SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulindac 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of sulindac

Excipients with known effect:
Each tablet contains 18 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

8mm flat bevel-edged orange yellow tablet marked “SD” breakline “100” on one side and “α” on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sulindac is a non-steroidal anti-inflammatory drug with analgesic and antipyretic activity and is indicated in rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankylosing spondylitis and musculoskeletal and periarticular disorders such as tendinitis, tenosynovitis, and bursitis.

4.2 Posology and method of administration

Posology:
For oral administration.

Sulindac should always be taken with fluids either with food or immediately after food and is normally taken twice a day. The usual adult dosage is 400 mg a day and doses above this level are not recommended. Lower doses may be found sufficient. Seven days treatment is usually sufficient for acute gouty arthritis. For peri-articular disorders treatment should be no longer than 7 to 10 days.

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

Paediatric population
Not recommended.

Older people
Older people are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. NSAIDS are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Severe hepatic, renal and cardiac failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6).

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

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

The use of Sulindac with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Older people:
Older people have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2)

Respiratory disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID 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 older people. Renal function should be monitored in these patients (see also section 4.3).

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 use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for sulindac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with sulindac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with our 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 lowest 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 section 4.5).

Patients with a history of GI toxicity, particularly older people, 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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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).

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for 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. Sulindac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.3).

Anti-hypertensives: May be a 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 glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity. Renal function should be carefully monitored.

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

Corticosteroids: Increased risk of GI ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Patients should be carefully monitored to ascertain that no change in their anticoagulant dosage is necessary.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Probenecid: Use of probenecid with sulindac leads to increased levels in plasma of sulindac and the inactive sulphone metabolite.

Diflunisal: Concurrent administration with diflunisal may lead to a reduction in plasma level of the active metabolite of sulindac.

Dimethyl sulfoxide: Concurrent use of dimethyl sulfoxide and sulindac is not recommended since this has been shown to lead to both a reduction in plasma levels of the active sulphide metabolite and to causing peripheral neuropathy.

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

4.6. Fertility, pregnancy and lactation

Sulindac has not been established as safe for use in pregnant or lactating women.

Pregnancy:
Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). From the 20th week of pregnancy onward, sulindac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. If sulindac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to sulindac for several days from gestational week 20 onward. Sulindac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, 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.

Consequently, sulindac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding:
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

Fertility:
The use of sulindac 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 sulindac should be considered.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in older people, may occur (see section 4.4). Nausea, vomiting, anorexia, diarrhoea, flatulence, constipation, gastrointestinal cramps, dyspepsia, abdominal pain, melaena, haematemesis, pancreatitis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis and gastroenteritis have been observed. Pancreatitis has been reported very rarely.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (hypersensitivity vasculitis) (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or epistaxis or (c) assorted skin disorders, including rashes of various types, sore or dry mucous membranes, pruritus, urticaria, purpura, angiodema, alopecia and, more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome).

Cardiovascular: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Less frequently, congestive heart failure, especially in patients with marginal cardiac function, palpitation, hypertension and arrhythmia have been reported with sulindac. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Other adverse events reported less commonly include:

Genito-urinary: urine discoloration, vaginal bleeding, haematuria, proteinuria, crystalluria, gynaecomastia

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis, cholestasis and jaundice.

Neurological and special senses: Visual disturbance including blurred vision, optic neuritis, decreased hearing, metallic or bitter taste, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, nervousness, confusion, hallucinations, convulsions, syncope, psychic disturbances including acute psychosis, tinnitus, vertigo, somnolence, insomnia, sweating, asthenia, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, leucopenia, bone marrow depression including aplastic anaemia, haemolytic anaemia, increased prothrombin time in patients on oral anticoagulants

Metabolic: hyperkalaemia, hyperglycaemia

Dermatological: photosensitivity, ecchymosis, purpura.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9. Overdose

a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, stupor, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions, hypotension and a reduction in urine output.
In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure
Patients should be treated symptomatically as required.
Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Sulindac is a fluorinated indene with a structural resemblance to indometacin. It has analgesic, anti-inflammatory and antipyretic actions.

5.2. Pharmacokinetic properties

Sulindac is incompletely absorbed from the gastro-intestinal tract. It is metabolised by reversible reduction to the sulphide metabolite, which appears

to be the biologically active form, and by irreversible oxidation to the sulphone metabolite. Peak plasma concentrations of the sulphide metabolite are achieved in about 2 to 4 hours. The mean half-life of sulindac is about 7 to 8 hours and of the sulphide metabolite about 16 to 18 hours. About 50% is excreted in the urine mainly as a sulphone metabolite and its glucuronide conjugate. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain:
Lactose monohydrate
Cellulose, microcrystalline
Povidone
Sodium starch glycolate
Magnesium stearate
Talc
Quinolone yellow (E104).

6.2. Incompatibilities

None stated

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25ºC. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Sulindac tablets are available either in PVC/aluminium foil blisters or polypropylene containers with polyethylene caps. The pack sizes available in both pack types are 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112 120, 168 and 180. In the polypropylene containers pack sizes of 50, 200 and 500 are also available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited
T/A Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL

8. MARKETING AUTHORISATION NUMBER

Sulindac Tablets BP 100 mg PL 04569/0187

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/11/1987 / 15/07/2005

10 DATE OF REVISION OF THE TEXT

24/02/2023