1. Product Name
Rheumon, 5% w/w, topical gel

2. Qualitative and Quantitative Composition
1 g of topical gel contains 50 mg of etofenamate.
For the full list of excipients, see section 6.1.

3. Pharmaceutical Form
Nearly transparent yellowish gel for topical application.

4. Clinical Particulars

4.1 Therapeutic indications
For the external supportive symptomatic treatment of pain in adults:
- caused by acute strains, sprains or bruises in the extremities after blunt trauma such as sports injuries;
- in soft tissue near a joint (e.g. bursa, tendon, cord and joint capsule) in cases of gonarthrosis.
If symptoms persist for longer than 3 days, a doctor must be consulted.

4.2 Dose and method of administration

Dose
Apply Rheumon Gel three times a day. Depending on the size of the painful areas, an about 5 to 10 cm long ribbon (equivalent to about 1.7 to 3.3 g of gel and 75 to 150 mg of etofenamate) will be required.

For treatment of blunt trauma, the maximum daily dose is 9 g of gel, equivalent to 450 mg of etofenamate.

Method of administration
Only for external application to the skin. Do not ingest.

Apply Rheumon Gel in a thin layer on the affected parts of the body and gently rub into the skin.

Before applying a dressing, Rheumon Gel should be left for a few minutes to dry on the skin. The application of an occlusive dressing is not recommended.
Usually, treatment for one week is sufficient. Therapeutic benefit of a longer use has not been verified.

### 4.3 Contraindications

Rheumon Gel should not be used in the following cases:

- Hypersensitivity to etofenamate, flufenamic acid, other non-steroidal anti-inflammatory drugs or to any of the excipients listed in section 6.1.
- On open injuries, inflammations or infections of the skin as well as on skin eczema or on mucous membranes.
- Third trimester of pregnancy.
- Children and adolescents, as clinical experience is limited.

### 4.4 Special warnings and precautions for use

Rheumon Gel should not be applied to damaged or eczematous inflamed skin and mucous membranes or the eyes. The hands should therefore be washed after applying the product, or contact with those parts of the body should be avoided.

Do not expose the treated area to sun and/or solarium during treatment and two weeks thereafter.

In patients suffering from asthma, chronic obstructive airway disease, hay fever or chronic swelling of the nasal mucous membranes (so-called nasal polyps), or chronic obstructive airway diseases or chronic airway infections, especially if they are combined with hay-fever-like manifestations, Rheumon Gel must only be used when certain precautions are taken and only under close medical supervision.

Systemic absorption will increase if the medicinal product is used for a longer period and/or if applied on a large surface. Therefore, this should be avoided.

Children should not get in contact with skin areas treated with Rheumon Gel.

### 4.5 Interaction with other medicines and other forms of interaction

No interactions are known when Rheumon Gel is used correctly.

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

There are no adequate data from the use of etofenamate in pregnant women. Since the impact of prostaglandin synthesis inhibition on human pregnancy has not yet been fully explored, Rheumon Gel should only be used in the first and second trimester of pregnancy after carefully weighing the risk/benefit ratio. The maximum daily dose must not be exceeded (see section 4.2).

Use of Rheumon Gel is contraindicated in the third trimester of pregnancy.

During the last three months of pregnancy, the mechanism of action of these medicinal products may lead to suppression of labor activity, prolongation of pregnancy and to a prolonged birth process. Further, it may cause cardiovascular (with premature closure of ductus arteriosus and pulmonary hypertension) and renal (with oliguresis and oligoamnios) toxicity in the child, increased bleeding tendency in mother and child as well as an increased risk of oedema formation in the mother.

#### Breast-feeding

Since etofenamate passes into the breast milk to a small extent, prolonged use of Rheumon Gel by breast-feeding mothers should be avoided. The recommended daily dose must not be exceeded.
In order to avoid absorption by the sucking baby, breast-feeding mothers must not use this medicinal product in the region of their breasts.

4.7 Effects on ability to drive and use machines
Rheumon Gel has no known influence on the ability to drive or use machinery.

