NEW ZEALAND DATA SHEET

BRUFEN® EXTRA

1. Product Name

Brufen Extra, 200 mg ibuprofen and 500 mg paracetamol, film coated tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 200 mg of ibuprofen and 500 mg of paracetamol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Brufen Extra is a white to off-white, oval shaped, biconvex, film-coated pearlescent tablet, plain on both sides.

4. Clinical Particulars

4.1 Therapeutic indications

For the temporary relief of pain and/or inflammation associated with: headache, migraine headache, tension headache, dental pain, back pain, muscular pain, period pain, rheumatic pain and non-serious arthritic pain, cold & flu symptoms and sore throat. Reduces fever.

4.2 Dose and method of administration

Dose

Adults and adolescents from 12 years

1-2 tablets every 6-8 hours as necessary (maximum 6 tablets in 24 hours).

Keep to the recommended dose. Don't take Brufen Extra for longer than 3 days at a time unless advised by a doctor.

Paediatric

Do not give Brufen Extra to children under 12 years.

4.3 Contraindications

Brufen Extra is contraindicated for use in:

- Patients with known hypersensitivity reaction to paracetamol, ibuprofen, other NSAIDs or any other ingredients in the product listed in section 6.1.
- Patients with severe heart and renal failure (glomerular filtration below 30 ml/min).
- Women during third trimester of pregnancy.

Paracetamol

Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatotoxicity.

Ibuprofen

Ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4).

Ibuprofen is contraindicated for use in patients with active gastrointestinal bleeding or peptic ulceration. Use of ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.6).

Brufen Extra should not be taken with other products containing ibuprofen, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction. Refer to section 4.5 for additional information.

4.4 Special warnings and precautions for use

Use in chronic liver disease or a history of liver disease

Paracetamol

Paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. Paracetamol can be used in patients with liver disease and has been studied in both one-time single (1500 mg) and multiple doses (4000 mg/day) in adult patients with chronic stable liver disease. A double-blind, two-period, crossover study was conducted to evaluate the use of 4000 mg/day of paracetamol for 13 days in patients with stable chronic liver disease. There were no abnormalities indicative of an adverse reaction to paracetamol. The metabolism following a single 1500 mg dose was compared in normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences in overall 24-hour urinary excretion of paracetamol and glucuronide, cysteine, and mercapturic acid conjugates of paracetamol. Following a single (10 mg/kg) dose of paracetamol, the pharmacokinetic profiles in patients with mild, moderate, or severe liver disease were not significantly different. Although the plasma half-life of paracetamol was prolonged in patients with severe liver disease, there were no significant differences in the 24-hour (adult) and 36-hour (children) urinary excretion of paracetamol or its conjugates (glucuronide, cysteine, mercapturic acid).

Ibuprofen

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. 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 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.

Use in renal disease

Paracetamol

Paracetamol can be used in patients with chronic renal disease without dosage adjustment. In a single-dose study, the disposition and metabolite kinetics of 1000 mg of paracetamol were compared in patients with renal disease and in healthy volunteers. The fractional urinary recovery of paracetamol and its conjugates (e.g., glucuronide, sulphate, cysteine, mercapturate) was similar in healthy volunteers and in patients with moderate renal failure. In a 10-day, multi-dose study, the disposition of paracetamol 3000 mg daily in healthy volunteers was compared with patients with chronic renal failure. A slight increase in predose trough paracetamol levels was noted in patients

with renal failure (3.1 µg/mL) compared with controls (1.1 µg/mL), but there was no evidence of accumulation of the glutathione-derived metabolites of paracetamol (e.g., cysteine, mercapturate). Although mean daily predose plasma concentrations of sulphate and glucuronide conjugates were higher in patients with chronic renal disease, these conjugates disappeared rapidly when paracetamol was discontinued. There is no significant risk of paracetamol toxicity in patients with moderate to severe renal failure.

Ibuprofen

Caution should be used when initiating treatment with ibuprofen in patients with considerable 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. 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.

Use in older patients

Paracetamol

No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than 10 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary.

Ibuprofen

Ibuprofen 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

Paracetamol

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency

In therapeutic doses, paracetamol does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells. It can alter the metabolism of oral anticoagulants (see section 4.5).

Ibuprofen

Haematological monitoring

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, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Gastrointestinal events

Ibuprofen

Upper GI ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment and are more common in patients over the age of 65 years.

Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when ibuprofen/paracetamol is used at the prescribed dose for a few days.

Ibuprofen should be used with extreme caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or ulcer since their condition may be exacerbated.

