SUMMARY OF PRODUCT CHARACTERISTICS

1.Name of the medicinal product
ETO MR GEL

2.Qualitative and quantitative composition
Each gram contains:
Aceclofenac BP 1.5%w/w
Thiocolchicoside BP 0.125%
w/w Linseed oil BP 3.0 %w/w
Menthol BP 5.0% w/w
Methyl Salicylate BP 10.0 % w/w
Capsaicin USP 0.01 %w/w

For the full list of excipients, See Section 6.1

3.Pharmaceutical form
Gel
White to off white colour Gel

4 Clinical Particulars
4.1 Therapeutic indications
Eto Mr Gel is used to relieve joint pain from arthritis. Aceclofenac belongs to a class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs).

4.2 Posology and method of administration
Use in Adults: Eto Mr Gel is applied locally to the skin 2 times daily and smoothed into the skin gently. The amount needed depends on the size of the lesion. Normally 0.5 grams (the size of a pea) of the gel is used on a 5 cm x 5 cm lesion site. The usual duration of therapy is from 60 to 90 days. Maximum efficacy has been observed with treatment duration towards the upper end of this range. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. A maximum of 8 grams daily should not be exceeded. Long term efficacy has not been established.
Use in the Elderly**:** The usual adult dose may be used.
Use in Children**:** Dosage recommendations and indications for the use of Eto Mr Gel have not been established for use in children.

4.3 Contraindications
Eto Mr Gel is contraindicated in patients with a known hypersensitivity to Aceclofenac, or any of the inactive ingredients.
Because of cross-reactions, the gel should not be used by patients who have experienced hypersensitivity reactions such as symptoms of asthma, allergic rhinitis or urticaria, to acetylsalicylic acid or other non-steroidal anti-inflammatory agents.
The use of Eto Mr Gel is contraindicated during the third trimester of pregnancy.

4.4 Special warnings and precautions for use

The likelihood of systemic side effects occurring following the topical application of Eto Mr Gel is very small compared to the frequency of side effects with oral Aceclofenac, owing to low systemic absorption with Eto Mr Gel. However, the possibility of systemic adverse events from application of topical Aceclofenaccannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see product information on systemic forms of Aceclofenac). This product should be used withcaution in patients with a history of and/or active gastrointestinal ulceration or bleeding, or reduced heart, liver or renal function, since isolated cases of systemic adverse reactions consisting of renal affection, has been reported with topically administered anti-phlogistics.

It is known that NSAIDs can interfere with platelet function. Although the likelihood of systemic side effects is very low, caution should be used in patients with intracranial haemorrhage and bleeding diathesis.

Direct sunlight, including solarium, should be avoided during treatment. If sensitivity skin reactions occur, discontinue use.

Eto Mr Gel should not be applied to skin wounds, infections or exfoliative dermatitis. It should not be allowed to come into contact with the eyes or mucous membranes and should not be ingested. Discontinue the treatment if a generalized skin rash develops after applying the product. Topical Aceclofenaccan be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

4.5 Interaction with other medicinal products and other forms of interaction

Since systemic absorption of Aceclofenacfrom a topical application is very low such interactions are very unlikely.

4.6 Pregnancy and lactation

Use in pregnancy: The systemic concentration of Aceclofenacis lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

• Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1.5 %. The risk is believed to increase with the dose and duration of therapy.

• Animal studies have shown reproductive toxicity. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and postimplantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Aceclofenacshould not be given unless clearly necessary. If Aceclofenacis used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low (< 30% of the body surface) and duration of treatment as short as possible (not longer than 3 weeks).

During the second and third trimester of pregnancy, all prostaglandin

synthesis inhibitors may expose the fetus to:
• Functional renal injury in the fetus. From the 12th week: oligohydramnios (usually reversible after the end of treatment), or anamnios (particularly with prolonged exposure). After birth: kidney failure may persist (particularly with late or prolonged exposure).
• Pulmonary and cardiac toxicity in the foetus (pulmonary hypertension with premature closure of the ductusarteriosus). This risk exists from the beginning of the 6th month and increases if administration is close to full term. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and the neonate, to:
• Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
• Inhibition of uterine contractions resulting in delayed or prolonged labour.
• Increased risk of oedema formation in the mother.
Consequently, Eto Mr Gel is contraindicated during the third trimester of pregnancy

Use during lactation:
Like other NSAIDs, Aceclofenacpasses into breast milk in small amounts. However, at the recommended therapeutic doses of Eto Mr Gel no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional.
Under this circumstance, Eto Mr Gel should not be applied on the breasts of nursing mothers, nor do elsewhere on large areas of skin or for a prolonged period of time

4.7 Effects on ability to drive and use machines
Cutaneous application of topical Aceclofenachas no influence on the ability to drive and use machines.

4.8 Undesirable effects
Most frequently reported reactions include skin reactions such as contact dermatitis, erythema and rash or application site reactions such as inflammation, irritation, pain and blistering. In studies there appeared to be no age specific increase or pattern of reactions.
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); Not known: cannot be estimated from the available data.

