New Zealand Data Sheet

1 PRODUCT NAME

Oruvail SR 200 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketoprofen (200mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release capsule.

Oruvail SR 200 mg capsules are presented pink/white capsules printed ORUVAIL SR 200.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oruvail is recommended in the management of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute articular and periarticular disorders (bursitis, capsulitis, synovitis, tendonitis), fibrositis, cervical spondylitis, low back pain, (strain, lumbago, sciatica), gout and dysmenorrhoea. Oruvail reduces joint pain and inflammation and facilitates increase in mobility and functional independence. It is also indicated in the treatment of post-operative pain.

As with other non-steroidal anti-inflammatory agents, ketoprofen does not cure the underlying disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

4.2.1 Dose

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used (see Section 4.4 Special warnings and precautions for

use). Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

200 mg once daily depending on the patient's weight and on the severity of symptoms. Oruvail SR should be taken with food.

Use in Pregnancy: see Section 4.3 Contraindications and Section 4.6 Fertility, pregnancy and lactation.

4.2.2 Elderly

It is generally advisable in the elderly to begin ketoprofen therapy at the lower end of the dosage range and to maintain such patients on the lowest effective dosage. Elderly patients are more prone to adverse effects. Caution must be taken with dosage in this group and also in patients with renal impairment.

4.3 CONTRAINDICATIONS

Active or history of gastrointestinal inflammatory disorder or ulceration, haemorrhage, chronic dyspepsia.

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

Known hypersensitivity reactions to ketoprofen, aspirin, other NSAIDs, or to any of the excipients listed in section 6.1.

Patients in whom aspirin or other NSAIDs induce symptoms of asthma, rhinitis or urticaria. Severe, rarely fatal anaphylactic reactions have been reported in such patients.

Third trimester of pregnancy (see Section 4.6 Fertility, pregnancy and lactation).

Severe heart failure.

Severe renal insufficiency.

Severe hepatic impairment.

Treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1 Cardiovascular thrombotic events

Observational studies have shown that non-selective NSAIDs may be associated with an increased risk of serious CV events including myocardial infarction, stroke and heart failure, which may increase with dose or duration of use. Additionally patients with CV disease, history of atherosclerotic CV disease or risk factors for CV disease may be at greater risk. However, to minimise the potential risk of an adverse CV event, especially in patients with CV risk factors, the lowest effective dose should be used for the shortest possible duration. There is no consistent

evidence to suggest that concurrent use of aspirin mitigates the increased risk of serious CV events associated with NSAID use.

Physicians and patients should remain alert for such CV events, even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

An increased risk for arterial thrombotic events has been reported in patients treated with non-aspirin NSAIDS for perioperative pain in the setting of coronary artery bypass surgery (see section 4.3).

4.4.2 Hypertension

NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension. Patients taking antihypertensives along with NSAIDs may have an impaired antihypertensive response and hence NSAIDs should be administered with caution in patients with hypertension. Furthermore, when given to patients with hypertension, blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Increased risk of atrial fibrillation has been reported in association with the use of NSAIDs.

4.4.3 Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs and NSAIDs should be used with caution in patients with fluid retention or heart failure.

4.4.4 Gastrointestinal events

All NSAIDs can cause GI discomfort and serious, potentially fatal GI 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.

Due to the possibility of severe gastrointestinal lesions, particular attention should be paid to any digestive disturbance and especially to gastrointestinal bleeding. This risk is especially high in patients who continue to receive anticoagulant therapy. Elderly patients are at greater risk for serious GI events. Other risk factors associated with increased risk of developing serious GI events include history of serious GI events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the medicine should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious GI toxicity and what steps to take if they occur. The risk of serious GI events associated with ketoprofen ranged from 0.03 to 1.7% with a higher incidence in elderly.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as other NSAIDs including COX-2 (cyclooxygenase-2 selective) inhibitors, oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors, nicorandil or anti-platelet agents such as aspirin (see section 4.5).

