Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oruvail 200mg Prolonged-Release Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of Ketoprofen.

Excipients: Sucrose 52.62mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release capsules, Hard.
Having a transparent pink body with opaque white cap with the product name 'Oruvail 200' imprinted on both sections and containing off-white to cream coloured spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oruvail is recommended in the management of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, non-infectious arthropathy, acute articular and periarticular disorders (bursitis, capsulitis, synovitis, tendonitis), sciatica, painful musculoskeletal conditions and management of the pain of dysmenorrhoea.

Oruvail reduces joint pain and inflammation, and facilitates increase in mobility and functional independence. As with other non-steroidal anti-inflammatory agents, it does not cure the underlying disease.

4.2 Posology and method of administration

To be taken orally.

Adults Only:
The usual total daily dose is 100 to 200 mg as a single dose to be taken with food.

The maximum daily dose is 200 mg. The balance of risks and benefits should be carefully considered before commencing treatment with 200 mg daily, and higher doses are not recommended (see also section 4.4).

Elderly:
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. It is advisable to reduce the initial dosage and maintain such patients on the minimal effective dose.

Patients with impaired renal function:
It is advisable to reduce the initial dose and maintain such patients on the minimal effective dose. Individual assessment may be considered only after good individual tolerance has been ascertained.

Patients with impaired hepatic function:
These patients should be carefully monitored and kept at the minimal effective daily dosage.

Children:
The safety and effectiveness of Oruvail has not been established.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

The lowest effective dose should be used for the shortest duration to relieve symptoms (See section 4.4).

Undesirable effects may be minimised by using the shortest duration necessary to control symptoms (see section 4.4).

4.3 Contraindications

- Use in patients hypersensitive (e.g. bronchospasm, asthmatic attacks, rhinitis, urticaria) to ketoprofen, aspirin or any other non-steroidal anti-inflammatory drugs. Severe, rarely fatal, anaphylactic reactions have been reported in such patients.
- Hypersensitivity to any of the excipients of Oruvail 200mg Prolonged Release Capsules.
- Active peptic ulcer, or a history of gastrointestinal bleeding, ulceration or perforation.
- Haemorrhagic diathesis
- Severe heart failure.
- Severe hepatic insufficiency.
- Severe renal insufficiency.
- Third trimester of pregnancy.

4.4 Special warnings and precautions for use

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, Posology and method of administration, and GI and cardiovascular risks below). Patients treated with NSAIDS long term should undergo regular medical supervision to monitor for adverse events.

The use of ketoprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. (see section 4.5)

<u>Masking of symptoms of underlying infections</u>
Oruvail 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 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.

<u>Gastrointestinal reactions</u>
Caution should be advised in patients receiving combination 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 or nicorandil (See Section 4.5).

Gastrointestinal bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2).

When gastrointestinal bleeding or ulceration occurs in patients receiving Oruvail 200mg Prolonged Release Capsules, the treatment should be withdrawn.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See Section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (See below and Section 4.5).

Patient with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Some epidemiological evidence suggests that ketoprofen may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially at high doses (see also section 4.2 and 4.3).

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Cardiovascular reactions

Clinical studies and epidemiological data suggest that use of non-aspirin NSAIDS, particularly at high doses and with long-term treatment, may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

As with all NSAIDs, careful consideration should be given when treating patients with existing uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease, as well as, before initiating long term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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 (CABG)

Caution is required in patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Skin Reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (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. Oruvail 200mg Prolonged Release Capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with asthma combined with chronic rhinitis, chronic sinusitis, and/or nasal polyposis have a higher risk of allergy to aspirin and/or NSAIDs than the rest of the population. Administration of this medicinal product can cause asthma attacks or bronchospasm, particularly in subjects allergic to aspirin or NSAIDs (see section 4.3).

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

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for ketoprofen.

At the start of treatment, 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.

Clinical studies have shown a few cases in which reversible increases in BUN or serum creatinine occurred during use of ketoprofen, particularly in patients with existing renal damage, or in concurrent diuretic therapy.

In patients with abnormal liver function tests or with a history of liver disease, transaminase levels should be evaluated periodically, particularly during long-term therapy. Rare cases of jaundice and hepatitis have been described with ketoprofen.

Many elderly patients have received the drug for periods of up to a year without development of renal dysfunction. However, care should be taken during use of the drug in patients with severe renal dysfunction and in the elderly particularly during prolonged therapy. Where prolonged therapy is required, patients should be reviewed regularly.

