Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Difene 75mg Dual Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75mg diclofenac sodium in a modified release formulation (25 mg gastro-resistant pellets and 50mg prolonged release pellets).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release capsule, hard.

Product imported from the UK:
Size 2, hard gelatin capsules with light blue opaque caps and colourless transparent bodies, printed with "D75M" in white, containing white to cream-coloured spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a non-steroidal anti-inflammatory analgesic in the symptomatic management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, acute musculo-skeletal disorders such as periarthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations, relief of pain in fractures, low back pain, acute gout, psoriatic arthropathy. In the management of pain and inflammation associated with orthopaedic, dental and minor surgery.
In the management of dysmenorrhoea and associated menorrhagia.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

For oral use only. The capsules should be swallowed whole with liquid.

Adults: One or two capsules (75-150 mg) in divided doses, daily. The daily dose should not exceed 150 mg.

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also section 4.4.

Children: Not recommended.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

4.3 Contraindications

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure.

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to diclofenac, aspirin, nonsteroidal anti-inflammatory drugs or any components of the preparation.

4.4 Special warnings and precautions for use

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

The use of Difene with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Gastrointestinal bleeding, ulceration and bleeding: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowese dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5)

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Difene the treatment should be withdrawn.

NSAIDs should be given with care to patienta with a history of gastrointestinal disease (ulcerative colitis, Chron’s disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Difene should be discontinued at the first appearance of skin rash, mucoal lesions, or any other sign oh hypersensitivity.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control the symptoms (see section 4.2, and GI and cardiovascular risks below)

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral aerterial disease, and/or cerebrovascular disease should not be treated with diclofensc after careful consideration.

Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs longterm should undergo regular medical supervision to monitor for adverse events.

In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Diclofenac should be used with caution in patients with a history of peptic ulceration or inflammatory bowel disease. As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4)
Anti coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):increased risk of gastrointestinal bleeding (see section 4.4)
Care should be taken in patients treated with any of the following drugs as interactions have been reported:
Anti-hypertensives: reduced anti-hypertensive effect.
Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
Lithium: decreased elimination of lithium.
Methoterexate: decreased elimination of methotrexate.
Cyclosporin: increased risk of nephrotoxicity with NSAIDs.
Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.
Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

4.6 Fertility, pregnancy and lactation

Although animal studies have not demonstrated teratogenic effects, Difene should not be used in pregnancy or lactation unless considered essential by the physician and if so the lowest effective dose should be used. Use of prostaglandin synthetase inhibitors in the third trimester may result in premature closure of the ductus arteriosus. Traces of drug are detectable in breast milk but are not clinically significant.

4.7 Effects on ability to drive and use machines

Isolated cases of disorientation and blurred vision have been reported with diclofenac sodium. If affected refrain from driving or operating machinery.

4.8 Undesirable effects

Gastro-intestinal :
The most commonly observed adverse events are gastronintestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and hron's disease (see section 4.4 – Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

If serious side-effects occur, Difene should be withdrawn.

Central Nervous System:

Occasional: headache, dizziness or vertigo.
Rare: drowsiness, tiredness.
Isolated cases: disturbances of sensation (paraesthesiae, memory disturbance, disorientation, disturbance of vision, blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

Skin:

Occasional: rashes or skin eruptions.*Rare:* urticaria
Isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney:
Isolated cases: acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:

Occasional: elevation of serum aminotransferase enzymes (SGOT, SGPT).
Rare: liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood*:*

Isolated cases: thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Other organ systems:

Rare: oedema, hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).
Isolated cases: impotence (association with Diclofenac sodium intake is doubtful), palpitation, chest pain, hypertension.

Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggests that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

4.9 Overdose

Management of acute poisoning with diclofenac and other non-steroidal anti-inflammatory drugs consists of supportive and symptomatic measures. Therapeutic measures that can be taken include; supportive and symptomatic treatment for the complications of overdosage such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression; Forced diuresis or dialysis are probably of no help in eliminating diclofenac and other non-steroidal anti-inflammatory medicines due to their high rate of protein binding.
Additional measures include gastric lavage and treatment with activated charcoal. Difene 75 mg and 100 mg Dual Release are controlled release systems which will continue to release diclofenac for some hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

MO1A B05 Anti-inflammatory and anti-rheumatic products, non-steroids, acetic acid derivatives and related substances diclofenac.

Diclofenac sodium is a phenylacetic acid derivative and a non-steroidal anti-inflammatory agent with analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is an inhibitor of cyclo-oxygenase and therefore reduces prostaglandin synthesis. Reduction in prostaglandin levels reduces the inflammatory response by the body.

5.2 Pharmacokinetic properties

The enteric coated pellet component of the preparation ensures quick availability, following rapid gastric passage, of the active component in the blood stream and the sustained release pellet causes a delayed release of the active component.

At therapeutic concentrations, diclofenac is extensively bound (more than 99%) to plasma proteins. It is subject to first pass metabolism and extensively metabolised in the liver (50-60%). Diclofenac is excreted mostly through the urine with a small amount excreted in the bile, it also enters the synovial fluid and is excreted in breast milk. Diclofenac has a short half-life of about 1-4 hours.

5.3 Preclinical safety data

Animal studies have been carried out in a number of species to determine the toxicity of diclofenac sodium. Acute toxicity studies have been carried out in the rat and when administered orally an LD50 of 53 mg/kg produced behavioural effects and respiratory stimulation. Acute oral toxicity studies in the rabbit showed no toxic effect at a dose of 157 mg/kg.
Reproductive toxicity has been studied in both the rat and the rabbit, a dose of 1 mg/kg/day for 21 days in rats has been shown to produce developmental abnormalities of the cardiovascular system. In the rabbit a dose of 10 mg/kg has been shown to reduce fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Povidone k25
Methacrylic acid copolymer type C
Talc
Ammonio methacrylate copolymer types A and B
Colloidal anhydrous silica
Propylene glycol
Sodium hydroxide
Dibutyl phthalate.
Gelatin (bovine)
Purified water
Titanium dioxide (E171)
Indigotine (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister. Pack size: 56 capsules

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/185/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th October 2006

Date of Last Renewal: 13th October 2011

10 DATE OF REVISION OF THE TEXT

January 2013