The concurrent use of NSAIDs and aspirin does increase the risk of serious GI events.

Because serious GI-tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up.

4.4.5 Serious skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (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 or duration of use. 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash or any signs of hypersensitivity.

4.4.6 Fixed Drug Eruption (FDE)

Cases of Fixed Drug Eruption (FDE) have been reported with Oruvail SR.

Oruvail SR should not be reintroduced in patients with history of related FDE.

4.4.7 Drug reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients using NSAIDs. Some of these events have been fatal or life-threatening. DRESS 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 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.

4.4.8 Steroid therapy

Withdrawal of concomitant steroid therapy. It is recommended that if steroids are reduced or discontinued during ketoprofen therapy, the dose should be reduced slowly and the patients should be monitored closely for adverse effects, particularly adrenal insufficiency and exacerbation of the symptoms of rheumatoid arthritis.

4.4.9 Infection

Masking of symptoms of underlying infections:

Oruvail SR can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial

community acquired pneumonia and bacterial complications to varicella. When Oruvail SR is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

4.4.10 Haematology

There have been sporadic reports of decreased haematocrit and haemoglobin values without progressive deterioration on prolonged administration of the medicine. Anaemia is commonly observed in rheumatoid arthritis patients and is sometimes aggravated by non-steroidal anti-inflammatory medicines which may produce fluid retention or significant gastrointestinal blood loss in some patients. Patients on long-term treatment with NSAIDs including ketoprofen, should have their haemoglobin or haematocrit checked if they develop signs or symptoms of anaemia.

4.4.11 Renal function

Inhibition of renal prostaglandin synthesis by NSAIDs may interfere with renal function, especially in the presence of existing renal disease. As with other NSAIDs, ketoprofen should be used with caution in patients with renal impairment. At the start of treatment and periodically, renal function must be carefully monitored in patients with heart failure, cirrhosis and nephrosis, in patients receiving diuretic therapy, in patients with chronic renal impairment, particularly if the patient is elderly. In these patients, administration of ketoprofen may induce a reduction in renal blood flow caused by prostaglandin inhibition and lead to renal decomposition. Abnormalities in LDH and BUN have occurred in patients on ketoprofen therapy.

4.4.12 Hyperkalaemia

Hyperkalaemia may occur, especially in patients with underlying diabetes, renal failure, and/or concomitant treatment with hyperkalaemia promoting agents. Potassium levels must be monitored under these circumstances (see section 4.5).

4.4.13 Hepatic function

Impaired hepatic function. Serious hepatic adverse events appear to be rare with ketoprofen. Rare cases of jaundice and hepatitis have been described with ketoprofen. With NSAIDs abnormal liver function test (such as elevation of AST, ALT and SAP) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.

Physicians and patients should remain alert for the hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the steps to take should these signs and/or symptoms occur. If an abnormal liver function test occurs, it should be monitored until it returns to normal. If a significant abnormality persists, ketoprofen should be discontinued. It is recommended that in those patients with a history of liver dysfunction periodic liver function test be carried out.

4.4.14 Plasma protein binding drugs

Ketoprofen is highly protein bound. Concomitant use of other protein binding medicines, eg. anticoagulants, sulphonamides, hydantoins, might necessitate modification of dosage in order to avoid increased levels of such medicines resulting from competition for protein binding sites.

4.4.15 Ophthalmological effects

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents; accordingly, in patients who develop visual disturbances during treatment with Oruvail SR, treatment should be discontinued pending a complete ophthalmological examination.

Patients should be warned about the potential for somnolence, dizziness or convulsions, and advised not to drive or operate machinery if these symptoms occur.

4.4.16 Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including Oruvail SR, from about 13 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 13 weeks and 30 weeks gestation, it should be managed under medical supervision and limit Oruvail SR use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Oruvail SR treatment extends beyond 48 hours. Discontinue Oruvail SR if oligohydramnios occurs and follow up according to clinical practice (see Section 4.6 Fertility, pregnancy and lactation).

