NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Nurofen 12 Hour, Modified release tablet, Ibuprofen 300mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 300 mg prolonged release tablet contain 300 mg of ibuprofen.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Nurofen 12 hour, Modified release tablet, Ibuprofen 300mg: White to off-white capsule-shaped tablets debossed with 'N12' on one side and plain on the other.

Do not halve the tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the temporary relief of pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, neuralgia, and colds and flu symptoms. Reduces fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The minimum effective dose should be used for the shortest time necessary to relieve symptoms.

Adults and children from 12 years:

Initial dose of 600 mg. Then, if necessary, another 600 mg can be taken. Leave at least 12 hours between doses. Do not take more than 1200 mg in 24 hours.

You should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3 days (in case it is taken for fever) or 5 days (in case it is taken for pain).

Paediatric population:

This medicine should not be used by children or adolescents under the age of 12 years.

Method of administration

For oral use and short term use only.

The tablets should be taken together with water and swallowed whole. Do not chew the tablets.

4.3 CONTRAINDICATIONS

Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity (e.g. asthma, rhinitis, or urticaria) to acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

History of ulcerative colitis, Crohn's disease, recurrent peptic ulcer or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure (NYHA IV)

Severe liver failure.

Severe renal failure (glomerular filtration below 30 mL/min).

Conditions involving increased tendancy or active bleeding.

During the third trimester of pregnancy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prolonged use of any painkillers may induce headaches, which must not be treated with increased doses of the painkillers, including ibuprofen.

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

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment 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 daily) is associated with an increased risk of myocardial infarction.

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.

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

Hypertension

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives 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 reported in association with ibuprofen, therefore, the medicine should be used with caution in patients with a history of heart failure or hypertension.

Cardiovascular and cerebrovascular effects

Cases of Kounis syndrome have been reported in patients treated with ibuprofen-containing products such as Nurofen 12 Hour. 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.

Gastrointestinal (GI) events

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

All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, as well as patients requiring concomitant low dose aspirin, or for other drugs likely to increase gastrointestinal risk (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The concomitant administration of ibuprofen and other NSAIDs, including cyclooxygenase-2 (Cox-2) selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur

in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about signs and symptoms of serious gastrointestinal toxicity.

Caution should be exercised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or antiplatelet drugs such as aspirin (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Severe cutaneous adverse reactions (SCARs)

NSAIDs may very rarely cause severe cutaneous adverse reactions (SCARs), such as exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) Syndrome), Stevens-Johnson syndrome (SJS) and acute generalised exanthematous pustulosis (AGEP), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. 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 withdrawn immediately, and an alternative treatment considered (as appropriate).

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissue 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. Infections and infestations

Exacerbation of skin infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of ibuprofen the patient is therefore recommended to go to a doctor without delay.

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.

Respiratory disorder

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease. Administer with caution in patients suffering from these conditions.

Ophthalmological effects

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

Impaired liver function or a history of liver disease

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.

Impaired renal function

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children and adolescents.

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, nephrotic 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 NSAIDs may result in deterioration of renal function.

Renal tubular acidosis and hypokalaemia may occur following treatment with ibuprofen. The risk is increased with higher doses of ibuprofen and following acute overdose, however it may also occur within the recommended dose range.

Presenting signs and symptoms may include reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

The long-term concomitant intake of various analgesics further increases the risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long term treated patients.

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

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

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

Masking signs of infection

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

Withdrawal of concomitant steroid therapy

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concurrent use of NSAIDs and warfarin has been associated with severe sometimes fatal haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin.

Ibuprofen should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

Lithium: There is evidence for potential decreases in renal clearance and increases in plasma levels of lithium.

Lithium plasma concentrations should be monitored in patients concurrent ibuprofen therapy.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increased plasma glycoside levels. Care should be therefore be taken in patients treated with cardiac glycosides.

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

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Other analgesics: Avoid concomitant use of two or more NSAIDS as this may increase the risk of adverse effects (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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. ***Ciclosporin or tacrolimus:*** Increased risk of nephrotoxicity when used with NSAIDs.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

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 hypoglycemia in patients on sulfonylurea medications receiving ibuprofen.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Others: Ibuprofen like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors, angiotensin II- receptor antagonists and beta-blockers with possible loss of blood pressure control and

can attenuate the natriuretic effects of diuretics. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined use of the three classes of drugs, diuretics, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Methotrexate: NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction of clearance of methotrexate may occur. Use of high doses of methotrexate concomitant with NSAIDs should be avoided. At low doses of methotrexate caution should be used if ibuprofen is administered concomitantly.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Use in pregnancy – Pregnancy Category C

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses 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.

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 or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. 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 Nurofen 12 Hour tablet if oligohydramnios occurs. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to the following:

- Cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions, which may result in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Use in labour and delivery

Administration of ibuprofen is not recommended during labour and delivery. The onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

Use in lactation.

Ibuprofen is not recommended for use in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Following treatment with ibuprofen, the reaction time of patients may be affected. Care should be taken when driving or operating machinery as the activity may be affected by dizziness, drowsiness, fatigue and visual disturbance. This applies to a greater extent in combination with alcohol.

