Professional Information for MOTIFINE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

MOTIFINE 75 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg diclofenac sodium (25 mg as enteric coated pellets and 50 mg as sustained release pellets).
Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

Hard gelatine capsules (size 2) with light blue opaque cap and colourless transparent body marked in white print “D75M”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOTIFINE is indicated for the emergency treatment of acute gout attacks.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment.

Adults

One capsule daily. Dose may be increased to two capsules daily, if necessary, with a maximum daily dose of 150 mg. The first dose should be taken in the morning with breakfast and the second if required 8 - 12 hours later. The maximum treatment period of 3 days should not be exceeded.

Children

Not for use in children.

Elderly

Elderly patients are at increased risk of the serious consequences of adverse reactions. If MOTIFINE is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during MOTIFINE therapy.

Method of administration

For oral administration.

The capsules should be swallowed whole with a liberal quantity of liquid.

To be taken preferably with or after food.

4.3 Contraindications

- Hypersensitivity to diclofenac sodium or to any of the excipients listed in section 6.1.
- Previous hypersensitivity reactions (e.g., asthma, urticaria, angioedema or rhinitis) in response to ibuprofen, aspirin or other nonsteroidal anti-inflammatory medication.
- Severe renal and hepatic failure.
- Pregnancy and lactation.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including MOTIFINE.
- Active or history of recurrent ulcer/ haemorrhage/ perforations.
- Porphyria.
- Children under the age of 12 years.

4.4 Special warnings and precautions for use

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Allergic reactions, including anaphylactic/ anaphylactoid reactions, can also occur without previous exposure to MOTIFINE. MOTIFINE may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The use of MOTIFINE with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 4.5).

Cardiovascular, renal and hepatic impairment: Close medical surveillance is required when prescribing MOTIFINE to patients with impaired hepatic function, as their condition may be exacerbated. Treatment with MOTIFINE can be associated with a rise in liver enzymes. During prolonged treatment with MOTIFINE, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, or if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g., eosinophilia, rash), MOTIFINE should be discontinued. Hepatitis may occur without prodromal symptoms. Caution is called for in patients with hepatic porphyria, since it may trigger an attack.

Appropriate monitoring and caution are required in patients with a history of hypertension and/ or heart failure as fluid retention and oedema have been reported in association with MOTIFINE therapy. In view of MOTIFINE's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Particular caution is called for in patients with impaired cardiac or renal function, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g., before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using MOTIFINE in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

The administration of MOTIFINE may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3).

Cardiovascular and cerebrovascular effects: Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Diclofenac treatment for patients with uncontrolled hypertension should be given only after careful consideration.

Caution is required in patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with diclofenac after careful consideration.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Elderly: Elderly patients have an increased frequency of adverse reactions to NSAIDs including MOTIFINE, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.
A reduction in dosage may be required in the elderly, especially the very frail or those with a low body mass.

Gastrointestinal bleeding, ulceration and perforation: The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of MOTIFINE, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving MOTIFINE, treatment with MOTIFINE should be stopped.

MOTIFINE should be given with caution to patients with a history of gastrointestinal disease (e.g., ulcerative colitis, Crohn’s disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated. Strict accuracy of diagnosis and close medical surveillance are imperative in these patients.

Dermatological: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. MOTIFINE should be discontinued at the first appearance of skin rash, mucosal lesions and any other sign of hypersensitivity.

Respiratory disorders: In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e., nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to NSAIDs, as contained in MOTIFINE, like asthma exacerbations, Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for a medical emergency). This is also applicable to patients who are known to be allergic to other substances and have previously presented with skin reactions, pruritus or urticaria.

Methotrexate: Serious interactions have been reported after concomitant use of methotrexate and MOTIFINE (see section 4.5).

SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Drug reaction with eosinophilia and systemic symptoms: Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as MOTIFINE. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue MOTIFINE and evaluate the patient immediately.

Haematological effects: MOTIFINE can reversibly inhibit platelet aggregation.

Renal tubular acidosis (RTA) and hypokalaemia: NSAIDs, such as MOTIFINE, is associated with an increased risk of RTA and hypokalaemia.

4.5 Interaction with other medicines and other forms of interaction

NSAIDs: the use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Anti-coagulants: MOTIFINE may enhance the effects of anti-coagulants such as warfarin. There are reports of an increased risk of haemorrhage in patients receiving concomitant diclofenac and anticoagulants. Close monitoring of such patients is therefore recommended.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

Acetylsalicylic acid / aspirin: The bioavailability of both MOTIFINE and acetylsalicylic acid may be reduced if used concurrently.