4.4.17 Risk of Fetal Death

Oruvail SR may increase risk of fetal death even after a single dose due to its cardiopulmonary and/or renal toxicity (constriction of the ductus arteriosus and the occurrence of oligohydramnios) (see Section 4.6 Fertility, pregnancy and lactation).

4.4.18 Fertility

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

4.4.19 Paediatric population

Ketoprofen is not recommended for children under 12 years since safety and efficacy in this age group have not been established.

4.4.20 Use in the elderly

In pharmacokinetic studies, ketoprofen clearance was reduced in older patients receiving ketoprofen, compared with younger patients. Peak ketoprofen concentrations and free drug AUC were increased in older patients. The glucuronide conjugate of ketoprofen, which can serve as a potential reservoir for the parent drug, is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. It is recommended that the initial dosage of ketoprofen should be reduced for patients over 75 years of age and it may be useful to monitor renal function. In addition, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients may be more sensitive to the anti-prostaglandin effects of NSAIDS (on the gastrointestinal tract and kidneys) than younger patients. In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Therefore, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose. See Section 4.2 Dose and Method of Administration.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

The following interactions have been studied using conventional ketoprofen at a dose of 200 mg daily.

4.5.1 Medicinal products that can promote hyperkalaemia.

The risk of hyperkalaemia can be enhanced when ketoprofen is administered concomitantly with potassium salts, potassium-sparing diuretics, ACE inhibitors and angiotensin II antagonists, NSAIDs, heparins (low molecular-weight or unfractioned), ciclosporin, tacrolimus and trimethoprim (see section 4.4).

4.5.2 Antacids

Concomitant administration of magnesium hydroxide and aluminium hydroxide does not interfere with the rate or extent of the absorption of ketoprofen.

4.5.3 NSAIDs (including cyclooxygenase-2 selective inhibitors) and high dose salicylates (eg. Aspirin)

Ketoprofen may present an additive effect with other NSAIDs (increased risk of gastrointestinal ulcer and/or haemorrhage). Therefore, concomitant administration is not advised.

Ketoprofen does not alter aspirin absorption. However, in a study of 12 normal subjects, concurrent administration of aspirin decreased ketoprofen protein binding and increased ketoprofen plasma clearance from 0.07 L/kg/hour without aspirin to 0.11 L/kg/hour with aspirin. The clinical significance of these changes has not been adequately studied. Therefore, concurrent use of aspirin and ketoprofen is not recommended.

4.5.4 Diuretics

Hydrochlorothiazide given concomitantly with ketoprofen produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients and particularly dehydrated patients, taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. Such patients should be rehydrated before initiating coadministration therapy and renal function monitored when the treatment is started.

4.5.5 Digoxin

In a study of 12 patients with congestive heart failure where ketoprofen and digoxin were concomitantly administered, ketoprofen did not alter the serum levels of digoxin. However, caution is advised, in particular in patients with renal impairment, since NSAIDS may reduce renal function and decrease renal clearance of cardiac glycosides.

4.5.6 Lithium

There is a risk of elevation of plasma lithium levels, sometimes reaching toxic levels, due to decreased lithium renal excretion. Where necessary, plasma lithium levels should be closely monitored and the lithium dosage levels adjusted during and after NSAIDs therapy.

4.5.7 Parenteral heparin and platelet aggregation inhibitors (ie. ticlopidine, clopidogrel)

Increased risk of bleeding. If concomitant administration is unavoidable, patient should be closely monitored including laboratory test results (bleeding time).

4.5.8 Thrombin inhibitors (such as dabigatran), Direct factor Xa inhibitors (such as apixaban, rivaroxaban)

Increased risk of bleeding. If coadministration is unavoidable, patient should be closely monitored.

