# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Ibuprofen 500 mg/150 mg powder for oral solution in sachet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains Paracetamol 500 mg and Ibuprofen (as lysine) 150 mg.

Excipients with known effect:
Aspartame (62.5 mg per sachet), Sucrose (1542.0 mg per sachet)

For the full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for oral solution in sachet
Light yellow to yellow-coloured powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For short-term symptomatic treatment of mild to moderate pain in adults. This product is especially suitable for pain which has not been relieved by ibuprofen or paracetamol alone.

### 4.2 Posology and method of administration

Posology

For oral administration and 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 symptoms persist or worsen or if the product is required for more than 3 days.

*Adults (body weight >50kg)*

The usual dosage is one to two sachets taken every six hours, as required, up to a maximum of six sachets in 24 hours. If single doses of one sachet do not control symptoms, a maximum of two sachets may be taken up to three times a day. The interval between single doses should be at least six hours. The maximum daily dose of 3000 mg paracetamol and 900 mg ibuprofen must not be exceeded in any 24-hour period.

The maximum daily dose of paracetamol should not exceed a maximum of 2g paracetamol per day in the following situations unless directed by a physician.

- Chronic alcoholism
- Dehydration
- Chronic malnutrition

*Children and adolescents under18 years*

This medicinal product is not intended for use in children and adolescents under 18 years.

*Elderly*

No special dosage modifications are required however in frail, immobile elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate(see section 4.4). The elderly are at increased risk of 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.

**Patients with renal/ hepatic impairment**

Caution should be taken in patients with mild to moderate renal/hepatic impairment. The dosage should be kept as low as possible (see section 4.4).
This product is contraindicated in patients with severe renal failure or patients with severe hepatic failure (see section 4.3).

Method of administration
To minimise side effects, it is recommended that patients should take this medicine after food.

Paracetamol/Ibuprofen should be taken by dissolving the content of the sachet in a glass of hot water.

**4.3 Contraindications**

This product is contraindicated for use:

- in patients with known hypersensitivity to the active substances, or to any of the excipients listed in section 6.1.
- in patients with severe heart failure (NYHA Class IV)
- 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 history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- in patients with active or history of recurrent peptic ulceration/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- in patients with severe hepatic failure or severe renal failure (see section 4.4.).
- in patients with cerebrovascular or other active bleeding.
- in patients with blood-formation disturbances.
- during the third trimester of pregnancy (see section 4.6.).
- in patients with severe dehydration.

Concomitant use with other medicinal products containing paracetamol, ibuprofen, acetylsalicylic acid above 75 mg daily, salicylates or with any other anti-inflammatory drugs (NSAIDs) (see section 4.5). Use of the low dose acetylsalicylic acid is not recommended (see section 4.5).

**4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2). This medicine is for short term use and is not recommended for use beyond 3 days.

To avoid the risk of overdose (see section 4.3 and 4.9):
- no other paracetamol-containing products should be taken at the same time.
- no other ibuprofen-containing products should be taken at the same time.

*Hepatic Impairment*

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. Dose reduction is recommended in patients showing signs of worsening hepatic function (see section 4.2). Treatment should be stopped in those patients who develop severe liver failure (see section 4.3).
Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though 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

medicines have been reported to cause hepatotoxicity and even hepatic failure, especially paracetamol.
Patients who regularly consume alcohol in excess of recommended amounts should not take this medicine.

*Renal Impairment*

Paracetamol can be used in patients with chronic renal disease without dosage adjustment. There is minimal risk of paracetamol toxicity in patients with moderate to severe renal failure. However, for the ibuprofen component of this product - caution should be used when initiating treatment with ibuprofen in patients with dehydration. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms: interstitial nephritis, nephritic syndrome and renal failure. Renal impairment from ibuprofen use is usually reversible. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of nonsteroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patients.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of medicine. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

*Elderly*
No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment.

*Haematological Effects*

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

*Coagulation Defects*

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, products containing ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

*Gastrointestinal Events*
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 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 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 medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

Due to the ibuprofen component, /.../ should be given with caution to patients with a history of GI disease (ulcerative colitis,

Crohn's disease) as well as in patients with porphyria.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

This product should be discontinued if there is any evidence of gastrointestinal bleeding or ulceration.

*Cardiovascular Thrombotic Events*
Clinical studies suggest that the use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

The risks are described as minimal at maximum daily doses which include ibuprofen at 1200 mg. The recommended maximum daily dose in this product is 900 mg (European Medicines Agency review concludes positive benefit-risk balance for non-selective NSAIDs, October 2006)

Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of 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 (as lysine). 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.

