CONTRAINDICATIONS (Mohrus® is contraindicated in the following patients.)

1. Patients with a history of hypersensitivity to this product and ingredients of this product. (See the article of “Important Precautions (1)”.

2. Patients with aspirin asthma (induction of the attacks of asthma by drugs; e.g., nonsteroidal anti-inflammatory analgesic drugs) or a history thereof (there is a risk of inducing the attacks of bronchial asthma).

DESCRIPTION

1. Composition
Mohrus® contains 30 mg of ketoprofen, JP, per ten grams of mass (one patch), as well as oxybenzone and aroma as excipients.

2. Product description
Mohrus® is a patch in which the mass is formed on the backing cloth and the surface of the mass is covered with the plastic film. Remove the plastic film from this product and put it on a white paper and observe it without delay: it is white to pale yellowish white in mass surface color and has a particular odor.

Preparation: 10 x 14 cm
Identification code: HP310P.

INDICATIONS
Relief of pain and inflammation in the following disorders and symptoms:
Osteoarthritis, humeroscapular periarthritis, tendinitis/tendovaginitis, peritendinitis, humeral epicondylitis (e.g., tennis elbow), myalgia, and post-traumatic swelling and pain.

PRECAUTIONS ON INDICATIONS
Since serious contact dermatitis and photosensitivity with some progressing to severe systemic rash have been reported after administration of this product, therapeutic necessity of this product for diseases should be considered sufficiently and this product should be used only when therapeutic benefits outweigh possible risks.

DOSAGE AND ADMINISTRATION
Apply Mohrus® to the affected site twice daily.

PRECAUTIONS
1. Careful Administration (Mohrus® should be used with caution to the following patients.)
Patients with bronchial asthma (there is a risk of the latent existence of patients with aspirin asthma). (See the article of “Severe adverse reactions 2”).

2. Important Precautions
(1) Do not use this product in patients with a history of hypersensitivity (including erythema, rash/redening, swelling, itching and irritation etc.) to this product and ingredients of this product.
(2) Since contact dermatitis and photosensitivity with some progressing to severe systemic rash have been reported after administration of this product, give the following instructions to patients. (See the article of “Severe adverse reactions 3), 4”).

1) Since contact dermatitis may occur irrespective of the presence or absence of exposure to ultraviolet light, discontinue the use of this product, avoid sunlight to the lesion and receive the medical examination from a physician immediately when any dermal symptom
such as rash/reddening, itching and irritation etc. was observed. Be careful because such a symptom may occur after the passage of a few days.

2) Since photosensitivity may occur, avoid an outside activity irrespective of the weather while using this product, and protect the application site from sunlight with clothes, supporter, etc. when usually going out. Since there is a fear of ultraviolet light penetrating the white clothes and thin clothes, wear colored clothes through which the ultraviolet light cannot penetrate easily. Since the symptom may occur even after the passage of a few days to a few months, take similar precautions for a while after completion of use of this product.

(3) Pay attention to the fact that treatment with anti-inflammatory analgesic drugs is not etiotropic but nosotropenic.

(4) Because of a risk of masking skin infections, appropriate antibiotics or antifungal agents should be combined when this product is used for inflammation with infection. Apply this product with care through sufficient observation of the patient's condition.

(5) Consider treatments other than pharmacotherapy when this product is used for chronic disorders (e.g., osteoarthritis). Pay attention to the development of any adverse reactions through sufficient observation of patient's condition.

3. Drug Interactions

None

4. Adverse Reactions

Of a total number of 6908 cases, 141 cases (2.04%) reported adverse reactions, and all of them were contact dermatitis. The symptoms thereof were as follows: 32 episodes of rash; 36 episodes of reddening; 29 episodes of itching; and 9 episodes of irritation, etc. (at the termination of the re-examination).

In addition to the above mentioned adverse reactions, voluntary report conducted by the physician and other medical professionals has reported anaphylactoid symptoms, induction of an asthmatic attack (aspirin-induced asthma), and photosensitivity.

(1) Severe adverse reactions

1) Anaphylactic symptoms: (less than 0.1%) Anaphylactic symptoms (e.g., urticaria, dyspnea and facial edema) may develop. Discontinue the use when such symptoms developed.