4.8 Undesirable effects
Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common ≥1/10</td>
<td>Erythema, Skin burning sensation</td>
</tr>
<tr>
<td>Common ≥1/100 to &lt;1/10</td>
<td></td>
</tr>
<tr>
<td>Uncommon ≥1/1000 to &lt;1/100</td>
<td></td>
</tr>
<tr>
<td>Rare ≥1/10,000 to &lt;1/1000</td>
<td></td>
</tr>
<tr>
<td>Very rare &lt;1/10,000</td>
<td></td>
</tr>
<tr>
<td>Not known Frequency cannot be estimated from the available data.</td>
<td></td>
</tr>
</tbody>
</table>

Although less likely with topical administration, some side effects normally associated with systemically administered etofenamate may also occur.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
<th>Description of selected adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Erythema, Skin burning sensation</td>
<td>Adverse reactions described under the System Organ Class - Skin and subcutaneous tissue disorders usually recede rapidly when medication is discontinued.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Dermatitis (e.g. intense itching, rashes, swelling, bullous eruption)</td>
<td><strong>Hypersensitivity reactions</strong>: have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis; (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea; or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme). As soon as one of these symptoms appears, which is already possible after the first administration, immediate medical help is called for.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity</td>
<td></td>
</tr>
</tbody>
</table>

4.9 Overdose
In case of incorrect use:

If the contents of a tube of Rheumon Gel, or more, is applied to the entire surface of the body within a short period, headaches, dizziness or epigastric discomfort can occur. The recommended countermeasure is to wash off the Rheumon Gel with water. There is no specific antidote.
5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antirheumatic, anti-inflammatory and analgesic agent; ATC code: M02AA06

Mechanism of action

Etofenamate acts on various points of the inflammatory process: in addition to inhibiting prostaglandin synthesis, inhibition of histamine release and inhibition of hyaluronidase release have been determined.

Pharmacodynamic effects

Etofenamate is a non-steroidal anti-inflammatory agent with analgesic properties. The pronounced antiphlogistic effect has been proven in animal experiments. In a kaolin-induced rat paw model, etofenamate topical administered inhibited oedema formation. Rat paw kaolin oedema was equally inhibited by topical administration of similar amounts of a 5% etofenamate gel formulation on the inflamed paw and on the non-inflamed contralateral paw indicating systemic absorption and distribution of the drug. A single or repeated application of 5% etofenamate gel provided slight and marked protection, respectively against UV-irradiation-induced erythema in the guinea pig.

Clinical efficacy and safety

In clinical trials including approximately 58,000 patients, different topical etofenamate formulations have demonstrated efficacy in improving blunt traumas, such as contusions, sprains, muscle-strains, and overexertion injuries (e.g. tendovaginitis or bursitis) as well as certain rheumatological disorders including spondylarthritis, epicondylitis, periarthritis humerodcapularis, lumbaro and gonarthrosis. About 3,100 patients were enrolled in randomised placebo or active-controlled clinical studies. In these clinical trials, topical etofenamate formulations showed superiority versus placebo treatment and comparable efficacy versus active topical comparator products.

There have been no deaths or serious adverse reactions causally related to topical etofenamate therapy in clinical trials. The local tolerability is excellent with only ~1% of patients suffering mild and reversible local reactions.

5.2 Pharmacokinetic properties

Absorption

After a single 300 mg cutaneous application of etofenamate gel (5% and 10%), cream, lotion and spray, similar plasma flufenamic acid concentrations were found. Maximum plasma fenamate levels were measured between 12 and 24 hours after administration. Cutaneous etofenamate absorption was found to be independent of the vehicle or the concentration if equal amounts of etofenamate (300 mg) were applied.

Distribution

In studies, it was shown that etofenamate gel formulation distributes into the target tissues under the cutaneous site of administration. Etofenamate and flufenamic acid levels were determined by GC/MS in fluids and tissues 18 – 24 hours after the last application in a study topically applying etofenamate 5% gel (3g) three times daily for 7 consecutive days. Etofenamate levels were 3313, 192, 114, and 105ng/g in skin, subcutaneous tissue, muscle, and joint capsule, respectively. Corresponding flufenamic acid levels were 470, 56.1, 27.4, and 10.0ng/g. The flufenamic acid plasma concentration was 22.1ng/ml, and that in synovial fluid was 17.7ng/ml.
Like other NSAIDs, etofenamate was found to be highly bound to plasma proteins (98%). The same study showed that plasma protein binding of the active metabolite flufenamic acid is >99%.

After cutaneous administration of etofenamate gel (5%), the relative bioavailability, i.e. the systemically available portion of the dose, is in the range of other etofenamate products (up to 20%).