4.5.9 Vitamin K antagonists (such as warfarin)

Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal haemorrhage. The exact mechanism of the interaction between NSAIDs and warfarin is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Ketoprofen should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of medicines should be closely monitored.

4.5.10 Probenecid

Probenecid increases both free and bound ketoprofen through reducing the plasma clearance of ketoprofen to about one-third as well as deceasing its protein binding. Therefore, the combination of ketoprofen and probenecid is not recommended.

4.5.11 Methotrexate

4.5.11.1 Methotrexate at doses greater than 15mg/week

Methotrexate is highly protein bound and may be displaced by NSAIDs including ketoprofen. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in severe haematologic and gastrointestinal toxicity which may lead to death.

4.5.11.2 Methotrexate at doses lower than 15mg/week

During the first weeks of combination treatment, full blood count should be monitored weekly. If there is any alteration of the renal function, or if patient is elderly, monitoring should be more frequent.

4.5.12 Ciclosporin and Tacrolimus

There is increased risk of nephrotoxicity.

4.5.13 Pentoxifylline

There is an increased risk of bleeding. More frequent clinical monitoring and monitoring of bleeding time is required.

4.5.14 Tenofovir

Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

4.5.15 Nicorandil

In patients concomitantly receiving nicorandil and NSAIDS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4)

4.5.16 Antihypertensive agents (beta-blockers, angiotensin converting enzyme inhibitors, diuretics)

Risk of decrease in antihypertensive potency (inhibition of vasodilator prostaglandins by NSAIDs).

4.5.17 ACE inhibitors and Angiotensin II antagonists

In patients with compromised renal function (e.g. dehydrated patients or elderly patients), the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure.

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

Concomitant use of a renin-angiotensin system inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of medicine. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter.

4.5.19 Thrombolytics

There is an increased risk of bleeding.

4.5.20 Gemeprost

The efficacy of gemeprost may be reduced.

4.5.21 IUD

The efficacy of IUDs may be reduced and result in a pregnancy.

4.5.22 Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

4.5.23 Selective serotonin reuptake inhibitors (SSRI's)

Increased risk of gastrointestinal bleeding (see Section 4.4 Special Warnings and Precautions for Use – Gastrointestinal Events).

4.6 FERTILITY, PREGNANCY AND LACTATION

4.6.1 Pregnancy

Pregnancy Category C - Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

4.6.1.1 During the first and second trimesters

In mice and rats there is no evidence of teratogenicity or embryotoxicity. In the rabbit slight embryotoxicity likely related to maternal toxicity has been reported. The use of Oruvail SR during the first and second trimesters of pregnancy should be avoided unless clearly necessary. If ketoprofen is used, the dose should be kept as low and duration of treatment as short as possible (see Section 4.4 Special warnings and precautions for use).

4.6.1.2 During the second and third trimesters

Use of NSAIDs, including Oruvail SR, from about 13 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment (see Section 4.4 Special warnings and precautions for use).

Fetal and neonatal toxicity

During the second and third trimesters of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (constriction/ premature closure of the ductus arteriosus and pulmonary hypertension); which resolves after treatment cessation in majority of cases. Premature closure of ductus arteriosus and pulmonary hypertension may lead to right fetal or neonatal heart failure or fetal death *in utero*. This risk is greater and less likely to be reversible when administered closer to term. This effect exists even after a single dose. Antenatal monitoring for ductus arteriosus constriction should be considered after exposure to Oruvail SR from gestational week 13 onward. Oruvail SR should be discontinued if ductus arteriosus constriction is found.
- renal dysfunction with associated oligohydramnios which may progress to renal failure and fetal death *in utero*.

NSAIDs have an inhibitory effect on prostaglandin synthesis and, when given during the latter part of pregnancy, may cause cardiopulmonary (closure of the fetal ductus arteriosus) and renal toxicity. When given at term, they prolong labour and delay parturition.

At the end of the pregnancy:

- prolonged bleeding time in both the mother and child may occur.
- inhibition of uterine contractions resulting in delayed or prolonged labour may occur.

