

Data Sheet

Orudis® SR Capsules

NAME OF THE MEDICINE

Non-proprietary Name

Ketoprofen

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.

PHARMACOLOGY

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.

Pharmacokinetics

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 Orudis 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.

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 '**PRECAUTIONS - Use in the elderly**').

INDICATIONS

Orudis 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. Orudis 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.

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 to ketoprofen, aspirin or other NSAIDs.

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.

Severe heart failure.

Severe renal insufficiency.

Severe hepatic insufficiency.

PRECAUTIONS

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 and patients with 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.

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.

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.

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 drug 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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see **PRECAUTIONS-Interactions with other Medicines**).

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

Serious Cutaneous Reactions

NSAIDs may very rarely cause serious cutaneous AEs such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), 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.

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.

Infection

As with other anti-inflammatory, analgesic, antipyretic drugs, ketoprofen may mask the usual signs of infection.

Haematology

There have been sporadic reports of decreased haematocrit and haemoglobin values without progressive deterioration on prolonged administration of the drug. Anaemia is commonly observed in rheumatoid arthritis patients and is sometimes aggravated by non-steroidal anti-inflammatory drugs 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.

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. Abnormalities in LDH and BUN have occurred in patients on ketoprofen therapy.

Hepatic Function

Impaired hepatic function. Serious hepatic adverse events appear to be rare with ketoprofen. Abnormalities in liver function test (such as elevations of AST, ALT and SAP) may occur. These are usually transient. 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.

Plasma protein binding drugs

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

Ophthalmological Effects

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

Use in Pregnancy

Category C

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.

During the first and second trimester

In mice and rats there is no evidence of teratogenic or embryotoxicity. In the rabbit slight embryotoxicity likely related to maternal toxicity has been reported. As the safety of ketoprofen in pregnant women has not been evaluated, the use of ketoprofen during the first and second trimester of pregnancy should be avoided.

During the third trimester

NSAIDs have an inhibitory effect on prostaglandin synthesis and, when given during the latter part of pregnancy, may cause cardiopulmonary (closure of the foetal ductus arteriosus) and renal toxicity. When given at term, they prolong labour and delay parturition and prolonged bleeding time in both mother and child may occur. Therefore ketoprofen is contraindicated during the last trimester of pregnancy.

Use in Lactation

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 drugs that are excreted in milk, ketoprofen is not recommended for use in nursing mothers.

Use in children

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

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.

Effect on Laboratory Tests

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.

Interactions with other Medicines

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

Antacids

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

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.

Diuretics

Hydrochlorothiazide given concomitantly with ketoprofen produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition.

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.

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.

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

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

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 drugs should be closely monitored.

Probenecid

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

Methotrexate

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.

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.

Pentoxifylline

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

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

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

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

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (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 drug. 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.

Thrombolytics

There is an increased risk of bleeding.

Gemeprost

The efficacy of gemeprost may be reduced.

IUD

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

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (see '**PRECAUTIONS – Steroid Therapy**' and '**Gastrointestinal Events**').

Selective serotonin reuptake inhibitors (SSRI's)

Increased risk of gastrointestinal bleeding (see '**PRECAUTIONS – Gastrointestinal Events**').

ADVERSE EFFECTS

The following adverse events have been observed with ketoprofen.

More Common Reactions

(Incidence greater than 1%)

Gastrointestinal

Dyspepsia (11.5%), nausea*, abdominal pain*, diarrhoea*, constipation*, flatulence*, anorexia, vomiting, stomatitis, gastralgia.

Central nervous system

Headache*, dizziness, CNS inhibition or excitation*.

Special senses

Tinnitus, visual disturbance.

Dermatological

Rash.

Urogenital

Impairment of renal function (oedema, increased BUN)*, signs or symptoms of urinary tract irritation.

* Incidence greater than 3%

Less Common Reactions

(Incidence less than 1%)

Gastrointestinal

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.

Central Nervous System

Amnesia, confusion, impotence, migraine, paraesthesia, vertigo, fatigue, tension, anxiety, drowsiness, convulsions, mood disorder.

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.

Special senses

Conjunctivitis, conjunctivitis sicca, eye pain, hearing impairment, retinal haemorrhage and pigmentation change, taste perversion.

Dermatological

Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, angio-oedema, bullous rash including Stevens-Johnson and toxic epidermal necrolysis, exfoliative dermatitis, photosensitivity discolouration, onycholysis, flushing.

Body as a whole

Chills, oedema, pain, allergic reaction, anaphylactic reactions (including shock).

Cardiovascular

Hypertension, palpitation, tachycardia, congestive heart failure, peripheral vascular disease, vasodilation, bruising, exacerbation of heart failure.

Haematological

Hypocoagulability, agranulocytosis, anaemia, haemolysis, purpura, thrombocytopenia, bone marrow aplasia.

Metabolic and nutritional

Thirst, weight gain, weight loss, hepatic dysfunction, hyponatraemia, elevations of transaminases levels, rare cases of hepatitis.

Mouth

Mouth ulcers, sore tongue, inflammation of the mouth and gum have been reported.

Musculoskeletal

Myalgia.

Respiratory

Dyspnoea, haemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm (particularly in patients with hypersensitivity to aspirin and other NSAIDs) laryngeal oedema, asthma.

Urogenital

Menometrorrhagia, haematuria, renal failure, abnormal renal function tests, interstitial nephritis, nephrotic syndrome.

Anorectal

These include local pain, burning, pruritus, tenesmus, rarely rectal bleeding, which have been reported in approximately 16% of patients. In clinical trials 5% of patients discontinued rectal therapy for these reasons.

Hypersensitivity reactions

Dermatological reactions, rash, pruritus, urticaria, angioedema.

DOSAGE AND ADMINISTRATION

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

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

Use in the 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.

OVERDOSAGE

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 Orudis SR it should be expected that ketoprofen will continue to be absorbed for up to 16 hours after ingestion.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Orudis SR 100 mg capsules are presented as pink/purple capsules printed ORUDIS SR 100). Each capsule contains 100 mg ketoprofen. Available in bottles of 50 and 100 capsules or a blister pack of 10, 50 and 100 capsules.

Orudis SR 200 mg capsules are presented pink/white capsules printed ORUDIS SR 200). Each capsule contains 200 mg. Available in bottles of 28, 30 and 100 capsules or a calendar pack of 28 capsules.

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

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis new zealand limited
Level 8 James and Wells Tower
56 Cawley Street
Ellerslie, Auckland
New Zealand

DATE OF PREPARATION

27 September 2011

This medicine is not currently marketed in New Zealand.