**Biotransformation**
Etofenamate is metabolized in the liver by oxidation and conjugation. The substance is degraded into 5-OH-, 4’-OH-, and 5,4’-dihydroxyetofenamate and to flufenamic acid (as active metabolite), 5-OH, 4’-OH and 5,4’-dihydroxyflufenamic acid.

**Elimination**
Etofenamate is excreted in the form of numerous metabolites (hydroxylation, ether and ester cleavage) and their conjugates, renally (55%) and in the faeces.

An elimination half-life of 3.3 hours after topical administration was found.

**5.3 Preclinical safety data**
When etofenamate is applied topically, the absorption must be borne in mind in the evaluation of the toxicological data (see section 5.2).

**Acute toxicity**
Investigations of the acute toxicity of etofenamate have been carried out with various forms of administration in rats, mice, guinea-pigs and rabbits. The safety margin with respect to cutaneous use in humans is estimated to exceed a factor of 100.

**Subchronic and chronic toxicity**
Subchronic toxicity has been investigated in various animal species. One-year studies with oral administration were carried out in rats (7, 27, 100 mg/kg body weight/day) and primates (7, 26, 100 mg/kg body weight/day). Rats given 100 mg/kg body weight/day developed gastrointestinal haemorrhages and ulcers with subsequent peritonitis and increased mortality. The high dose led to a reduction in body weight, thymus weight and haemoglobin in primates.

**Mutagenicity and cancerogenicity**
*In-vitro* and *in-vivo* investigations of gene and chromosome mutation induction produced negative results. The possibility of the substance having a mutagenic effect appears to have been excluded with sufficient reliability. Long-term studies involving oral administration to rats (7, 21, 63 mg/kg body weight/day) and mice (15, 45, 140 mg/kg body weight/day) provided no evidence of a tumorigenic potential of etofenamate.

**Reproduction toxicology**
Etofenamate crosses the placental barrier.

There is no experience with administration to humans. In animal experiments, the embryotoxic dose was lower than the maternotoxic dose. In rats, there was an increased incidence of dilation of the renal pelvis from a dose of 21 mg/kg body weight/day administered orally (days 6-15 p.c.) and an increased incidence of 14 rib pairs from 7 mg/kg body weight/day administered orally (days 6-15 p.c.) in pups whose mothers had been treated.

Etofenamate is excreted as flufenamic acid in breast milk. The concentrations in breast milk are so low that short-term dermal treatment of small areas is not considered as a reason to stop breast-feeding.
6. Pharmaceutical Particulars

6.1 List of excipients
Alpha-[hexadecyl,(Z)-octadec-9-en-1-yl]-ω-hydroxypoly(oxyethylene)-8
Macrogol 400
Sodium hydroxide
Carbomer 940
Propan-2-ol
Purified water.

6.2 Incompatibilities
No incompatibilities are known.

6.3 Shelf life
Unopened: 5 years.
After first opening of the tube: 12 weeks.

6.4 Special precautions for storage
Store at or below 30°C.

6.5 Nature and contents of container
Aluminium tube with polyethylene cap. Pack size of 50 g.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

Rheumon Gel can cause discoloration or damage to the surface of polished furniture or plastics. The hands should therefore be washed after applying the product or contact with the above items should be avoided.

7. Medicines Schedule
Pharmacy Medicine

8. Sponsor Details
Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Freephone: 0800-168-169

9. Date of First Approval
2 March 2000
## Summary of Changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of New Information</th>
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<td>4.3</td>
<td>Addition of hypersensitivity to flufenamic acid and other non-steroidal anti-inflammatory drugs.</td>
</tr>
<tr>
<td>4.4</td>
<td>Warning on applying to damaged or inflamed skin and exposure to sun and/or solarium. Avoiding treatment on a large surface or use for a long time.</td>
</tr>
<tr>
<td>4.8</td>
<td>Included side effects normally associated with systemically administered etofenamate. Expansion of information regarding hypersensitivity reactions.</td>
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<tr>
<td>4.9</td>
<td>Reworked this section.</td>
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<tr>
<td>5.1</td>
<td>Corrected pharmacotherapeutic group. Included Pharmacodynamic effects and Clinical efficacy and safety.</td>
</tr>
<tr>
<td>5.2</td>
<td>Expanding information on Absorption and Distribution. Included Biotransformation section.</td>
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</tbody>
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