ANNEX I

NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTES OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDER

Member State	Applicant or Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose
Belgium, Czech Republic, Denmark, Spain, Finland, Italy, Luxembourg, The Netherlands, Norway, Poland and Slovakia	Vetcare Ltd. P.O.Box 99 24101 Salo Finland	Dolovet vet 2.4g	Powder	2.4g ketoprofen per sachet of 15g powder	Cattle (adult animals weighing about 600 kg).	One bag of 15g once daily for 1 - 3 days. The powder should be mixed with water e.g. in a bottle using ½ litres of water, shaked well and administered immediately per orally to an animal.	One bag of 15g once daily for 1 - 3 days. This corresponds to 4mg ketoprofen per kg body weight.
Austria and Hungary	As above	Rifen 2.4g	As above	As above	As above	As above	As above

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

1. Introduction and background

Dolovet vet 2.4g oral powder is a powder presented in sachets of 15g, containing 2.4g ketoprofen each. In Finland the product has been authorised for the indication: "The treatment of fever and inflammation in cattle". This is also the indication applied for at the start of the mutual recognition procedure (MRP). Following discussions in the CMD(v), the proposed indication was changed during the course of the MRP to: "For the treatment of painful disorders (lameness; abdominal pain) in individual animals".

The Reference Member State for the Mutual Recognition Procedure regarding Dolovet vet 2.4g oral powder, Finland, notified the EMEA on 2 March 2006 that the CMD(v) failed to reach an agreement regarding the product. Pursuant to Article 33(4) of Directive 2001/82/EC, as amended, the matter was referred to the CVMP.

The reason for this was that the national competent authorities of Belgium and Norway considered that this medicinal product could present a potential serious risk to animal health on the ground that the efficacy has not been sufficiently substantiated in the dossier.

The CVMP during its meeting of 14-16 March 2006 started a referral procedure under Article 33(4) of Directive 2001/82/EC, as amended, for Dolovet vet 2.4g oral powder. The Marketing Authorisation Holder (MAH) was requested to substantiate the indication and posology as discussed during the recent MRP. The MAH was also requested to substantiate the bridging of pharmacokinetic studies and dose-confirmation studies data to prove efficacy. The responses were submitted to the EMEA on 12 September 2006.

2. Discussion

In his response the Marketing Authorisation Holder (MAH)did not develop any further the preclinical argument already presented during the mutual recognition procedure. However, a dose confirmation study, submitted with the response, is considered pivotal for the assessment of the efficacy: "Dose confirmation of oral ketoprofen in endotoxin-induced mastitis in cows, Study 06-131-LC, August 7th, 2006". This study was not available to CMD(v).

The experimental design of the study mimics an acute toxic mastitis. 36 healthy lactating cows were challenged in one hindquarter, infused with endotoxin Bacto *E. coli* 026:B6 lipopolysaccharide B (LPS). Treatment was conducted two hours after challenge and the groups were Group A: Saline, Group B: 2 mg/kg ketoprofen orally, Group C: 4 mg/kg ketoprofen orally, and Group D: 3 mg/kg ketoprofen intramuscularly. General and local clinical signs, milk production, somatic cell counts, thromboxane B_2 levels in milk and in plasma, and serum levels of zinc, calcium, magnesium, and copper were studied.

After challenge and treatment, rectal temperature, ruminal contractions, and respiratory rate were significantly higher in the non-treated group than in the treated groups. Udder size, poor milk aspect, and pain also showed to be generally higher in the non-treated group. Milk yield dropped for all groups and rose again after challenge, similarly for all groups. Somatic cell counts were affected by the challenge, and few differences exist between the groups.

The results are clearly better for the treated groups when compared to non-treated animals for respiratory rate, rectal temperature, and ruminal contractions.

A trend exists for udder size of the inoculated quarter, pain as reported on a visual analog scale (VAS) after palpation, and poorer milk aspect (milk production was equally affected in all groups). Both pain in the infected quarter and increased size are indicative of inflammation. That a difference in udder size in the inoculated quarter is reported at all under these experimental conditions is noteworthy. An

anti-oedemic effect is usually evaluated over several days, and an NSAID may be considered limited in its efficacy here.

Thromboxane levels were measured in both milk and plasma. Opposed to injectable ketoprofen the results for milk are not “as clear” for Dolovet as what they are for plasma. Although not all effects of ketoprofen are covered by thromboxane activity (ketoprofen also has lipooxygenase activity), thromboxane activity is a sensitive parameter, not only for evaluating inflammation in this experimental model, but also for allowing extrapolation to the field condition up to a certain point.