2) Induction of the attacks of asthma (aspirin asthma): (less than 0.1%) This product may rarely induce the attacks of asthma. Discontinue the use when early symptoms, e.g., dry rale, wheezing, and dyspnea, developed. Caution should be exercised because patients with aspirin-induced asthma are considered to exist latently in about 10% of patients with bronchial asthma.

Furthermore, an asthmatic attack induced by this product has developed in several hours after application (See the article of “Contraindications (2”)).

3) Contact dermatitis: (less than 5%, incidence unknown for serious cases) Itching, irritation, erythema, rash/reddening which occurred in the application site may be worsened and result in severe dermatitis such as swelling, edema, and blister/erosion, and pigmentation and depigmentation, and dermatitis may become serious by extending to the whole body. Discontinue the use immediately when any abnormality was observed, avoid sunlight to the lesion, and take appropriate treatment. Such a symptom may occur after the passage of a few days.

4) Photosensitivity: (incidence unknown) Exposure of the application site to ultraviolet light may induce severe dermatitis such as strong itching-accompanied erythema, rash, irritation, swelling, edema, and blister/erosion, and pigmentation and depigmentation and dermatitis may become serious by extending to the whole body. Discontinue the use immediately when any abnormality was observed, avoid sunlight to the lesion, and take appropriate treatment. Such a symptom may occur after the passage of a few days to a few months.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Incidence</th>
<th>0.1% - &lt;5%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Note</td>
<td>Local rash, reddening, swelling, itching, irritation, blister/erosion, pigmentation etc.</td>
<td>Subcutaneous bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Note) Discontinue the use immediately when such a symptom occurred.

5. Use in the Elderly

The post-marketing surveillance study on use results revealed that the incidence of contact dermatitis in the elderly over the age of 65 (2.14%: 43/2,007 patients) was significantly higher than that in patients under the age of 65 (1.06%: 33/3,118 patients). Therefore, this product should be used with caution particularly in the use for the elderly over the age of 65 while observing the skin condition at the application site carefully.

6. Use during Pregnancy, Delivery or Lactation

(1) The safety of this product during pregnancy, delivery or lactation etc. has not been established. Therefore, this product should be used only in the case that the therapeutical benefit for these patients is considered to outweigh the risk.

(2) There are reports in foreign countries1-2) which described that administration of ketoprofen (oral, intravenous, and transrectal) at the late stage of pregnancy provoked persistent fetal circulation (PFC) and fetal renal failure.
7. Pediatric Use
The safety of this product has not been established for premature infants, neonates, babies, infants, or children (a few experience of use).

8. Effects on Laboratory Tests
None

9. Overdosage
None

10. Precautions concerning Use
Application site:
Since this product may provoke skin irritation, it should not be used in the following sites:
(1) Damaged skin or mucosa.
(2) Site of eczema or rash.

11. Other Precautions
None

PHARMACOKINETICS

1. One sheet of this product was applied to the back of seven healthy adult male volunteers for 12 hours. Consequently, serum concentrations of ketoprofen reached to be 43.11 ng/ml at 12 hours after application, and ketoprofen was nearly completely eliminated from serum at 48 hours after application. The rate of transdermal absorption at that moment was 13.3% of the application. The majority of the total amount of elimination of ketoprofen was eliminated by 48 hours after application, and the rate of urinary excretion was 35.8% of the amount of absorption.

2. Serum concentrations and amounts of urinary excretion of ketoprofen became almost constant on day 7 and thereafter when one sheet of this product was applied to the back of six healthy adult male volunteers by twice-a-day, 28-day repeated application. And these concentrations and amounts decreased rapidly after the termination of the application.

3. This product was given to patients with osteoarthritis of the knee and other disorders by single or repeated application. Consequently, concentrations of ketoprofen at any of the skin, subcutaneous fat, muscle, and synovial membrane existing beneath the application site were higher than serum concentrations. Concentrations of ketoprofen decreased in a concentration gradient fashion at deeper sites.

(References) Pharmacokinetics in animal (guinea pigs)

1. In a study in which one sheet of 7 cm² (1.5 mg of ketoprofen) was given to guinea pigs by 24-hour application, 26.7% of the dose was absorbed from the intact skin, and 97.4% of the dose from the stratum corneum-removed abraded skin.