DRa SOC	**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**
Blood and lymphatic system disorders			**Anaemia**	**Bone Marrow depression, Granulocytopenia Thrombocytopenia Neutropenia Haemolyticanaemia**

Immune system disorders			**Anaphylactic reaction (including shock)**	
			Hypersensitivity	
Metabolism and nutrition disorders				**Hyperkalemia**
Psychiatric disorders				**Depression Abnormal dreams Insomnia**
Nervous system disorders	**Dizziness**			**Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)**
Eye disorders			**Visual disturbance**	
Ear and labyrinth disorders				**Vertigo Tinnitus**
Cardiac disorders			**Cardiac failure**	**Palpitations**
Vascular disorders			**Hypertension**	**Flushing Hot flush vasculitis**
Respiratory, thoracic and mediastinal disorders			**Dyspnoea**	**Bronchospasm Stridor**
Gastrointestinal disorders	**Dyspepsia Abdominal pain Nausea Diarrhoea**	**Flatulence Gastritis Constipation Vomiting Mouth ulceration**	**Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration**	**Stomatitis Intestinal perforation Exacerbation of Crohn's disease and colitis Ulcerative Haematemesis Pancreatitis**
Hepatobiliary disorders	**Hepatic enzyme increased**			**Hepatic injury (including hepatitis) Jaundice Blood alkaline phosphatase increased**

Skin and subcutaneous tissue disorders		**Pruritus Rash Dermatitis Urticaria**	**Angioedema**	**Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and**
				Toxic Epidermal Necrolysis)
Renal and urinary disorders		**Blood urea increased Blood creatinine increased**		**Renal failure Nephrotic syndrome**
General disorders and administration site conditions				**Oedema Fatigue Cramps in legs**
Investigations				**Weight incre**

Temporary hair discolouration at the application site has been reported. This is usually reversed on stopping treatment. Patch testing of previously treated patients indicate a 2.18% probability of allergic contact dermatitis sensitisation (type IV) to Aceclofenacwith as yet unknown clinical relevance. Cross-reactivity to other NSAIDs is not likely. Serum testing more than100 patients indicated no presence of type I anti-Aceclofenacantibodies.

Reporting of suspected adverse reactions

Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Due to the low systemic absorption of Eto Mr Gel, Overdosage is extremely unlikely as a result of topical use. However, the skin should be rinsed with water. There have been no clinical cases of ingestion of Eto Mr Gel inducing Overdosage. In the event of accidental ingestion resulting in significant systemic side effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti inflammatories should be used. Supporting and symptomatic treatment should be given for complications such as renal failure, convulsions, gastrointestinal irritation and respiratory depression. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion. Specific therapies such as forced diuresis and dialysis will probably not be therapeutic in eliminating NSAIDs due to their high rate of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanisms of action: This drug has several mechanism of action.

1. It inhibits cyclooxygenase (COX) activity and to suppress the PGE2 production by inflammatory cells, by inhibiting IL-Beta & TNF in the inflammatory cells (Intracellular Action).
2. It blocks degeneration and stimulates synthesis of extra cellular matrix of cartilages by inhibiting the action of different cytokines.
3. Drug and its metabolites inhibit IL-6 production by human chondrocytes. This leads to inhibition of increase of inflammatory cells in synovial tissue, inhibition of IL-1 amplification, inhibition of increased MMP synthesis and thus ensuring proteoglycan production.
4. It inhibits IL-1 and TNF production by human chondrocytes, inflammatory cells and synovial cells and therefore blocks suppression of GAG and collagen synthesis and stimulates growth factors mediated synthesis of GAG and collagen.
5. 4`-hydroxyaceclofenac a metabolite of aceclofenac inhibits pro MMP1 and pro MMP3 produced by synovial cells (Rheumatoid Synovial Cells) in serum and in synovial fluid and thus inhibits progressive joint destruction by MMPs.
6. Aceclofenac inhibits Neutrophil Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.
7. Aceclofenac is also an NSAID with greater COX-2 specificity

5.2 Pharmacokinetic properties Absorption:

Mean absorption through the skin varies between <1-12% with large inter-individual variability. Absorption is dependent on the amount of the topical dose applied and the site of application.

Distribution:
Widely distributed in the body as protein-bound form. It is highly protein-bound (>99.7%). Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 60% of those in plasma.

Biotransformation:
Biotransformation of Aceclofenacinvolves partly conjugation of the intact molecule, but mainly single and multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to glucuronideconjuguates. Two of these phenolic metabolites are biologically active, however to a much lesser extent than Aceclofenac.Metabolism of Aceclofenacfollowing percutaneous and oral administration is similar.Metabolized into metabolites in the liver. Main metabolite is 4-hydroxyaceclofenac

Elimination:
It is excreted through urine mainly as conjugated hydroxymetabolites.

5.3 Preclinical safety data

Published animal studies have shown that when given orally, the principal adverse effect is on the gastrointestinal tract. Aceclofenacinhibited ovulation in the rabbit and impaired implantation, as well as early embryonic development in the rat. The embryo/foeto-toxic potential of Aceclofenac was evaluated in three animal species (rat, mouse and rabbit). Foetal death and growth retardation occurred at maternal toxic doses, however, on the basis of the available data, Aceclofenacis not considered to be teratogenic. The gestation period and the duration of parturition were extended by

Aceclofenac. Doses lower than maternal toxic ones did not affect the postnatal development. Results from extensive genotoxicity and carcinogenicity testing suggest that it is unlikely that Aceclofenacwould pose a significant carcinogenic hazard to humans.

6. Pharmaceutical particulars

6.1 List of excipients

Purified Water
Carbomer 940
Sodium
Hydroxide
Glycerin
Poly ethylene glycol
400 Tween 80
Camphor 5% w/w
Benzyl Alcohol
1%w/w

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a cool place,
Protect from light. Do not freeze.
Replace the cap tightly after use.

6.5 Nature and contents of container

30 gm lami tube packed in one carton pack.
Pack size: 30 gmlami tube in one carton box along with packing leaflet.

6.6 Special precautions for disposal

Not applicable

7. Registrant

Eastleigh Pharmaceuticals Co. Ltd
P.O Box 167-00610 Nairobi, Kenya

8. Market Authorization Holder

MARS REMEDIES PVT LTD
Address: 635, GIDC Estate, Waghodia-391760, Vadodara, GUJARAT INDIA

9. Market Authorization Number

H2024/CTD10280/20986

10. Date of revision of the text

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