As NSAIDS can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

As with other NSAIDs, in the presence of an infectious disease, it should be noted that the anti-inflammatory, analgesic and the antipyretic properties of ketoprofen may mask the usual signs of infection progression such as fever.

If visual disturbances such as blurred vision occur, treatment should be discontinued.

The use of NSAIDs may impair female fertility and is not recommended for use 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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose- iso maltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended drug associations

Anticoagulants: Increased risk of bleeding.

- Heparin
- Vitamin K antagnoists (such as warfarin)
- Platelet aggregation inhibitors (such as ticlopidine, clopidogrel)
- Thrombin inhibitors (such as dabigatran)
- Direct factor Xa inhibitors (such as apixaban, rivaroxaban, edoxaban)

If coadministration is unavoidable, patient should be closely monitored.

Other NSAIDS (including cyclooxygenase-2 selective inhibitors) and high dose salicylates: avoid concomitant use of two or more NSAIDs. Increased risk of gastrointestinal ulceration and bleeding.

Lithium: Risk of elevation of lithium plasma 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 NSAID therapy.

Methotrexate at doses greater than 15mg/week:
Increased risk of haematologic toxicity of methotrexate, particularly if administered at high doses (> 15 mg/week), possibly related to displacement of protein-bound methotrexate and to its decreased renal clearance. In patients receiving ketoprofen therapy previously, treatment by ketoprofen should be interrupted for at least 12 hours before administration of methotrexate. When ketoprofen is to be administered following the end of methotrexate therapy, a period of at least 12 hours should also be observed before initiation of treatment.

Drug associations requiring precautions for use
Medicinal products and therapeutic categories that can promote hyperkalaemia (i.e. potassium salts, potassium-sparing diuretics, ACE inhibitors and angiotensin II antagonists, NSAIDs, heparins (low molecular-weight or unfracioned), cyclosporine, tacrolimus and trimethoprim): The risk of hyperkalaemia can be enhanced when the drugs mentioned above are administered concomitantly.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Patients and particularly dehydrated patients taking diuretics are at a 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 treatment is started (see section 4.4 Special warnings and special precautions for use).

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 the patient is elderly, monitoring should be done more frequently.

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

Tenofovir: Contomitant administration of tenofovir disoproxil fumarate and NSAID's may increase the risk of renal failure.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

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.

Drug associations to be taken into account

Anti-hypertensive agents (beta-blockers, angiotensin converting enzyme inhibitors, diuretics): Risk of decreased antihypertensive potency (inhibition of vasodilatator prostaglandins by NSAIDs).

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Cardiac glycosides: NSAIDS may exacerbate cardiac failure, reduced GFR and increase plasma cardiac glycoside levels.

Cyclosporin: increased risk of nephrotoxicity with NSAIDS.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Probenecid: Concomitant administration of probenecid may markedly reduce the plasma clearance of ketoprofen.

Thrombolytics: Increased risk of bleeding.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal 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-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. From the 20th week of pregnancy onward, Oruvail use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ketoprofen should not be given unless clearly necessary. If ketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Oruvail for several days from gestational week 20 onward. Oruvail should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction (see above), which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Lactation:
No data are available on excretion of ketoprofen in human milk. Ketoprofen is not recommended in nursing mothers.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Classification of expected frequencies:
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).

The following adverse reactions have been reported with ketoprofen in adults:

Blood and lymphatic system disorders:
- rare: haemorrhagic anaemia
- not known: agranulocytosis, thrombocytopenia, bone marrow failure, haemolytic anaemia, leucopenia

Immune system disorders:
- not known: anaphylactic reactions (including shock)

Psychiatric disorders:
- not known: depression, hallucinations, confusion, mood altered

Nervous system disorders:
- uncommon: headache, dizziness, somnolence
- rare: paraesthesia
- not known: aseptic meningitis, convulsions, dysgeusia, vertigo

Eye disorders:
- rare: vision blurred (see section 4.4)

Ear and labyrinth disorders:
- rare: tinnitus

Cardiac disorders:
- not known: heart failure

Vascular disorders:
- not known: hypertension, vasodilatation, vasculitis (including leukocytoclastic vasculitis)