Methotrexate: Caution should be exercised if MOTIFINE and methotrexate are administered within 24 hours of each other. MOTIFINE can inhibit the tubular renal clearance of methotrexate thereby increasing methotrexate levels, leading to toxicity.

Diuretics and anti-hypertensives: Reduced diuretic and anti-hypertensive effect may be seen. The combination should be administered with caution, and patients, especially the elderly, should have their blood pressure monitored. Patients should be adequately hydrated and renal function monitored after initiation of concomitant therapy and periodically thereafter, particularly for those patients on diuretics and MOTIFINE, due to the increased risk of nephrotoxicity.
Diuretics can increase the risk of nephrotoxicity of MOTIFINE. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.
Deterioration in renal function has been attributed to the use of MOTIFINE with triamterene.

Quinolone antibiotics: There have been reports of convulsions which may have been due to concomitant use of quinolone antibiotics and NSAIDs, such as MOTIFINE.

Ciclosporin: Nephrotoxicity of ciclosporin may be increased by the effects of MOTIFINE on renal prostaglandins.

Lithium and digoxin: Decreased elimination of lithium and digoxin may occur, therefore increasing the plasma concentrations if taken with MOTIFINE.

Cardiac glycosides: MOTIFINE may exacerbate cardiac failure, reduce GFR (Glomerular Filtration Rate) and increase plasma digoxin levels. Monitoring of serum digoxin levels is recommended.

Mifepristone: MOTIFINE should not be used for 8 -12 days after mifepristone administration as MOTIFINE can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when MOTIFINE is given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when MOTIFINE is given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Phenytoin: Monitoring of phenytoin plasma concentrations is recommended due to an expected increase in phenytoin levels.

Colestipol and colestyramine: These medicines can induce a delay or decrease in absorption; therefore, it is recommended that MOTIFINE is administered at least one hour before or 4 - 6 hours after administration of colestipol/ cholestyramine.

Potent CYP2C9 inhibitors: Caution recommended when co-prescribing MOTIFINE with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to MOTIFINE.

Antidiabetics: Studies have shown that MOTIFINE can be given together with oral antidiabetic medicines without influencing their clinical effect. However, there have been reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic medicines during treatment with MOTIFINE. Therefore, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

MOTIFINE should not be used in pregnancy (see section 4.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/ or the embryo/ fetal development. Data from epidemiological studies raise concern about 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 dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Use of nonsteroidal anti-inflammatory drugs during the third trimester of pregnancy, may cause:

- Cardiopulmonary toxicity (premature closure of the fetal ductus arteriosus *in utero*, and possibly, persistent pulmonary hypertension of the newborn.
- Renal dysfunction, which may progress to renal failure with oligo-hydramnios (see section 4.4).

The onset of labour may be delayed and its duration increased.

Breastfeeding

MOTIFINE should not be used by mothers who are breastfeeding their infants (see section 4.3).

Fertility

The use of MOTIFINE may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigations of infertility, withdrawal of MOTIFINE should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, drowsiness, fatigue and visual disturbances, vertigo, somnolence or other central nervous system disturbances while taking MOTIFINE, should refrain from driving a vehicle or operating machinery.

4.8 Undesirable effects

The most commonly observed adverse events are gastrointestinal in nature.

Blood and lymphatic system disorders

Less frequent: Leucopoenia, neutropenia, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis.

Immune system disorders

Less frequent: Non-specific allergic reactions, anaphylactoid reactions (including hypotension and shock) and anaphylaxis. Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, angioedema, angioneurotic oedema (including face oedema).

Psychiatric disorders

Frequent: Nervousness

Less frequent: Disorientation, insomnia, irritability, depression, anxiety, nightmares, psychotic reactions, confusion, hallucinations.

Nervous system disorders

Frequent: Headache, dizziness.

Less frequent: Tiredness, disturbances of sensation (including paraesthesia), memory disturbance, convulsions, tremor, aseptic meningitis (see section 4.4) (with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation), fatigue, somnolence, malaise, drowsiness, taste disturbances, cerebrovascular accident.

Eye disorders

Less frequent: Disturbances of vision (diplopia, blurred vision), optic neuritis.

Ear and labyrinth disorders

Frequent: Vertigo.

Less frequent: Ringing or buzzing in ears, impaired hearing.

Cardiac disorders

Less frequent: Oedema, hypertension, vasculitis, chest pain, cardiac failure, angina pectoris or exacerbation thereof, cardiac dysrhythmias, palpitations.