Therefore, Oruvail SR is contraindicated during the last trimester of pregnancy.

4.6.2 Breast-feeding

No data are available on excretion of ketoprofen in human milk. In rats, ketoprofen at doses of 9mg/kg (54 mg/m2/day; approximately 0.3 times the maximum recommended human therapeutic dose) did not affect perinatal development. Upon administration to lactating dogs, the milk concentration of ketoprofen was found to be 4 to 5% of the plasma drug level. As with other medicines that are excreted in milk, ketoprofen is not recommended for use in nursing mothers.

4.6.3 Fertility

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about the potential for somnolence, dizziness or convulsions and be advised not to drive or operate machinery if these symptoms occur.

4.8 UNDESIRABLE EFFECTS

4.8.1 a. Summary of the safety profile

More common reactions observed with ketoprofen with incidence greater than 3% include dyspepsia (11.5%), nausea, abdominal pain, diarrhoea, constipation, flatulence, headache, CNS inhibition or excitation, impairment of renal function (oedema, increased BUN).

4.8.2 b. Tabulated summary of adverse reactions

The undesirable effects are presented in the following table by system/organ class, and are ranked by frequency, using the following convention:

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
Not known cannot be estimated from the available data

4.8.3 System organ class	4.8.4 Frequency and symptom
Blood and lymphatic system disorders	**4.8.5 Uncommon** Hypocoagulability, agranulocytosis, anaemia, haemolysis, purpura, thrombocytopenia, bone marrow aplasia, hemolytic anemia, leucopenia.
Immune system disorders	**4.8.6 Uncommon** Chills, oedema, pain, allergic reaction, anaphylactic reactions (including shock).
Metabolism and nutrition disorders	**4.8.7 Uncommon** Thirst, weight gain, weight loss, hepatic dysfunction, hyponatraemia, hyperkalaemia, elevations of transaminases levels, rare cases of hepatitis.
Nervous system disorders	**4.8.8 Common** Headache, dizziness, CNS inhibition or excitation. **4.8.9 Uncommon** Amnesia, confusion, impotence, migraine, paraesthesia, vertigo, fatigue, tension, anxiety, drowsiness, convulsions, depression, hallucinations, aseptic meningitis, mood disorder. Taste perversion. **4.8.10 Rare** Aseptic meningitis has been reported as a potential rare adverse effect from the administration of several anti-inflammatory medications, including selective and non-selective COX inhibitors.
Eye disorders	**4.8.11 Common** Visual disturbance. **4.8.12 Uncommon** Conjunctivitis, conjunctivitis sicca, eye pain, retinal haemorrhage and pigmentation change.

4.8.3 System organ class	4.8.4 Frequency and symptom
Ear and labyrinth disorders	**4.8.13 Common** Tinnitus. **4.8.14 Uncommon** Hearing impairment.
Cardiac disorders	**4.8.15 Uncommon** Palpitation, tachycardia, congestive heart failure, exacerbation of heart failure, atrial fibrillation.
Vascular disorders	**4.8.16 Uncommon** Hypertension, peripheral vascular disease, vasodilation, vasculitis (including leukocytoclastic vasculitis), bruising.
Respiratory disorders	**4.8.17 Uncommon** Dyspnoea, haemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm (particularly in patients with hypersensitivity to aspirin and other NSAIDs), laryngeal oedema, asthma.
Gastrointestinal disorders	**4.8.18 Very Common** Dyspepsia (11.5%). **4.8.19 Common** Nausea, abdominal pain, diarrhoea, constipation, flatulence, anorexia, vomiting, stomatitis, gastralgia. **4.8.20 Uncommon** Appetite increase, dry mouth, eructation, gastralgia, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, constipation, flatulence, gastritis, stomatitis, rectal haemorrhage, melaena, faecal occult blood, salivation, peptic ulcer, gastrointestinal perforation, haematemesis, intestinal ulceration, gastrointestinal bleeding, exacerbation of colitis and Crohn's disease, pancreatitis. Mouth ulcers, sore tongue, inflammation of the mouth and gum.