*Hypertension*

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

*Heart failure*

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

*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).

*Pre-existing asthma*

Products containing ibuprofen should not be administered to patients with acetylsalicylic acid sensitive asthma and should be used with caution in patients with pre-existing asthma.

*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 which includes central vision fields.

*Aseptic Meningitis*

For products containing ibuprofen aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

*Potential Laboratory Test Interferences*

Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

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.

*Masking of symptoms of underlying infections*

Paracetamol/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 Paracetamol/Ibuprofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

*High anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis*

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.

*Excipients*

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

This medicine contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Paracetamol/Ibuprofen contains 1542.0 mg of sucrose per sachet. This should be taken into account in patients with diabetes mellitus.

This medicine contains 62.5 mg aspartame in each dosage unit, which is equivalent to 0.0625 g /2.5 g sachet.
Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

**4.5 Interaction with other medicinal products and other forms of interaction**

The concomitant use of this medicinal product with other medicinal products containing paracetamol, ibuprofen, acetylsalicylic acid above 75 mg daily, salicylates or with any other anti-inflammatory drugs (NSAIDs) is contraindicated (see section 4.3).

The following interactions of paracetamol with other medicines have been reported:

- anticoagulant medicines (e.g. warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time. In this case, a regular control of INR is recommended
- paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide or domperidone.
- paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.
- paracetamol may increase chloramphenicol plasma concentrations.
- the risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or substances that induce liver microsomal enzymes such as alcohol and anticonvulsant agents (barbiturates, carbamazepine, phenytoin, primidone).
- paracetamol excretion may be affected and plasma concentrations altered when given with probenecid. A reduction of paracetamol dosage should be considered in case of concomitant treatment with probenecid.
- cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other medicines for tuberculosis such as rifampicin.
- Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole. Concomitant administration of paracetamol and zidovudine can induce neutropenia and hepatotoxicity. Frequent use of paracetamol in patients treated with zidovudine should be avoided.
- Due to a possible induction of hepatic metabolism, paracetamol can decrease lamotrigine bioavailability with a possible reduction of therapeutic effect.
- Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk factors. (see section 4.4.)

The following interactions of ibuprofen with other medicines have been noted:

- 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 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)
- anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- Ibuprofen may decrease renal clearance and increase plasma concentration of lithium.
- Ibuprofen may reduce the anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments.
- Ibuprofen reduces methotrexate clearance.
- Ibuprofen may increase plasma levels of cardiac glycosides.
- Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids.
- Ibuprofen may prolong bleeding time in patients treated with zidovudine.
- Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.
- Ibuprofen may also interact with tacrolimus, ciclosporin, sulphonylureas, quinolone antibiotics and CYP2C9 inhibitors (voriconazole, fluconazole).
- Ciclosporin: Increased risk of nephrotoxicity.
- 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 with tacrolimus.

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

*Effects on laboratory tests*
Paracetamol can interfere with laboratory tests for serum uric acid using phosphotungstic acid and blood sugar tests using glucose-oxidase-peroxidase.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

There is no experience of use of this product in humans during pregnancy. Because of the ibuprofen-component Paracetamol/Ibuprofen is contraindicated during the third trimester of pregnancy (see below).

**For 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, Paracetamol/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, Paracetamol/Ibuprofen should not be given unless clearly necessary. If Paracetamol/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 Paracetamol/Ibuprofen for several days from gestational week 20 onward. Paracetamol/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, Paracetamol/Ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3 and 5.3).

**For paracetamol**

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

Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount and available published data do not contraindicate 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 evidence it is not necessary to interrupt breastfeeding, for short-term treatment with the recommended dose of this product.

Fertility

The use of the 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 product should be considered. There is some evidence that medicines which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on stopping the medicine.

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

Clinical trials with paracetamol 500 mg/ibuprofen 150 mg film-coated tablets in adults have not indicated any other undesirable effects other than those for paracetamol alone or ibuprofen alone.
Adverse reactions have been ranked under headings of frequency using the following convention:
1. Very common (≥ 1/10);
2. Common (≥ 1/100, < 1/10);
3. Uncommon (≥ 1/1000, < 1/100);
4. Rare (≥ 1/10000, < 1/1000);
5. Very rare (< 1/10000)
6. Not known (cannot be estimated from the available data).