4.8 UNDESIRABLE EFFECTS

The frequencies of adverse effects are defined as follows:
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,* including isolated reports.
Not known: Cannot be estimated from the data available

Blood and Lymphatic System Disorders:
Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis)
No frequency information available: aplastic anemia and haemolytic anaemia

Investigations:
Very rare:, Haemoglobin decreased
No frequency information available: Haematocrit decreased

Eye Disorders
No frequency information available: Visual disturbance

Gastrointestinal disorders:
Uncommon: Abdominal pain, nausea, dyspepsia
Rare: Diarrhoea, flatulence, constipation and vomiting
Very rare: Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis, Ulcerative stomatitis, gastritis.
Not known: Exacerbation of ulcerative colitis and Crohn's disease,
No frequency information available: heartburn, loss of appetite, abdominal upper pain, abdominal distension

Nervous System Disorders:
Uncommon: Headache
Very rare: Aseptic meningitis
No frequency information available: Dizziness, fatigue, cerebrovascular accident

Psychiatric disorders:
No frequency information available: Nervousness

Immune System disorders
Uncommon: Hypersensitivity reactions with urticaria and pruritus
Very rare: severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, , tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties are usually transient and reversible on cessation of treatment.

Cardiac Disorders:
Unknown: Cardiac failure, Fluid retention, oedema and Kounis syndrome
No frequency information available: myocardial infarction, angina pectoris
Vascular Disorders:
Unknown: Hypertension
Ear and labyrinth Disorders:
Frequency information not available: Tinnitus, vertigo

Hepatobiliary Disorders
Very rare: Liver Disorder
Hepatic function abnormal, hepatitis, jaundice

Infections and Infestations:
Very rare: Meningitis aseptic, meningitis

Renal and Urinary Disorders:
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.
Frequency information not available: Haematuria, interstitial nephritis, nephrotic syndrome, proteinuria, renal tubular acidosis*, hypokalaemia*

*The risk is increased with higher doses of ibuprofen and following acute overdose, however it may also occur within the recommended dose range.

Respiratory, Thoracic and Mediastinal Disorders
Not known: Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea

Frequency information not available: wheezing

Skin and Subcutaneous Tissue Disorders:

Uncommon: Various skin rashes

Very rare: Severe cutaneous adverse reactions (SCARs), bullous reactions including Stevens Johnson Syndrome, erythema multiform and toxic

epidermal necrolysis, exfoliative dermatitis, maculopapular, purpura, uticaria, Rash.
Unknown: Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS), Acute generalized exanthematous pustulosis (AGEP), Photosensitivity reactions
Frequency information not available: Face oedema, rash maculopapular

Pregnancy, puerperium and perinatal conditions:
Unknown: Oligohydramnios, neonatal renal impairment

General disorders and administration site conditions:
Frequency information not available: Oedema, swelling, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine 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 at https://pophealth.my.site.com/carmreportnz/s/

4.9 OVERDOSE

Toxicity:

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Symptoms:

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 – 6 hours. The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include tinnitus, headache, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. Renal tubular acidosis and hypokalaemia may occur. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8). In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

Treatment:

There is no specific antidote for ibuprofen overdose. Gastric emptying followed by supportive measures is recommended if the quantity ingested exceeds 400 mg/kg within the previous hour. For advice on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroidal

ATC code: M01AE01

Mechanism of action

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Clinical trials

Experimental data suggests that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane of platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusion can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

The analgesic effects of a 2 tablet -dose (600 mg) of prolonged release ibuprofen last for up to 12 hours.

In a multiple dose dental pain study a 600 mg dose of Nurofen 12 hour modified release tablets was studied when dosed every 12 hours for 2 days. Nurofen 12 hour modified release tablets were statistically significantly superior to placebo across all endpoints, at all time points from 30 minutes postdose for pain intensity difference ($p < 0.05$) and at all time points from 15 minutes for pain relief ($p < 0.05$). Early onset of efficacy was indicated by the shorter time to confirmed first perceptible relief after active (median time = 42 minutes) compared to placebo treatment ($p < 0.0001$) and shorter time to meaningful relief for active (median time = 108 minutes) compared to placebo treatment ($p < 0.0001$). Median time to first rescue medication was not achieved for active treatment over the first 12 hour dosage period.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins. Peak serum concentration occurs approximately 1-2 hours after administration for immediate-release ibuprofen. Nurofen 12 hour is designed to mimic the early-release characteristics of immediate-release ibuprofen with prolonged release properties that maintain consistent release over a 12-hour dosing interval.

The pharmacokinetic profile of 600 mg of Nurofen 12 hour, compared with that of three doses of 200 mg immediate-release tablets (4 hourly), showed that the prolonged release formulation achieved consistent release throughout the interval evaluated. The time to the minimum effective concentration (6.4 μg/ml) was similar between the prolonged release and immediate-release tablets (0.829 hours for the prolonged release tablets and 0.619 hours for the immediate-release tablets). The prolonged release tablet also remained at significant levels at 12 hours (8.4 μg/ml).

Compared with immediate-release tablets, the area under the plasma concentration-time curve (AUC) for prolonged release tablets was similar.

Biotransformation

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen.

Elimination

Excretion by the kidney is both rapid and complete. Elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Silicon dioxide, hypromellose, silicified microcrystalline cellulose, croscarmellose sodium, glycine, stearic acid, opadry yellow (consisting of: hypromellose, quinoline yellow, titanium dioxide, macrogol and polysorbate 80), carnauba wax.

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25^{o}C.

6.5 NATURE AND CONTENTS OF CONTAINER

Ibuprofen 300 mg tablets: Blister packs comprised of Alu/Alu enclosed in an outer carton containing 6, 8, 10, 12, 16, 20 or 24 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

Restricted medicine.

8 SPONSOR

Reckitt Benckiser (New Zealand) Ltd
Private Bag 93523
Takapuna
Auckland 0740

9 DATE OF FIRST APPROVAL

TBA

10 DATE OF REVISION OF THE TEXT

9 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of information on severe cutaneous adverse reactions (SCARs), Kounis syndrome, renal tubular acidosis and hypokalaemia
4.8	Addition of severe cutaneous adverse reactions (SCARs), Kounis syndrome, renal tubular acidosis and hypokalaemia
4.9	Addition of renal tubular acidosis and hypokalaemia