4.8.3 System organ class	4.8.4 Frequency and symptom
Skin and subcutaneous tissue disorders	**4.8.21 Common** Rash. **4.8.22 Uncommon** Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, angio-oedema, bullous rash including Stevens-Johnson and toxic epidermal necrolysis, exfoliative dermatitis, photosensitivity discolouration, onycholysis, flushing, acute generalized exanthematous pustulosis. Dermatological reactions, rash, pruritus, urticaria, angioedema.
Musculoskeletal and connective tissue disorders	**4.8.23 Uncommon** Myalgia.
Renal and urinary disorders	**4.8.24 Common** Impairment of renal function (oedema, increased BUN), signs or symptoms of urinary tract irritation. **4.8.25 Uncommon** Menometrorrhagia, haematuria, renal failure, abnormal renal function tests, interstitial nephritis, nephrotic syndrome.
Infections and Infestations	**4.8.26 Unknown** 4.8.27 Oruvail SR can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of infection (including bacterial community-acquired pneumonia and bacterial complications to varicella (see Section 4.4 Special warnings and precautions for use).

4.8.28 c. Post Marketing Experience:

Pregnancy, puerperium and perinatal conditions

Unknown: Oligohydramnios, neonatal renal impairment, fetal death (see Section 4.4 Special warnings and precautions for use and Section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders

Unknown: Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS), Fixed Drug Eruption (FDE).

Gastrointestinal disorders

Unknown: Formation of intestinal diaphragm-like strictures.

Intestinal diaphragm disease has been reported in association with chronic use.

4.8.29 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://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Signs and symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, abdominal pain, nausea and vomiting which are generally reversible with supportive care. Respiratory depression, coma or convulsions have occurred following large ketoprofen overdoses. Gastrointestinal bleeding, hypotension, hypertension, or acute renal failure may occur but are rare.

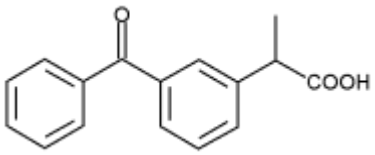
Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients with symptoms seen within 4 hours (longer for sustained release products) or following a large overdose (5 to 10 times the usual dose). Administration of activated charcoal in an attempt to reduce absorption of ketoprofen should be considered. Forced diuresis, alkalinization of the urine, haemodialysis or haemoperfusion would probably not be useful due to ketoprofen's high protein binding.

Owing to the sustained release characteristics of Oruvail SR it should be expected that ketoprofen will continue to be absorbed for up to 16 hours after ingestion.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1.1 Chemical Structure



5.1.2 CAS Number

22071-15-4

5.1.3 Description

Ketoprofen is DL-2-(3-benzoylphenyl) propionic acid. It is a white or off-white powder with melting point of about 93°C. MW: 254.3. Ketoprofen is very slightly soluble in water at 20°C, 2% soluble in dimethylformide and readily soluble in benzene, ethanol, chloroform, acetone and ethyl acetate at 20°C.

5.2 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, ATC code: M01AE03

Animal pharmacological studies have shown that ketoprofen has anti-inflammatory, analgesic and antipyretic properties. It also inhibits prostaglandin synthetase. Ketoprofen has been shown to possess antibradykinin activity in guinea pigs and mice. Inhibition of platelet aggregation has been demonstrated in rabbits.

Ketoprofen reduces joint pain and inflammation and facilitates increase in mobility and functional independence. As with other NSAIDs, it does not cure the underlying disease.

