SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

KETAVEL Gel 1.25%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
1 g of gel contains 18.5 mg dexketoprofen trometamol equivalent to 12.5 mg dexketoprofen.

Excipient(s):
Propylene glycol
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel
Colorless, transparent gel with a homogeneous appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used to treat pain and inflammation due to trauma or degenerative disorders in the joints, tendons, ligaments and muscles.

4.2 Posology and method of administration

Posology / Frequency and duration of administration
KETAVEL may be applied onto the painful and inflammatory area 2-3 times a day.
The total daily dose should not exceed 7.5 g (which corresponds approximately to 14 cm gel).
The duration of treatment should be limited to a maximum of 7 days.

Method of administration
KETAVEL gel is applied topically. The gel should be rubbed slightly to provide absorption completely.
Mucosa and eye contact should be avoided.

Additional information on special populations
Renal/hepatic impairment
Although systemic effects in gel form is minimum, systemic effects of non-steroidal anti-inflammatory drugs (NSAIDs) may appear depending on transdermal absorption, the quantity of the gel applied, the application surface, integrity grade of the skin, treatment period and application of any occlusive dressing (effects on the digestive system and kidneys). Therefore, it should be used with caution, especially in patients with severe renal failure or severe liver failure.

Pediatric population
Use in children below 6 years of age is not recommended.

Geriatric population:
No dose adjustments necessary for elder patients.

4.3 Contraindications

It is contraindicated in patients with hypersensitivity to dexketoprofen, ketoprofen or any of the ingredients of KETAVEL.
It is contraindicated in patients with known sensitivity symptoms such as asthma, allergic rhinitis or urticaria after use of aspirin or other non-steroidal anti-inflammatory drugs.
It should not be used in patients with a history of bronchial asthma, skin allergy due to tiaprofenic acid, fenofibrate or cosmetic products.
It should not be applied on exudative dermatoses, eczema, any dermal lesions independent of lesion types, burn, wound, mucosa, eye, anal or genital areas.

4.4 Special warnings and precautions for use

Topical medications, especially medications which are used for a long period may cause sensibility and local irritation. Exposure to direct sunlight, UVA and solarium should be avoided during the treatment and two weeks after the treatment to prevent possible light sensitivity or hypersensitivity.
It should not be applied on open wounds or permanently present skin lesions.
It should not be applied onto the mucosa, eyes and anal or genital areas.
KETAVEL should not be applied with any occlusive dressing.
Hands should be washed after use of KETAVEL.
KETAVEL may cause skin irritation due to the propylene glycol it contains.
In case of any dermal reaction after application of KETAVEL, the treatment should be discontinued immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Since only very small amounts of dexketoprofen pass into systemic circulation, interactions with drugs and other substances are very rare, almost never.
It should not be used with other non-steroidal anti-inflammatory drugs because the risk for side effects may increase.

Additional information on special populations
There are no studies conducted with special populations.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C

Women of child-bearing potential/Contraception
Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/ fetal development/ and-or/ parturition/ and-or/ postnatal development.
The potential risk for humans is unknown.
KETAVEL should not be used during pregnancy unless necessary.

Pregnancy
Although the experimental animal studies and epidemiological data have not shown any toxic effect of dexketoprofen on the embryo, use of KETAVEL is not recommended during pregnancy because of possible toxic effects of non-steroidal anti-inflammatory drugs.

Breast-feeding
It is not known whether dexketoprofen is excreted in human breast milk. Therefore, KETAVEL is

not recommended during breastfeeding.

Reproductive ability / Fertility
No toxicity on fertility was observed in the animal studies conducted with dexketoprofen trometamol.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Local skin reactions which may develop secondary to the application site are reported. Erythema, pruritus and photosensitization were reported.

The following system was used to classify the undesirable effects:
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).

Skin and subcutaneous tissue disorders
Rare: Dermatitis (erythema, pruritus, inflammation)
Very rare: Systemic hypersensitivity reactions (urticaria, bronchospasm)
Unknown: Photosensitivity reactions (erythema, inflammation and slight vesicle formation in some cases)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9 Overdose

No overdose based on topical application is observed. In case of swallowing accidentally, it may cause systemic effects depending on the quantity swallowed. In this case, supportive and symptomatic treatment and gastric lavage should be applied. Dexketoprofen trometamol can be removed from the body through dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs for topical use
ATC code: M02AA96

Dexketoprofen trometamol is the tromethamine salt of S-(+)-2-(3-benzoylphenyl) propionic acid, an analgesic, anti-inflammatory and antipyretic drug, which belongs to the non-steroidal anti-inflammatory group of drugs.

The mechanism of action of non-steroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway. Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG_2 and PGH_2, which produce prostaglandins PGE_1, PGE_2, $PGF_{2\alpha}$ and PGD_2 and also prostacyclin PGI_2 and

thromboxanes (TxA_2 and TxB_2). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action which would be additional to the direct action.
In animal and human experiments, dexketoprofen has been shown to be an inhibitor of COX-1 and COX-2 activities.
Clinical studies performed on several pain models demonstrated effective analgesic activity of dexketoprofen trometamol. The onset of the analgesic activity was obtained in some studies at 30 minutes post-administration. The analgesic effect persists for 4 to 6 hours.

5.2 Pharmacokinetic properties

General properties
Absorption:
Topical application of dexketoprofen shows very low percutaneous absorption. Systemic effect is not expected due to low systemic bioavailability.

Distribution:
The distribution half-life value of dexketoprofen trometamol is 0.35 hours. As with other drugs with a high plasma protein binding (99%), its volume of distribution has a mean value below 0.25 l/kg.

Biotransformation:
After administration of dexketoprofen trometamol only the S-(+)-enantiomer is obtained in urine, demonstrating that no conversion to the R-(-)-enantiomer occurs in humans. In multiple-dose pharmacokinetic studies, it was observed that the AUC after the last administration is not different from that obtained following a single dose, indicating that no drug accumulation occurs.

Elimination:
The elimination half-life value of dexketoprofen trometamol is 1.65 hours. The main elimination route for dexketoprofen is glucuronide conjugation followed by renal excretion.

Linearity/Nonlinearity:
Dexketoprofen trometamol showed a linear pharmacokinetics by a dose dependent increase during systemic exposure following oral dose.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenetic potential and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 980
Propylene glycol
Polyethylene glycol (PEG 400)
Ethyl alcohol (96%)
Sodium hydroxide solution 18%
Lavender flavor
Deionized water

6.2 Incompatibilities

It does not have any known incompatibilities.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

It is packaged in an aluminum tube with a plastic HDPE closure.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece-ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2014/275

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 07.04.2014
Date of last renewal :

10. DATE OF REVISION OF THE TEXT