Regulatory Affairs Dept

24 January 2003

The Secretary
Medicines Classification Committee
Medsafe
PO Box 5013
WELLINGTON

Dear Sir/Madam

RE: Application for Reclassification of Oruvail Gel :
ORUVAIL ketoprofen 2.5% 25mg/g topical gel (TT50-2197/6)

Aventis Pharma requests approval for ORUVAIL ketoprofen 2.5% 25 mg/g topical gel to be reclassified from Pharmacy Only Medicine to General Sale Medicine.

Oruvail Gel was registered in New Zealand in 1991 for the short-term topical treatment of musculo-skeletal inflammation and injury. As a result of the reclassification of transdermal non-steroidal anti-inflammatory agents (NSAIAs) in October 1991, Oruvail Gel has been marketed as a Pharmacy Only Medicine.

The reclassification of the topical presentation of piroxicam to General Sale Medicine was recommended at the May 2000 MCC meeting, and the topical presentation of diclofenac is also currently classified as a General Sale Medicine. Aventis Pharma wishes to propose that Orudis Gel, being a topical NSAIA with a similar safety profile to that of piroxicam and diclofenac, should also be classified as a General Sale Medicine.

In support of the safety of Oruvail Gel, Aventis Pharma provides four years of safety data in the form of Periodic Safety Update Reports (PSUR). These reports include data for all presentations of ketoprofen, including the topical gel. An appendix tabulation of adverse drug reactions per formulation was included in the most recent PSUR. This appendix shows that of the 109 cases recorded, only 14 were due to use of the topical gel.

In support of the comparability of Oruvail Gel with other topical NSAIAs, a copy of a published paper on the comparison of ketoprofen, piroxicam, and diclofenac gels has been included in this application. The study concludes that in the topical treatment of acute soft tissue injuries, ketoprofen gel was superior to piroxicam and diclofenac in efficacy and also showed excellent tolerability including the lowest level of reported adverse events.

Oruvail Gel is indicated for the short term treatment of musculo-skeletal inflammation and injury, such as sports injuries, sprains, tendinitis, musculo-skeletal contusions, swelling and post-traumatic pain. This indication is for acute, self limiting conditions that are easily identified and treated by the customer. There is no need for the intervention of a health care professional and the labelling on the carton provides all the information needed for the safe and correct use of Oruvail Gel.

Should you require and further information, please do not hesitate to contact me directly on 02 9422 6419 or by email at karena.keane@aventis.com.

Yours faithfully,

Karena Keane
Senior Regulatory Affairs Associate

APPLICATION FOR RECLASSIFICATION OF

ORUVAIL ketoprofen 2.5% 25mg/g gel

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Part A :

1. International non-proprietary name : ketoprofen gel.
2. Proprietary name : Oruvail Gel.
3. Name of company requesting reclassification : Aventis Pharma Limited.
4. Dose form and strength : topical gel 2.5% (25mg/g).
5. Pack size : 30g tube and 60g tube
6. Indications : No change is proposed. Currently indicated for *"the treatment of musculoskeletal inflammation and injury, especially sports injuries; sprains, musculotendinous bruising and swelling."*
7. Present classification : Pharmacy-Only Medicine
8. Classification sought : General Sale Medicine
9. Classification status in other countries :

Country	Regulatory Status	Marketing Status
France	Approved October 1987	Prescription medicine only
Australia	Approved March 1994	Pharmacy medicine (30g and 60g)
		Rescheduling submission pending.
Sweden	Approved October 1995	Pharmacy medicine (60g)
		Prescription medicine (2 x 60g)
United Kingdom	Approved April 1992	Pharmacy medicine (30g)
		Prescription medicine (100g)
Canada	Not Registered	Not Marketed
USA	Not Registered	Not Marketed

10. Extent of usage in NZ and elsewhere : Original consent to distribute was granted in July 1991. Sales volumes for New Zealand for the calendar year 2002 were 4970 units of 30g, and 7056 units of 60g pack. According to the most recent PSUR (page 8) the world-wide exposure to ketoprofen gel is estimated at 1.6 million patients.

11. Proposed labelling: No change to the labelling is proposed, other than deletion of the signal header statement "Pharmacy-Only Medicine". A copy of the labelling, with the hand amended deletion, has been included in this submission (page 113).

12. Proposed warning statements : No change to the current warning statements is proposed. The current warning statement on the carton labelling: "***Warnings** : for external use only. Do not use if you have an asthmatic or allergic type reaction to ketoprofen. Do not apply to broken skin. Avoid contact with eyes or mucous membranes. Keep out of reach of children. Keep away from naked flame. Store in a cool place."*

13. Other products containing the same active ingredient : Aventis Pharma Limited is not aware of any other topical ketoprofen gel currently on the New Zealand market.

