New Zealand Datasheet

1 PRODUCT NAME
IBUGESIC

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ibuprofen tablets 200 mg

3 PHARMACEUTICAL FORM
White to off-white circular biconvex film coated tablets, plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
IBUGESIC tablets are indicated for analgesic and anti-inflammatory effect in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, IBUGESIC tablets are indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low-back pain.

IBUGESIC tablets can also be used in soft-tissue injuries such as sprains and strains.

IBUGESIC tablets are also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain.

IBUGESIC tablets are also indicated for the relief of neuralgia, migraine, headache, feverishness and for the relief of the symptoms of cold and influenza.

4.2 Dose and method of administration
After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest duration should be used.

Adults: The recommended initial daily dose of IBUGESIC tablets is 1200-1800 mg per day in divided doses. Some patients can be maintained on 600 -1200 mg per day. In severe of acute conditions it can be advantageous to increase the dosage until the acute phase is brought under control, providing that the total daily dose does not exceed 2400 mg in divided doses.

Children: The daily dosage of IBUGESIC tablets is 20 mg per kg of body weight in divided doses. In juvenile rheumatoid arthritis up to 40 mg per kg of bodyweight in divided doses may be given. In children weighing less than 30 kg the total dose should not exceed 500 mg in a 24 hour period.

Elderly: Elderly patients are more prone to adverse effects. Caution must be taken with dosage in this group and also in patients with renal impairment or impaired liver function.

4.3 Contraindications
Known hypersensitivity to ibuprofen.

Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other non-steroidal anti-inflammatory drugs. As with other non-steroidal anti-inflammatory agents, ibuprofen should not be given to patients vulnerable to gastrointestinal ulceration and bleeding and haemorrhagic diathesis.

Severe heart failure, severe liver failure, severe renal failure (glomerular filtration below 30 mL/min).

Conditions involving an increased tendency or active bleeding.

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

During the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Ibuprofen should not be given to patients in whom aspirin and other non-steroidal anti-inflammatory medicines induce the symptoms of asthma, rhinitis or urticaria.

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents. Any patient who develops visual disturbances during treatment with ibuprofen should have an ophthalmological examination. In patients with systemic lupus erythematosus the risk/benefit ratio has to be analysed before prescribing ibuprofen. This is a danger due to the possibility of severe generalised hypersensitivity reaction.

Non-steroidal anti-inflammatory agents have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In patients with renal cardiac or hepatic impairment, caution is required since the use of non-steroidal anti-inflammatory agents 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.

Cardiovascular Thrombotic Events

Epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg/ daily) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events such as 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 arterial thrombotic events, particularly myocardial infarction.

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 longer-term 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 NSAID use.

Infections and infestations

Exacerbation of 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.

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 initiation 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.

Hypertension
NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives 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.

Gastrointestinal Events
All NSAIDs can cause gastrointestinal discomfort and rarely 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 approximately 1% of patients treated for 3-6 months and in about 2-4% patents 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.

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 the signs and symptoms of serious gastrointestinal toxicity.

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

Severe Skin Reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in association with the use of NSAIDSs (see section 4.8). 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. 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.

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen, like other NSAIDs can reduce the antihypertensive effect ACE inhibitors and beta blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and frusemide.

Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal haemorrhage. The mechanism of this interaction is not known but may be involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with anticoagulant effect of warfarin. Ibuprofen should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

NSAIDs may increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Anti-platelet agents
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding

Aminoglycosides:
NSAIDs may decrease the excretion of aminoglycosides

ACE Inhibitors
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 Warnings and Precautions).

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Corticosteroids:
Increased risk of gastrointestinal bleeding.

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 Actions).

Cyclosporin 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.

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

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

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.

Pregnancy
Category C
Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given in the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and delay labour and birth. Continuous treatment with non-steroidal anti-inflammatory drugs during the last trimester of pregnancy should be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandins synthesis should be avoided.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/foetal development. Some data from epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early

pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. During the first and second trimester of pregnancy, Ibugesic should not be given unless clearly necessary. If Ibugesic is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible.

Lactation
In the limited studies so far available, ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely. However, it is not recommended for nursing mothers unless the expected benefits to the mother outweigh the potential risk to the neonate.

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
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 Warnings and Precautions). 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

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
Acute generalised exanthematous pustulosis (AGEP)
Drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders:
Conjunctivitis, diplopia, optic neuritis, cataracts

Blood and lymphatic system disorders
Bleeding episodes (eg 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

Additional Post-Marketing Adverse Reactions
Gastrointestinal:
Exacerbation of colitis and Crohn's Disease (see Contraindications). Pancreatitis has been reported very rarely.

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
Clinical features of overdose with ibuprofen that may result are depression of the central nervous system and the respiratory system.

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 advice on the management of overdose contact the Poisons Information Centre on 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-inflammatory and Antirheumatic Products, Non-Steroids. ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory agent. Its mode of action, like that of other non-steroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition. Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both human and animal studies. These properties provide symptomatic relief of inflammation and pain.

5.2 Pharmacokinetic properties
Ibuprofen is well absorbed after oral administration. A single dose of 200mg taken on an empty stomach by volunteers produced peak serum levels after approximately 45 minutes. When taken after food, the absorption of ibuprofen was slower, and peak serum levels appeared between 1.5 and 3 hours.

The apparent volume of distribution is 0.14 l/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant rats and rabbits. It is not known if ibuprofen enters the CSF or is excreted in breast milk.

Approximately 99% of ibuprofen is protein bound. The high protein binding should be kept in mind when prescribing ibuprofen together with other protein bound drugs that bind to the same site on human serum albumin.

Approximately 90% of ibuprofen is metabolised to two major metabolites (A and B). These are: Metabolite A (+) 2-4-(2-hydroxy-2-methylpropylphenyl) propionic acid and Metabolite B (+) 2-4-(2-carboxypropylphenyl) propionic acid. Both metabolites are dextrorotary and do not exhibit anti-inflammatory and analgesic activity.

Patients with rheumatoid arthritis and normal volunteers were given 800mg of ibuprofen as a single dose. After 14 to 24 hours the plasma levels of ibuprofen and metabolites were less than 0.25 mcg/ml.

The major route of excretion is via the kidney, with 95% of ibuprofen being excreted in the urine within 24 hours of a single dose of 500mg. Of this 35 % was excreted as metabolite A (15% free, 20% conjugated), 51% as metabolite B (42% free, 9% conjugated) and 9% as ibuprofen (1% free, 8% conjugated).

The plasma half life of ibuprofen is between 1.9 to 2.2 hours.

5.3 Preclinical safety data
Not applicable

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Hypromellose, propylene glycol, purified talc, titanium dioxide, colloidal silicon dioxide, magnesium stearate, maize starch, sodium laurilsulfate.

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Ibugesic tablets are available in PVC/Al blister packs of 120 and 1000 tablets.

6.6 Special precautions for disposal
No special requirements

7 MEDICINE SCHEDULE
Prescription Medicine

8 SPONSOR
Rex Medical Limited
PO Box 18-119, Glen Innes
Auckland

Telephone (09) 574 6060

9 DATE OF FIRST APPROVAL
10 April 2014

10 DATE OF REVISION OF THE TEXT

7 July 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of reference to Severe Skin reactions (AGEP and Masking of symptoms of underlying infections
4.8	Undesirable effects Skin and Subcutaneous Tissue Disorders Not known – Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acture generalized exanthematous pustulosis (AGEP)