5.3 PHARMACOKINETIC PROPERTIES

Ketoprofen is readily absorbed from the gastrointestinal tract, peak plasma concentration occur 0.5 to 2 hours after a single dose. Some retardation in absorption occurs with food. The plasma half-life is about 1.6 to 1.9 hours. Binding to serum proteins (to albumin) of about 62 to 93% has been observed. Major route of metabolism involves glucuronide formation. Traces also of ring hydroxylated derivatives have been detected. Metabolites are not biologically active. Ketoprofen does not induce hepatic microsomal enzymes. Excretion of mainly metabolised (up to 55%) ketoprofen after oral administration varies greatly amongst patients, 30 to 90% of the dose being excreted in urine in 24 hours. Apparent faecal excretion of metabolites ranges over 1 to 8% of orally administered dose in 5 day collections.

The bioavailability of the suppositories is 93.6% with peak serum levels attained approximately one hour after a single dose. The absorption and elimination profiles from oral and rectal administration are identical.

The sustained release form of ketoprofen is based upon a multiple pellet system, each pellet acting as an individual delivery system bounded by a pH sensitive dialysing membrane which prevents release of ketoprofen in the stomach. About 100 pellets are needed to deliver each 100 mg of ketoprofen. Owing to gradual release of ketoprofen, maximum plasma concentrations occur around 6 hours after administration of a single dose of 200 mg of ketoprofen. These are considerably lower (3.5+1 microgram/mL) than those after a single dose of 100 mg of

conventional ketoprofen (10 microgram/mL). The release characteristics of Oruvail SR result in an apparent elimination half-life of 8.4 hours. There is some evidence that a heavy meal delays the absorption of ketoprofen from the sustained release formulation. However, the bioavailability of the product is unaffected.

Ketoprofen is eliminated by hepatic metabolism as an ester glucuronide conjugate; a minor pathway being aromatic hydroxylation, the resulting inactive metabolites being excreted by the kidney.

Peak plasma concentration of ketoprofen were higher (5 microgram/mL) and occurred later (10.1 hours) in elderly population (mean age 81) than in young healthy subjects (4.2 microgram/mL, 5.6 hours). The apparent elimination half-life was not significantly altered.

In a study using conventional ketoprofen, a decrease in ketoprofen conjugates and reduction in ketoprofen clearance was reported in elderly subjects (mean age 86.3 years).

Accumulation does not occur upon repeated administration of full adult doses of 200 mg/day provided there is no severe impairment of renal or hepatic function.

Severe impairment of renal function may result in impairment of excretion of conjugated ketoprofen and possible consequent regeneration of free ketoprofen from the conjugate.

Ketoprofen is highly protein bound.

5.3.1 Elderly: clearance & unbound fraction

The plasma and renal clearance of ketoprofen is reduced in the elderly (mean age, 73 years) compared to a younger normal population (mean age, 27 years). Hence ketoprofen peak concentration and AUC increase with increasing age. Data from one trial suggest that the increase is greater in women than in men. It has not been determined whether age-related changes in absorption among the elderly contribute to the changes in bioavailability of ketoprofen (see section 4.4).

5.4 PRECLINICAL SAFETY DATA

No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Erythrosine, ethylcellulose, gelatin, non-pareil beads (PI 1014), shellac, colloidal anhydrous silica, sodium lauryl sulfate, purified talc and titanium dioxide. The 200mg capsules also contain OPACODE BLUE (PI 12300).

6.2 INCOMPATIBILITIES

None Stated.

6.3 SHELF LIFE

36 months from the date of manufacture stored at or below 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Each capsule contains 200 mg. Pack sizes: blister pack 7◆, 28, 30◆, 100◆, bottle 28◆, 30◆, 100◆, calendar pack 1x 28◆.

◆non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

None Stated.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644

Freecall: 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

10 April 1984

10 DATE OF REVISION OF THE TEXT

30 October 2025

SUMMARY TABLE OF CHANGES

Section	Updated text
4.4	Addition of COX-2 inhibitors to cautionary statements regarding concomitant medication use
4.8	Addition of intestinal diaphragm-like strictures to adverse effects with unknown frequency