Ibuprofen/paracetamol should be discontinued if there is any evidence of gastrointestinal bleeding.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular thrombotic events

Ibuprofen

Epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg/daily), may be associated with an increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (≤ 1200 mg/ daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAIDs use.

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 skin reactions

Ibuprofen

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

DRESS syndrome has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever, or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Pre-existing asthma

Ibuprofen

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects

Ibuprofen

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

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

Ibuprofen

The use of an ACE inhibiting drug (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 drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Aseptic meningitis

Ibuprofen

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

Masking signs of infection

Ibuprofen

As with other drugs of this class, ibuprofen may mask the usual signs of infection.

Special precautions

Ibuprofen

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

Potential laboratory test interferences

Paracetamol

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:

Blood tests

Paracetamol at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose meters. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

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.

4.5 Interaction with other medicines and other forms of interaction

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding.

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

Cholestyramine

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

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Other analgesics

Avoid concomitant use of two or more NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, because of the potential of increased adverse effects. Ibuprofen antagonizes the irreversible inhibition of platelet cox-1 induced by low dose aspirin. To reduce this effect, ibuprofen should be administered at least 8 hours before or 30 minutes after taking low dose aspirin. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5).

Cyclosporine or tacrolimus

Increased risk of nephrotoxicity when used with NSAIDs.

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.

Sulfonylureas

NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

CYP2C9 Inhibitors

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

Paracetamol

The following interactions have been noted:

- Anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.
- 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 drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.
- Paracetamol excretion may be affected and plasma concentrations altered when given 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 drugs for tuberculosis.
- Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole.

Ibuprofen

The following interactions have been noted:

- 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Brufen Extra is contraindicated in third trimester of pregnancy.

Brufen Extra should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.

Data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy.

Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Brufen Extra if oligohydramnios occurs.

NSAID use during the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the third trimester of pregnancy is therefore contraindicated.

Breast-feeding

Brufen Extra is not recommended for nursing mothers.

Fertility

The use of ibuprofen 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 ibuprofen should be considered.

4.7 Effects on ability to drive and use machines

Following treatment with ibuprofen, the reaction time of patients may be affected. NSAIDs may cause dizziness, drowsiness, fatigue and visual disturbances. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Paracetamol

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Ibuprofen

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of non-specific allergic reaction and anaphylaxis, respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea, or assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and very rarely, bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

More common reactions: (greater than 1%)

Gastrointestinal

The most commonly observed adverse events are gastrointestinal in nature. Gastrointestinal complaints include nausea, epigastric pain, heartburn, diarrhoea, abdominal distress, nausea and vomiting, dyspepsia, constipation, abdominal cramps or pain, gastrointestinal haemorrhage, haematemesis, melaena, fullness of the GI tract (bloating and flatulence).

Ear and labyrinth disorders

Tinnitus, hearing impaired.

General disorders and administration site conditions

Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug.

Nervous system disorders

Dizziness, headache, nervousness.

Skin and subcutaneous tissue disorders

Rash (including maculopapular type), pruritus.

General disorders

Decreased appetite, fatigue.

Less common reactions: (less than 1%)

Nervous system disorders

Depression, insomnia, anxiety, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma.

Skin and subcutaneous tissue disorders

Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia.

Gastrointestinal

Gastric or duodenal ulcer with bleeding and/or perforation, mouth ulceration, ulcerative stomatitis, pancreatitis, gastritis.

Hepatobiliary disorders

Hepatitis, jaundice, abnormal liver function.

Blood and lymphatic system disorders

Neutropenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia and decrease in haemoglobin and haematocrit.

Cardiac disorders

Cardiac failure, myocardial infarction.

Vascular disorder

Hypertension.

Respiratory, thoracic and mediastinal disorders

Asthma, bronchospasm, dyspnoea.

Infections and infestations

Rhinitis and meningitis aseptic.

Eye disorders

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 (see section 4.4). Visual impairment and toxic neuropathy have also been reported.

Allergic

Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis.

Precise incidence unknown (but less than 1%) causal relationship unknown

Nervous system disorders

Paraesthesias, hallucinations, dream abnormalities, vertigo.

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis, photoallergic skin reactions.

Eye disorders

Conjunctivitis, diplopia, optic neuritis, cataracts.

Blood and lymphatic system disorders

Bleeding episodes (e.g. epistaxis, menorrhagia).

Metabolism and nutrition disorders

Gynaecomastia, hypoglycaemic reaction, acidosis.