Part B :

1. Statement of benefits : The main benefit to be expected from reclassification of Oruvail Gel to a General Sale Medicine is the improved accessibility of the medicine to patients. In lifting the restriction of supply of Oruvail Gel, the product would become more readily available to patients at a time more convenient to them, for example, on weekends when sporting injuries commonly occur and pharmacies are often closed.

2. Ease of self-diagnosis : As per the Data Sheet (page 115) Oruvail Gel is indicated for the short term treatment of musculo-skeletal inflammation and injury, such as sports injuries, sprains, tendinitis, musculo-skeletal contusions, swelling and post-traumatic pain. This indication is for acute, self limiting conditions that are easily identified and treated by the customer. There is no need for the intervention of a health care professional and the labelling on the carton provides all the information needed for the safe and correct use of Oruvail Gel.

3. Relevant comparative data for like compounds : Oruvail Gel is comparable with other topical NSAIAs such as diclofenac and piroxicam. In support of the comparability of Oruvail Gel with other topical NSAIAs, a copy of a published paper on the comparison of ketoprofen, piroxicam, and diclofenac gels has been included in this application (Reference 1, page 122). The study concludes that in the topical treatment of acute soft tissue injuries, ketoprofen gel was superior to piroxicam and diclofenac in efficacy and also showed excellent tolerability including the lowest level of reported adverse events.

4. Local data or special considerations relating to NZ : There is no local data separately available for Oruvail Gel. Also there are no special considerations relating to New Zealand, that Aventis Pharma is aware of.

5. Interactions with other medicines : Known incompatibilities of ketoprofen with other drugs include diuretics, warfarin, methotrexate and digoxin. However, these incompatibilities relate to systemic dosing and the significantly lower plasma concentration following topical administration of ketoprofen renders the risk of incompatibility to be very small.

6. Contraindications: As per the Data Sheet, Oruvail Gel should not be applied to exudative dermatoses, eczema, infected skin lesions or broken skin. A warning to the effect that the gel should not be applied to broken skin has been included in the carton labelling.

7. Possible resistance: Tolerance for the effects of ketoprofen is not known to develop. This has been confirmed by long term efficacy in the treatment of chronic conditions such as rheumatoid arthritis and osteoarthritis. Accumulation of ketoprofen is not known to occur. In fact, systemic exposure to ketoprofen when topically administered is around one hundred times lower than local exposure. (Reference 2, page 133).

8. Adverse events: In a clinical study on the comparison of ketoprofen, piroxicam and diclofenac topical preparations, the tolerability of ketoprofen was found to be significantly better than that of piroxicam. The incidence of drug related adverse events amongst the 1575 patients recruited was very low: 0.7% with ketoprofen gel, 1.1% with diclofenac gel,

and 2.3% with piroxicam gel. This demonstrates the equal or better safety profile of ketoprofen gel. (Reference 1, page 122).

The safety aspects of the application are supported by significant clinical data in the form of PSURs covering the last four years (1998 – 2002). These reports provide safety data on the patient exposure to Oruvail Gel and demonstrate this product to have an excellent safety profile. In contrast to oral NSAID therapy, the adverse events observed with topical ketoprofen are predominantly local reactions of limited extent.

According to Appendix 11 of PSUR #9 (page 38), in a total of 181 diagnoses of adverse drug reaction there were 19 diagnoses associated with the topical gel (ie. less than 11%). The majority of these were localised skin reactions : application site reaction, dermatitis, dermatitis atopic, dermatitis bullous, erythema, photosensitivity reaction, pruritus, rash maculo-papular, rash papular, skin eruption. These adverse reactions were localised and not considered to be serious.

9. Potential for abuse or misuse : The habituation potential is extremely low. Ketoprofen is not a classic drug of dependence and possesses none of the characteristics of drugs likely to cause habituation, such as tolerance, withdrawal symptoms, alteration of consciousness, or enhancement of awareness.

   The abuse potential is also extremely low. Ketoprofen is not associated with any stimulating or eupohoric effects which may encourage abuse of the drug. Even if a deliberate attempt to overdose were made by ingestion of an entire 60g tube, the ketoprofen content is only 1.5g which is insufficient to cause a life-threatening adverse event.

   Accidental ingestion of Oruvail Gel is unlikely since the product is supplied in a tube and does not look or smell like a food. It is not likely to be attractive to children. Furthermore, the package labelling clearly states this product is for external use only.