2. In the intact skin, blood concentrations of ketoprofen peaked at 4 hours after application, while concentrations of ketoprofen in the fascia and muscle underneath the application site peaked at 6 hours after application. In the abraded skin, however, concentrations of ketoprofen in blood and all organs peaked at 2 hours after application.

3. Following application to the intact skin, 24.4% of the amount of application was excreted in urine by 120 hours after application, and 0.5% of the amount was excreted in feces. Following application to the abraded skin, 96.7% of the amount of application was excreted in urine.

PHARMACOLOGY

1. Ketoprofen has shown a significant inhibitory action on both the models of acute inflammation, e.g., carrageenin-induced paw edema and bruise-induced paw edema in rats, and the models of chronic inflammation, e.g., cotton pellet-induced growth of granuloma and adjuvant-induced arthritis in rats.

2. Ketoprofen has shown significant analgesic actions on pain of kaolin- and carrageenin-inflamed paws and sliver nitrate-induced arthritis in rats.

3. The main mechanisms by which ketoprofen exerts its anti-inflammatory and analgesic actions are considered to involve the following actions: a prostaglandin synthesis-inhibitory action; a vascular hyperpermeability-inhibitory action; a leukotaxis-inhibitory action; a protein heat denaturation-inhibitory action; cell membrane-stabilizing action; and bradykinin release-inhibitory action.

<table>
<thead>
<tr>
<th>Name of disorder</th>
<th>Dose</th>
<th>Test Period</th>
<th>Rate of improvement (in &quot;Moderately improved&quot; or &quot;better&quot; cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td></td>
<td></td>
<td>58.8% (410/697)</td>
</tr>
<tr>
<td>Humeroscapular periartthritis</td>
<td></td>
<td></td>
<td>55.7% (54/97)</td>
</tr>
<tr>
<td>Tendinitis/ tendovaginitis and peritendinitis</td>
<td>1 patch 2 times/day</td>
<td>2 weeks</td>
<td>80.4% (37/46)</td>
</tr>
<tr>
<td>Humeral epicondylitis</td>
<td></td>
<td></td>
<td>77.8% (21/27)</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td></td>
<td>72.2% (135/187)</td>
</tr>
<tr>
<td>Post-traumatic swelling and pain</td>
<td>1 week</td>
<td></td>
<td>83.4% (361/433)</td>
</tr>
</tbody>
</table>
**PHYSICOCHEMISTRY**

Nonproprietary name: Ketoprofen
Chemical name: (RS)-2-(3-benzoylphenyl) propanoic acid
Molecular formula: $C_{16}H_{14}O_3$
Molecular weight: 254.28
Structural formula:

![Structural formula of Ketoprofen]

Description:
Ketoprofen occurs as a white crystalline powder. It is very soluble in methanol, freely soluble in ethanol and ether, and practically insoluble in water. It is colored by light.
Melting point: 94 to 97°C

**PRECAUTIONS FOR HANDLING**

**CONDITIONS FOR APPROVAL**

**PACKAGING**

- 60 sheets [6 sheets/pack, 10 packs]
- 70 sheets [7 sheets/pack, 10 packs]
- 240 sheets [6 sheets/pack, 40 packs]
- 840 sheets [7 sheets/pack, 120 packs]
- 960 sheets [6 sheets/pack, 160 packs]

**REFERENCES**

7) Documents collected by Hisamitsu Pharmaceutical Co., Inc.

**REQUEST FOR LITERATURE SHOULD BE MADE TO:**
Medical & Pharmaceutical Information Department
Hisamitsu Pharmaceutical Co., Inc.
PCP Buildings 21F, 1-11-1, Marunouchi, Chiyoda-ku, Tokyo, 100-6221, Japan
Tel.: +81-3-5293-1707 Fax: +81-3-5293-1723

**INFORMATION ON LONG-TERM ADMINISTRATION**

Manufactured by:
Hisamitsu Pharmaceutical Co., Inc.
408, Tashirodaikan-machi, Tosu, Saga, 841-0017, Japan

**BRAND NAMES IN OTHER COUNTRIES**
None