Frequency unknown: Kounis syndrome.

Vascular disorders

Less frequent: Small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Less frequent: Asthma (including dyspnoea), pneumonitis.

Gastrointestinal disorders

Frequent: Peptic ulcer, perforation or gastrointestinal bleeding (sometimes fatal). Nausea, vomiting, diarrhoea, flatulence, anorexia, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Less frequent: Abdominal distention, bloody diarrhoea, lower gastrointestinal disorders such as haemorrhagic colitis, glossitis, oesophageal lesions, diaphragm-like intestinal strictures, and pancreatitis.

Frequency unknown: Ischaemic colitis.

Hepato-biliary disorders

Frequent: Elevated transaminase levels (ALT, AST).

Less frequent: Hepatitis with or without jaundice, fulminant hepatitis, abnormal liver function, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Frequent: Skin rash and skin reactions.

Less frequent: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), itching, skin rash, hair loss, photosensitivity reaction, purpura

including allergic purpura, urticaria, skin eruptions, eczema, erythema multiforme, loss of hair, exfoliative dermatitis, pruritus.

Frequency unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Renal and urinary disorders

Less frequent: Acute renal failure, urinary abnormalities such as haematuria, proteinuria, interstitial nephritis, nephritic syndrome, renal papillary necrosis.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of MOTIFINE is important. It allows continued monitoring of the benefit/ risk balance of MOTIFINE. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms included headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, and occasional convulsions. In case of significant poisoning, acute renal failure and liver damage are possible.

Treatment is symptomatic and supportive, especially for hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression.

Absorption should be prevented as soon as possible after an overdose by means of activated charcoal.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Specific therapies such as forced diuresis, dialysis or haemoperfusion are of little value in eliminating MOTIFINE because of its high protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: Acetic acid derivatives and related substances.

ATC code: M01AB05.

Diclofenac is a nonsteroidal anti-inflammatory compound (NSAID) with analgesic, antipyretic and anti-inflammatory activities. It causes decreased formation of prostaglandins and thromboxanes through inhibition of the activity of the enzyme cyclo-oxygenase. Prostaglandins play a major role in the causation of inflammation, pain and fever and the inhibition of prostaglandin synthesis may have an important bearing on diclofenac's mechanism of action. Diclofenac inhibits platelet aggregation *in vitro.*

In addition, diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of the fatty acid.

5.2 Pharmacokinetic properties

Diclofenac is well absorbed after oral administration. Therapeutic plasma concentrations occur about ½ hour after administration of MOTIFINE.

There is a substantial first-pass effect (only 50 % of diclofenac is available systemically). Diclofenac is extensively bound to plasma proteins (99 %) and its plasma half-life for the terminal elimination phase is 1 - 2 hours.

Diclofenac is metabolised in the liver by a cytochrome P450 isozyme of the CYP2C subfamily and excreted in the form of glucuronide and sulphate conjugates. Approximately 60 % of the administered dose is excreted via the kidneys in the form of metabolites and less than 1 % in unchanged form. The remainder of the dose is excreted via the bile in metabolised form.

Following rapid gastric passage, the enteric coated pellet component of MOTIFINE ensures quick availability of the active component in the blood stream. The sustained release pellets cause a delayed release of the active component, which means one single daily dose is usually sufficient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Enteric coated pellets:

Microcrystalline cellulose

Povidone

Colloidal anhydrous silica

Methacrylic acid ethyl acrylate copolymer

Propylene glycol

Talc.

Sustained release pellets:

Microcrystalline cellulose

Povidone

Colloidal anhydrous silica
Ammonio methacrylate copolymer
Triethylcitrate
Talc.
Capsule shell:
Indigocarmine (E132)
Titanium dioxide (E171)
Gelatine.
Capsule body:
Gelatine
Ink (containing shellac, propylene glycol, titanium dioxide [E171]).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store at or below 25 °C. Protect from moisture.
The capsules should be stored in the blister strips until required for use.

6.5 Nature and contents of container
The capsules are blister packed in white opaque PVC/ PVDC and silver aluminium foil and packed into outer cardboard cartons.
Pack size: 6 capsules.

6.6 Special precautions for disposal and other handling
Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Biotech Laboratories (Pty) Ltd
Ground Floor, Block K West, Central Park
400 16th Road, Randjespark, Midrand 1685
South Africa

8. REGISTRATION NUMBER

45/3.1/1150

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18 February 2016

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21 July 2023