The statistical report indicates that the number of animals used does not allow to establish equivalence (nor non-inferiority) between Dolovet containing ketoprofen administered orally at the dose of 4 mg/kg bodyweight, and Ketofen containing ketoprofen administered intramuscularly at the dose of 3 mg/kg. However, given that the pharmacokinetic data allowed to optimise the dose (keeping overall exposure comparable between the two products), it is concluded that a bridge exists that allows well-established use to apply to Dolovet. Even though equivalence has not been formally shown, the two products perform similarly when compared to placebo in regards to a number of critical parameters, both clinical and otherwise (thromboxane B2 levels in plasma). If one accepts that a bridge exists, then the clinical indications that exist for Ketofen, as evidence in the literature, should apply in large part to Dolovet. For example, in generic applications, a preclinical bridge is made that allows extrapolation to the field situation. For generic applications bioequivalence must be demonstrated. For well-established use dossiers the bridge can be constructed a bit more tentatively.) To restrict the indications of Dolovet to only those that were tested (endotoxemic mastitis control) would be inappropriate.

3. Conclusion

Reducing of pyrexia or fever and alleviation of inflammation are considered important clinical claims that should be retained as they have been demonstrated clearly enough.

Considering then the data provided and the well-established use of ketoprofen, CVMP is of the opinion that the following claim can be substantiated:

Alleviation of inflammation and reduction of fever in individual animals.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dolovet vet 2.4 g oral powder.

In Austria and Hungary: Rifen 2.4 g oral powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 sachet= 15 g powder contains:

Active substance:

Ketoprofen 2.4 g

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (adult cattle weighing about 600 kg).

4.2 Indications for use, specifying the target species

Alleviation of inflammation and reduction of fever in individual animals

4.3 Contraindications

Do not use for animals hypersensitive to ketoprofen or other non steroid anti-inflammatory (NSAID) drugs. Do not use for animals with gastrointestinal ulcers or severe renal insufficiency, coagulation disorders or severe hypovolemia.

4.4 Special warnings for each target species

Not known.

4.5 Special precautions for use

Special precautions for use in animals

The recommended dose and treatment time must not be exceeded. Do not use in animals which have completely lost their appetite because this could lead to insufficient absorption of ketoprofen.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAID) should avoid contact with the veterinary medicinal product. Hands should be washed after the administration of the drug. If a person accidentally swallows a 2.4 g bag of Dolovet powder (= 2400 mg ketoprofen), it may cause a serious intoxication. In these cases take immediate contact to a doctor.

4..6 Adverse reactions (frequency and seriousness)

Ketoprofen may cause adverse reactions typical to non-steroidal anti-inflammatory drugs such as diarrhoea which is caused by gastro-intestinal irritation and ulceration.

4.7 Use during pregnancy, lactation or lay

No teratogenic or embryotoxic effects in laboratory animals with the recommended dose of ketoprofen has been recorded. No such studies have been conducted with cattle. The induction of parturition in laboratory animals have been found to be delayed when ketoprofen was given just before parturition. Therefore the use of the product in cattle close to parturition should be avoided.

4.8 Interaction with other medicinal products and other forms of interaction

Other non steroidal anti-inflammatory drugs (NSAID) must not be used simultaneously with the product and within 24 hours after the last dose of Dolovet because the substances may compete in binding with proteins thus leading to toxic effects. Simultaneous use of glucocorticoids may add undesirable effects on GI-canal. Simultaneous use of loop-diuretics (for example furosemid) may decrease the effect of the diuretic.

4.9 Amounts to be administered and administration route

For adult cattle weighing about 600 kg bw.: One bag of 15 g once daily for 1 - 3 days. This corresponds to 4 mg ketoprofen /kg. The powder should be mixed with water e.g. in a bottle using ½ litres of water, shaked well and administered immediately per orally to an animal.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Ketoprofen may cause adverse reactions typical to non-steroidal anti-inflammatory drugs, such as diarrhoea which is caused by gastro-intestinal irritation and ulceration. There is no specific antidote. In cases of overdose symptomatic therapy should be given.

4.11 Withdrawal period(s)

Meat and offal: 1 day.
Milk: zero days.

5. PHARMACOLOGICAL PROPERTIES

ATCvet code: QM01AE03

5.1 Pharmacodynamic properties

Ketoprofen is a non steroid anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic effect. The anti-inflammatory action of ketoprofen is based on the inhibition of cyclo-oxygenase and lipo-oxygenase enzymes. The blocking of cyclo-oxygenase

enxyme inhibits the formation of the inflammation mediators PGE_2 and PGI_2. The inhibition of lipo-oxygenase enzyme reduces the synthesis of leucotriens. Ketroprofen inhibits the secretion of bradykinin, which is a chemical mediator of pain and inflammation. Ketoprofen has been documented to stabilise lysosomal cell membranes. Ketoprofen has been shown to inhibit the intravenously injected E.coli endotoxin induced tromboxane B2 production in the bovine.

5.2 Pharmacokinetic particulars

In cattle, after the recommended dose of 4 mg/kg of ketoprofen per os before feeding the concentrate, the highest concentration of ketoprofen in plasma (C_{max}3,9 µg/ml) was achieved in about 2 hours. The variation between individual cows was 1-3 hours. The elimination half life after per oral administration was about 4,5 hours. Concentrations over 0,1 µg/ml in plasma were measured 24 hours after the administration of the drug. The anti-inflammatory effect in tissues has been documented to continue even after the plasma concentration has decreased. The bioavailability after per-oral dosing is about 76 %.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Maltodextrin
- Carmellose sodium

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

A 15 g aluminium-laminate sachet, which are further packed to a cardboard box.
3 x 15 g.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vetcare Oy, P.O. Box 99, 24101 Salo.