Respiratory, thoracic and mediastinal disorders:
- rare: asthma
- not known: bronchospasm (particularly in patients with known hypersensitivity to ASA and other NSAIDs), rhinitis

Gastrointestinal disorders:
- common: dyspepsia, nausea, abdominal pain, vomiting

- uncommon: constipation, diarrhoea, flatulence, gastritis
- rare: stomatitis, peptic ulcer
- not known: exacerbation of colitis and Crohn's disease, gastrointestinal haemorrhage and perforation, pancreatitis

Hepatobiliary disorders:
- rare: hepatitis, transaminases increased, elevated serum bilirubin due to hepatitis disorders

Skin and subcutaneous disorders:
- uncommon: rash, pruritis
- not known: photosensitivity reaction, alopecia, urticaria, angioedema, bullous eruption including Stevens-Johnson syndrome and toxic epidermal necrolysis, acute generalised exanthematous pustulosis

Renal and urinary disorders:
- not known: renal failure acute, tubulointerstitial nephritis, nephritic syndrome, renal function tests abnormal

General disorders and administration site conditions:
- uncommon: oedema
- not known: fatigue

Metabolism and nutritional disorders:
- unknown: hyponatraemia, hyperkalaemia (see section 4.4)

Investigations:
- rare: weight increased

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product 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 via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Cases of overdose have been reported with doses up to 2.5 g of ketoprofen. In most instances, the symptoms observed have been benign and limited to lethargy, drowsiness, nausea, vomiting and epigastric pain.
There are no specific antidotes to ketoprofen overdosages. In cases of suspected massive overdosages, a gastric lavage is recommended and symptomatic and supportive treatment should be instituted to compensate for dehydration, to monitor urinary excretion and to correct acidosis, if present.
If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ketoprofen is a non-steroidal anti-inflammatory arylcarboxylic acid derivative belonging to the propionic acid group of NSAIDs.

Ketoprofen has anti-inflammatory, antipyretic properties and has central and peripheral analgesic activity.

However its mode of action is not fully explained.

It inhibits prostaglandin synthetase and platelet aggregation.

5.2 Pharmacokinetic properties

General characteristics:

Absorption: Ketoprofen is rapidly and completely absorbed from the gastrointestinal tract. When administered with high caloric food, a slight decrease of bioavailability (13%) has been observed for sustained release formulations.

Distribution: The drug is 99% bound to plasma protein. The ketoprofen diffuses into synovial fluid and in intraarticular, capsular, synovial and tendon tissues. Ketoprofen crosses the brain blood barrier and the placenta barrier. For sustained release formulations, after the plateau (5th to 12th hour) ketoprofen levels decrease with an apparent half- life of 3 to 4 hours. No accumulation of the drug has been found after repeated doses.

Biotransformation: The biotransformation of ketoprofen is characterised by two main processes, hydroxylation and conjugation with glucuronic acid, the latter being the main pathway in man. Excretion of ketoprofen as unchanged drug is very low (less than 1%). Almost all administered ketoprofen is excreted as metabolites in the urine, of which 65 to 85% of administered dose is excreted as a glucuronide metabolite.

Excretion: The drug is mainly excreted in the urine. Within five days following the oral administration, 75 to 90% of the dose is excreted in the urine. Fecal excretion is very low (1 to 8%).

Characteristics in patients:

Elderly patients:
Absorption of ketoprofen is not modified; there is an increased half-life (3h) and decreased renal and plasma clearance.

Patients with renal insufficiency:
There is a decreased renal and plasma clearance and increased half-life correlated with severity of renal failure.

Patients with hepatic insufficiency:
There are no significant changes in the plasma clearance and elimination half-life. However, the unbound fraction is approximately doubled.

5.3 Preclinical safety data

There is no other information available which could be of relevance to the prescriber in recognising the safety profile of Oruvail and which is not included in the relevant sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Sugar Spheres (sucrose & maize starch)
Colloidal Anhydrous Silica
Shellac
Ethylcellulose
Talc

Capsule Shell
Erythrosine E127
Titanium Dioxide E171
Gelatin

Printing ink
Shellac Glaze
Indigo carmine aluminium lake (E132)
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Outer cardboard carton containing blister pack made of 250 µg opaque white, unplasticated, uPVCfilm coated with 40gsm PVdC and 20 µg hard temper aluminium foil, PVC-Acrylat heat seal lacquer.

Blister strip packs of 4, 14, 28, or 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/119/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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