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| **Infections and infestations** | **Very rare:** Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. |
| **Blood and lymphatic system disorders** | **Uncommon**: Decrease in haemoglobin and haematocrit. Bleeding episodes (e.g. epistaxis, menorrhagia).<br>**Very Rare**: Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia with or without purpura). |
| **Immune system disorders** | **Uncommon**: Other allergic reactions, Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein purpura, angioedema.<br>**Very Rare**: Hypersensitivity reactions including skin rash and cross-sensitivity with sympathomimetics.<br>**Not known:** anaphylactic shock. |
| **Metabolism and nutrition disorders** | **Uncommon**: Gynaecomastia, hypoglycaemic reaction.<br><br>**Very Rare**: Metabolic side effects have included hypokalemia.<br>**Not known**: High anion gap metabolic acidosis. |
| **Nervous system disorders** | **Common**: Dizziness, headache, nervousness<br><br>**Uncommon**: Depression, insomnia, confusion, emotional lability, |

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| | somnolence, aseptic meningitis with fever and coma<br><br>**Rare**: Paraesthesia, hallucinations, dream abnormalities<br>**Very Rare**: Paradoxical stimulation, optic neuritis, psychomotor impairment, extrapyramidal effects, tremor and convulsions. |
| **Eye disorders** | **Uncommon**: Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields. |
| **Ear and labyrinth disorders** | **Common**: Tinnitus (for medicines containing ibuprofen)<br><br>**Very Rare**: Vertigo. |
| **Cardiac disorders** | **Common**: Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the medicine.<br>**Very Rare**: Palpitations; tachycardia; arrhythmia and other cardiac dysrhythmias. Hypertension and cardiac failure.<br>Not Known: Kounis syndrome |
| **Respiratory and thoracic and mediastinal disorders** | **Uncommon**: Thickened respiratory tract secretions<br><br>**Very Rare**: Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea. |
| **Gastrointestinal Disorders** | **Common**: Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting<br><br>**Uncommon**: Flatulence and constipation, peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease. Less frequently gastritis has been observed and pancreatitis reported.<br><br>**Very rare:** Oesophagitis, formation of intestinal diaphragm-like strictures |
| **Hepatobiliary disorders** | **Very Rare**: Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury. |
| **Skin and subcutaneous tissue disorders** | **Common**: Rash (including maculopapular type), pruritus.<br><br>**Rare:** urticaria, hyperhidrosis<br><br>**Very Rare**: Alopecia, Hyperhidrosis, purpura and photosensitivity. Very rare cases of serious skin reactions have been reported, such as exfoliative dermatoses and bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.<br>**Not known**: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP) |
| **Renal and urinary disorders** | **Uncommon**: Urinary retention<br><br>**Very Rare**: Sterile pyuria (cloudy urine). Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.<br>Adverse renal effects are most often observed after overdose, after chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity.<br>Acute tubular necrosis usually occurs in conjunction with liver failure, |

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| | but has been observed as an isolated finding in rare cases. A possible increase in the risk of renal cell carcinoma has been associated with chronic paracetamol use as well. |
| **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.<br>Blood creatinine increased and blood urea increased.<br><br>**Uncommon**: Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, haemoglobin decreased and platelet count increased. |

*Description of selected adverse reactions*

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

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

**4.9 Overdose**

***Symptoms***

Paracetamol:
Liver injury and even failure can occur following paracetamol overdose, in particular; in elderly patients, in young children, in case of liver or renal insufficiency, chronic alcoholism, chronic malnutrition, use of enzymatic inductors or in adults weighing less than 50 kg. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is possible in adults who have taken 10 g or more of paracetamol or in children who have taken 150 mg/kg of paracetamol, due to excess quantities of a toxic metabolite. Increased transaminases (ALT, AST), lactate dehydrogenase and bilirubin have also been observed, with a prolonged prothrombin time (12 to 48 hours after ingestion).
The threshold for liver toxicity may be lowered in the presence of one of the risk factors listed above.

Ibuprofen
Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

In serious poisoning metabolic acidosis may occur.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