8. MARKETING AUTHORISATION NUMBER(S) : FI 17182

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

FI: 22.09.2003

10 DATE OF REVISION OF THE TEXT

10.11.2006

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dolovet vet 2.4 g oral powder.

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Ketoprofen 2.4 g, constit. q.s. ad 15g.

3. PHARMACEUTICAL FORM

Oral powder.

4. PACKAGE SIZE

3 x 15g

5. TARGET SPECIES

Cattle (adult cattle weighing about 600 kg).

6. INDICATION(S)

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7. METHOD AND ROUTE(S) OF ADMINISTRATION, POSOLOGY

Orally for adult cattle weighing about 600 kg bw.: One bag of 15 g once daily for 1 - 3 days. This corresponds to 4 mg ketoprofen /kg.

8. WITHDRAWAL PERIOD

Meat and offal: 1 day
Milk: zero days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package insert before use.

10. EXPIRY DATE

EXP

11. SPECIAL STORAGE CONDITIONS

-

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS , IF ANY

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13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OF RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

The marketing authorisation holder: Vetcare Oy, P.O. Box 99, 24101 Salo

The manufacturer responsible for batch release: Galena Oy, P.O.Box 1450, 70501 Kuopio, Finland

16. MARKETIN AUTHORISATION NUMBER

XXXXX

17. MANUFACTURER'S BATCH NUMBER

Batch

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dolovet vet 2.4 g oral powder.

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Ketoprofen 2.4 g

3. CONTENTS BY WEIGHT, BY VOLUME OR NUMBER OF DOSES

15 g

4. ROUTE(S) OF ADMINISTRATION AND POSOLOGY

Orally for adult cattle weighing about 600 kg bw.: One bag of 15 g once daily for 1 - 3 days. This corresponds to 4 mg ketoprofen /kg.

5. WITHDRAWAL PERIOD

Meat and offal: 1 day
Milk: zero days

6. BATCH NUMBER

Batch

7. EXPIRY DATE

EXP

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only. (Cattle)

PACKAGE LEAFLET

PACKAGE LEAFLET

Dolovet vet 2.4 g oral powder

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE IN THE EEA, IF DIFFERENT

Marketing authorisation holder: Vetcare Oy, P.O.Box 99, 24101 Salo, Finland.

Manufacturer for the batch release: Oy Galena Ltd, P.O.Box 1450, 70501 Kuopio, Finland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dolovet vet 2.4 g oral powder.

3. STATEMENT OF THE ACTIVE AND OTHER INGREDIENTS

1 sachet= 15 g powder contains of 2.4 g ketoprofen and exipients to 15 g.

4. INDICATION(S)

Alleviation of inflammation and reduction of fever in individual animals

5. CONTRAINDICATIONS

Do not use for animals with gastrointestinal ulcers or severe renal insufficiency, coagulation disorders or severe hypovolemia. Do not use for animals hypersensitive to ketoprofen or other non steroid anti-inflammatory (NSAID) drugs (like aspirin or flunixin).

Other non steroidal anti-inflammatory drugs (NSAID) must not be used simultaneously with the product and within 24 hours after the last dose of Dolovet, because the substances may compete in binding with proteins thus leading to toxic effects. Simultaneous use of loop-diuretics (for example furosemid) may decrease the effect of the diuretic.

6. ADVERSE REACTIONS

Ketoprofen may cause adverse reactions typical to non-steroidal anti-inflammatory drugs such as diarrhoea which is caused by gastro-intestinal irritation and ulceration.
If you notice any other side effects, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle (adult cattle weighing about 600 kg).

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

For adult cattle weighing about 600 kg bw.: One bag of 15 g once daily for 1 - 3 days. This corresponds to 4 mg ketoprofen /kg.

Route of administration: Oral use.

9. ADVICE ON CORRECT ADMINISTRATION

The powder should be mixed with water e.g. in a bottle using ½ litres of water, shaked well and administered immediately per orally to an animal.

10. WITHDRAWAL PERIOD

Meat and offail: 1 day
Milk: zero days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.
Do not use after the expiry date stated on the carton and bag.
This veterinary medicinal product does not require any special storage conditions.

12. SPECIAL WARNING(S)

To the user:
People with known hypersensitivity to non steroidal anti-inflammatory drugs (NSAID) should avoid contact with the veterinary medicinal product. Hands should be washed after the administration of the drug. If a person accidentally swallows a 2.4 g bag of Dolovet powder (= 2400 mg ketoprofen), it may cause a serious intoxication. In these cases take immediate contact to a doctor.

To the target species:
The induction of parturition can be delayed when ketoprofen is given just before parturition. Therefore the use of the product in cattle close to parturition should be avoided.
Do not use in animals which have completely lost their appetite because this could lead to insufficient absorption of ketoprofen.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS , IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

3.8.2005 (revised2 10.11.2006)

15. OTHER INFORMATION

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.