Renal and urinary disorders

Renal nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatobiliary disorders

Abnormal liver function, hepatic failure, hepatitis and jaundice.

Cardiac disorders

Arrhythmias (sinus tachycardia, sinus bradycardia).

Immune system disorders

Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.

Not known

Skin and subcutaneous tissue disorders

Acute generalised exanthematous pustulosis (AGEP).

Drug reaction with eosinophilia and systemic symptoms (DRESS).

Photosensitivity reactions.

Additional post-marketing adverse reactions

Gastrointestinal

Exacerbation of colitis and Crohn's Disease (see section 4.3). Pancreatitis has been reported very rarely.

Pregnancy, puerperium and perinatal conditions

Oligohydramnios, neonatal renal impairment

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

Paracetamol

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. 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 likely in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite becoming irreversibly bound to liver tissue.

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.

Treatment

Paracetamol

Prompt treatment is essential in the management of paracetamol overdosage even when there are no obvious symptoms, and should not be delayed while waiting for laboratory results. Any patient who has ingested 7.5 g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Specific therapy with an antidote such as acetylcysteine (intravenous) or methionine (oral) should be instituted as soon as possible.

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 overdosage 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.

Methionine is given orally as 2.5 g every 4 hours up to 10 g. Methionine treatment must be started within 10 hours after ingestion of paracetamol; otherwise it will be ineffective and may exacerbate liver damage.

Evidence of serious symptoms may not become apparent until 4 or 5 days following overdosage and patients should be carefully observed for an extended period.

Ibuprofen

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount of ibuprofen, use of activated charcoal should be considered. Alternatively, in adults gastric lavage may be considered for potentially life-threatening overdoses.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics, ATC code: N02BE51.

Mechanism of action

Paracetamol

Although the exact site and mechanism of analgesic action is not clearly defined, paracetamol appears to produce 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

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition.

5.2 Pharmacokinetic properties

Paracetamol

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

Distribution

Paracetamol is distributed into most body tissues.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 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 overdosage and if left untreated has the potential to cause irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

Elimination

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

Ibuprofen

Absorption

Ibuprofen is well absorbed from the gastrointestinal tract.

Distribution

Ibuprofen is highly bound (90-99%) to plasma proteins.

Metabolism

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

Elimination

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 in the range of 1.9 to 2.2 hours.

The fixed dose combination

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

Metabolism

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 to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

5.3 Preclinical safety data

Carcinogenicity/mutagenicity

Paracetamol

Various animal bioassays on a weight-of-evidence basis have demonstrated no evidence of carcinogenic potential for paracetamol.

Carcinogenicity (human)

Although it has been hypothesized that long-term use of analgesics may be associated with a slight increase in urinary tract tumours and renal cell cancer in man, a number of population-based, case-controlled studies have shown that it is unlikely that paracetamol use plays a major role in renal cell cancer.

A comprehensive and conclusive review, accepted by the Committee for Proprietary Medicinal Products (CPMP) of the European Union, considered the genotoxic and carcinogenic properties of paracetamol. This review concluded that genotoxic effects of paracetamol are not reached at therapeutic dosage.

Reproductive and teratogenic effects (animal)

There was no effect on pregnancy or offspring when paracetamol was given at dose levels of 600 mg/kg/d in the diet of male rats for 60 days prior to mating and to female rats from 14 days before mating to the end of pregnancy. An oral dose of 600 mg/kg/d produced no teratogenicity or embryotoxicity when given from days 6 through 15 of pregnancy. When paracetamol was given from day 16 of pregnancy through a 3-week lactation period, no deleterious effect was noted on pregnancy rate or on percent of live births, but a decrease in body weight gain and survival rate was

noted among offspring of drug-treated females. In another study, paracetamol 250 mg/kg/d did not affect foetal length or weight, incidence of resorptions, or placental weight.

6. Pharmaceutical Particulars

6.1 List of excipients

Brufen Extra contains:

- colloidal silicon dioxide
- crospovidone
- hypromellose
- magnesium stearate
- microcrystalline cellulose
- opadry silver special effects 63F97546
- povidone
- pregelatinized maize starch
- purified talc
- purified water
- titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Al/PVC/PVdC Blister packs of 36, 60 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Pharmacy Only Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

20 December 2018

10. Date of Revision of the Text

15 May 2023

Section Changed	Summary of New Information
4.4	Addition of DRESS syndrome
4.6	Updated warning information regarding use during pregnancy
4.8	Addition of Photosensitivity reactions
5.2	Minor editorial update

BRUFEN® is a Viatris company trade mark.