***Treatment***

Paracetamol**:**

Prompt treatment is essential in the management of paracetamol overdose even when there are no obvious symptoms, because of the risks of liver injury, which presents after some hours or even days delay. Medical treatment is advised, without delay in any patient who has ingested 7.5 g or more of paracetamol in the preceding 4 hours.
Urgent procedure:
- Immediate hospitalisation.
- Blood sample to determine the initial paracetamol plasma concentration.
- Gastric lavage should be considered.
- Administration of activated charcoal, if possible, within one hour after ingestion.
- Administration of the antidote acetylcysteine (intravenous) to be instituted as soon as possible, if possible within 8 hours after ingestion. Acetylcysteine is most effective when administered during the first 8 hours following ingestion of the overdose and the effect diminishes progressively between 8 and 16 hours. It used to be believed that starting treatment more than 15 hours after overdose was of no benefit and might possibly aggravate the risk of hepatic encephalopathy. However, late administration has now been shown to be safe, and studies of patients treated up to 36 hours after ingestion suggest that beneficial results may be obtained beyond 15 hours. Furthermore, administration of intravenous acetylcysteine to patients who have already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.
An initial dose of 150 mg/kg of acetylcysteine in 200 mL 5% glucose is given intravenously over 15 minutes, followed by an I.V. infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and then 100 mg/kg in 1 litre 5% glucose over 16 hours. The volume of I.V. fluids should be modified for children.

- Symptomatic treatment.

Ibuprofen**:**
Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric lavage is only recommended within 60 minutes after ingestion of a life-threatening dose. Because the medicine is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen sachets.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**ATC Code:** N02BE51 –Analgesics. Other analgesics and antipyretics.

Mechanism of action

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 anti-pyretic activity. The medicine's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis.
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 (81mg), 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).

The exact mechanism of action of ibuprofen is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition.

*Clinical trials*

Randomized, double-blind studies were conducted with a tablet formulation of the combination for adults using the acute dental pain model of post-operative pain. A clinical study has demonstrated that when taken at equivalent doses, the powder for oral solution formulation is bioequivalent to comparable doses of the fixed dose combination oral film-coated tablet formulation in terms of rate and extent of absorption (AUC). The studies showed that:

- Over the 48 hours, Paracetamol/Ibuprofen 500 mg/150 mg film-coated tablet had a faster onset than either of its two active ingredients and provided superior analgesia than the same daily dose of paracetamol (p=0.007 at rest, p=0.006 on activity) and ibuprofen (p=0.003 at rest, p=0.007 on activity)

- All three doses evaluated (half tablet or one tablet or two tablets) were effective when compared with placebo (p=0.004-0.002) and the highest dose [two tablets] had the greatest response rate (50%), lowest maximum VAS pain scores, longest time to rescue medication and lowest % of patients requiring rescue medication. All these measures were significantly different to placebo (p<0.05).

**5.2 Pharmacokinetic properties**

Absorption

Both paracetamol and ibuprofen, are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

In clinical trials comparing the absorption of the hot drink sachet formulation to the equivalent fixed-dose combination tablets, the hot drink sachet formulation has a higher peak plasma concentration of paracetamol and ibuprofen when taken during fasting. The overall exposure for both medicines is bioequivalent to the tablet formulation.
The rate and absorption of both paracetamol and ibuprofen from the combination product is slightly delayed following administration after food.

Distribution

As for any product containing paracetamol, it is distributed into most body tissues.
Ibuprofen is highly bound (90-99%) to plasma proteins.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less that 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdose and if left untreated has the potential to cause severe and even irreversible liver damage.
Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.
In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen (such as in Paracetamol/Ibuprofen) This study clears any added hepatic risks from the hepatotoxic metabolite, NAPQI, from paracetamol if administered with ibuprofen.

Elimination

Paracetamol elimination half-life varies from about 1 to 3 hours.

Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life if ibuprofen is around 2 hours.

Pharmacokinetic relationship
A specific study to investigate possible effects of paracetamol on the plasma clearance of ibuprofen and vice versa did not identify any drug interactions.

**5.3 Preclinical safety data**

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments

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.

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. There are no new preclinical data of relevance which are additional to the data already presented in this Summary of Product Characteristics.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Aspartame (E 951)
Turmeric Extract 95%
Lemon flavour
Sodium citrate
Sucrose

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Do not store above 30 °C.

**6.5 Nature and contents of container**

Paracetamol/Ibuprofen is supplied in sachet formed by thermo-sealing two multi-layer foils, in cartons containing 10, 16, or 20 sachets.
The primary packaging consists of sachets (Paper, Aluminium, Polyethylene)

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

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

Paracetamol/Ibuprofen should be taken by dissolving the content of the sachet in a glass of hot water. Paracetamol/Ibuprofen forms a yellow solution when dissolved.

**7 MARKETING AUTHORISATION HOLDER**

Vale Pharmaceuticals Limited
Dungarvan Enterprise Centre Lower Main Street
Dungarvan
Co. Waterford
X35 FX45
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA1535/020/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 29th August 2025

**10 DATE OF REVISION OF THE TEXT**