduces (by 25%) the absorption of ibuprofen. These medicinal products should be administered at an interval of at least 2 hours.
- Ciclosporin: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Lithium: The concomitant use of ibuprofen with lithium preparations may increase serum level of lithium. A check of serum-lithium is not as a rule required on correct use (maximum over 3 days).
- Phenytoin: The concomitant use of ibuprofen with phenytoin preparations may increase serum level of phenytoin. A check of serum-phenytoin levels 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.
- 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 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.
- Sulfonylureas: NSAIDs may increase the effects of sulfonylureas. Rare cases of hypoglycemia were reported in patients with concomitant administration of sulfonylurea and ibuprofen. A check of blood-glucose values is recommended as precaution on concomitant treatment.
- 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.

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

– Chloramphenicol: Increased plasma concentration of chloramphenicol.
– Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.

- Active substances that increase gastric emptying, e.g. metoclopramide and domperidone: The absorption of paracetamol is increased.
- Active substances that decrease gastric emptying: The paracetamol absorption can be decreased by active substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.
- Hepatotoxic 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 antidepressant, and alcohol.
- Probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid, the paracetamol dose should be reduced.
- 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.
- Zidovudine: increased frequency of neutropenia. Therefore, paracetamol and zidovudine should only be administered concomitantly on medical advice.
- 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. Monitoring of the INR in patients with prolonged concomitant use is recommended.
- 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Due to the presence of ibuprofen

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

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

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

The mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, [Product name] is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Due to the presence of paracetamol
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.

Breast-feeding
Paracetamol is excreted into breast milk but not in a clinically significant amount and available published data do not contraindicate its use during breastfeeding.
Ibuprofen and its metabolites can pass in very small amounts into breast milk. No harmful effects to infants are known.
In light of the above evidences it is not necessary to interrupt breastfeeding, for short-term treatment with the recommended dose of this product.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials with ibuprofen/paracetamol 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 (2 400 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 reactions 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 reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very rare	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis); in exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection.
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders[1]
Immune system disorders		Hypersensitivity reactions[2] have been reported. These may consist of non-specific allergic reactions and anaphylaxis.
	Uncommon	Urticaria and pruritus.
	Very rare	Severe hypersensitivity reactions. Symptoms can include: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock) [2].
Psychiatric disorders	Very rare	Confusion, psychotic reactions, depression, hallucinations
Nervous system disorders	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
	Rare	Paraesthesia, dream abnormalities
	Very rare	Aseptic menigitis[3], optic neuritis, somnolence.
Eye disorders	Very rare	Visual disturbances.
Ear and labyrinth disorders	Very rare	Hearing loss, tinnitus and vertigo
Cardiac disorders	Common	Oedema, fluid retention.
	Very rare	Palpitations, tachycardia, arrhythmia and other cardiac dysrhythmias have been reported. Cardiac failure, myocardial infarction.
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	Uncommon	Thickened respiratory tract secretions.
	Very rare	Respiratory tract reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea[2].
Gastrointestinal disorders	Common	Gastrointestinal complaints such as abdominal pain, diarrhoea, dyspepsia, nausea, flatulence, constipation, heartburn, vomiting 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 diaphragm-like 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 skin rashes[2].
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis[2]), Purpura, alopecia.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions.
Renal and urinary disorders	Uncommon	Urinary retention
	Rare	Kidney-tissue damage (papillary necrosis)
	Very rare	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, acute and chronic renal failure. Adverse renal effects are most often observed after overdose, after chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity. Acute tubular necrosis usually occurs in conjunction with liver failure, but has been observed as an isolated finding in rare cases.
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 and platelet count increased.
	Rare	Elevated uric acid concentrations in the blood
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[7].

Description of selected adverse reaction

[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, 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 medicinal product 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] High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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
The symptoms of overdose can include nausea, vomiting, abdominal 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. Hypothermia and hyperkalaemia may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. 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.

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

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

cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
The pharmacological actions of paracetamol and ibuprofen differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception than the single actives 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 ADP- and collagen-induced platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. 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).

Clinical efficacy and safety

The clinical efficacy of ibuprofen 200 mg/ paracetamol 500 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 $p<0.0001$).

In a randomized, double-blind active-controlled clinical trial, 892 patients with chronic knee pain, were treated with 1 or 2 tablets of the combination product, or 1000 mg paracetamol or 400 mg ibuprofen mono-therapy for 13 weeks (TID).

- Short-term efficacy was assessed with the WOMAC subscale for pain (0-100mm VAS) at Day 10. Results indicate that two tablets (not 1 tablet) of the combination were more effective than 1000 mg paracetamol (-5.3 [-8.5, -2.1]; $p=0.0012$), but two tablets did not significantly differ from 400 mg ibuprofen.
- Long-term efficacy was assessed at Week 13 as patients' satisfaction with the study medication (5-point Likert; 1= excellent, 5= unacceptable).

Results indicate that in the long-term patients were more satisfied with the combination (1 and 2 tablets) compared to 1000 mg paracetamol (-0.28 [-0.51, -0.05], $p=0.0152$ and -0.43 [-0.66, -0.20], $p=0.0002$, resp.), but not compared to 400 mg ibuprofen.

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Following administration of a single oral dose of ibuprofen/paracetamol 200 mg/500 mg tablets, plasma levels of total ibuprofen (C_{max}) were achieved within 75 minutes after ingestion on an empty stomach. The mean plasma AUC value and C_{max} values for total ibuprofen (R- and S-ibuprofen) were 61.467 µg h/ml and 17.537 µg/mL, respectively. When ibuprofen/paracetamol 200 mg/500 mg tablets were taken with food, peak plasma levels for S-ibuprofen were 8.934 µg/mL and achieved at 80 minutes. AUC value was 33.985 µg h/ml.

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. maximum plasma levels of paracetamol from ibuprofen/paracetamol 200 mg/500 mg tablets are achieved at 30 minutes after ingestion on an empty stomach. The mean plasma AUC value and C_{max} values for paracetamol were 27.157 µg h/ml and 8.969 µg/mL, respectively. When ibuprofen/paracetamol 200 mg/500 mg tablets were taken with food, peak paracetamol plasma levels were 5.762 µg/mL and occurred at 1.0 hours. AUC value was 23.555 µg h/ml.

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.

Special populations
No significant differences in the paracetamol or ibuprofen pharmacokinetic profile are observed in the elderly.

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

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

5.3 Preclinical safety data

Ibuprofen: The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat, mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta. For maternally toxic doses, an increased incidence of malformations (ventricular septal defects) was observed.
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.

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

Paracetamol: Paracetamol in hepatotoxic doses showed genotoxic and carcinogenic potential (liver and bladder tumours), in mice and rat. However, it is considered that this genotoxic and carcinogenic activity is related with changes in the metabolism of paracetamol when in high doses/concentrations and does not represent a risk for the clinical use.
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 (E1202)
Silica, colloidal anhydrous (E551)

Povidone (E1201)
Starch, pregelatinised (maize)
Talc (E553b)
Stearic acid

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

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blisters and perforated unit dose blisters packed in carton boxes of 10, 20, 20x1 film-coated tablets.

Child resistant aluminium-PVC/PVDC blisters and perforated unit dose blisters packed in carton boxes of 10, 20, 20x1 film-coated tablets.

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

Teva B.V.
Swensweg 5
2031 GA Haarlem
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 133421

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 23 december 2025

10. DATUM VAN HERZIENING VAN DE TEKST

<Detailed information on this medicinal product is available on the website of: {name of Member State/Agency}>