SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Product Name: SYNOVACE 100

(Aceclofenac Tablets 100mg)

Strength :

100mg/Tablets

Pharmaceutical Dosage Form

Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Aceclofenac BP 100 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Visual description of finished product:

Visual description of finished product: Light yellow colour oblong film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications and Usage

Synovace tablet is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2. Posology and method of administration

Synovace film-coated tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid.

To be taken preferably with or after food.

When Synovace was administered to fasting and fed healthy volunteers only the rate and not the extent of aceclofenac absorption was affected. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Adults

The recommended dose is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening.

Children

There are no clinical data on the use of Synovace in children and therefore it is not recommended for use in children.

Elderly

The elderly, who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication, 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.

The pharmacokinetics of Synovace are not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

Renal insufficiency

There is no evidence that the dosage of Synovace needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised (see also Precautions).

Hepatic insufficiency

There is some evidence that the dose of Synovace should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

4.3. Contraindications

Hypersensitivity to aceclofenac or to any of the excipients.

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

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 nonsteroidal

anti-inflammatory drugs.

Severe heart failure, hepatic failure and renal failure.

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

Synovace should not be prescribed during pregnancy, especially during the last trimester of

pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

4.4. Special Warning and Precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. The use of Synovace with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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 the elderly. Renal function should be monitored in these patients.

Renal:

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Synovace

Hepatic:

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Synovace should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms. Use of Synovace in patients with hepatic porphyria may trigger an attack.

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 aceclofenac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aceclofenac 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 or without warning symptoms or a previous history of serious GI events.

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis or with Crohn's disease, bleeding diathesis or haematological abnormalities.

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 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.

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 antiplatelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving aceclofenac, 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.

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.

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. 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. Synovace should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility:

The use of Synovace 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 Synovace should be considered.

Hypersensitivity reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological:

Synovace may reversibly inhibit platelet aggregation (see anticoagulants under 'Interactions').

Long-term treatment:

All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure, hepatic function (elevation of liver enzymes may occur) and blood counts.

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

Anti-hypertensives: NSAIDs may reduce the effect of anti-hypertensives. The risk of acute renal insufficient, which is usually reversible, may be increased in some patients with compromised

renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Lithium and digoxin: Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of both. The combination should be avoided unless frequent monitoring of lithium and digoxin levels can be performed.

Methotrexate: Decreased elimination of methotrexate. The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

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 gastrointestinal ulceration or bleeding.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin. Close monitoring of patients on combined anti-coagulants and Aceclofenac Tablets therapy should be undertaken.

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.

Cisclosporin, Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function

.*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.

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Other NSAIDs: Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

4.6 Fertility, pregnancy and lactation

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) and on the possible risk of persistent pulmonary hypertension of the new born, use in the last trimester of pregnancy is contraindicated. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. 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.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some foetuses.

Usage in Nursing Mothers

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations.

NSAIDs should, if possible, be avoided when breastfeeding. See section 4.4 Special warnings and precautions for use, regarding female fertility.

The use of Synovace should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, vertigo, drowsiness, fatigue, visual disturbances or other central nervous system disorders 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 the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has 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 (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular:

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

Aceclofenac is both structurally related and metabolised to diclofenac for which a greater amount of clinical trial and epidemiological data consistently point towards an increased risk of general arterial thrombotic events (for example myocardial infarction or stroke , particularly at high doses or in long treatment). Epidemiological data has also found an increased risk of acute coronary syndrome and myocardial infarction associated with the use of aceclofenac (see

section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use). Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment

Other adverse reactions reported less commonly include:

Renal:

interstitial nephritis

Neurological and special senses:

optic neuritis, 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) , confusion, hallucinations, malaise, and drowsiness.

Haematological:

agranulocytosis, aplastic anaemia

Dermatological:

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

If serious adverse reactions occur, Aceclofenac tablets should be withdrawn.

4.9 Overdose

Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally and convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

Treatment

Patients should be treated symptomatically as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group : Anti-inflammatory and analgesic

ATC CODE: M01AB16

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

5.2 Pharmacokinetics:

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein- bound >99%). Aceclofenac circulates mainly as unchanged drug. 4'- Hydroxyaceclofenac is the main metabolite detected in plasma. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.

No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

5.3 Preclinical safety data

There are no pre-clinical data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients (s)

Aceclofenac (Micronised)
Micro Crystalline Cellulose (DC)
Beta Cyclodextrin
Starch (For Lubrication)
Magnesium Stearate
Talcum Powder
Aerosil -200
Instacoat Aqua III White - 40001(Ideal Cures)
Colour yellow Oxide of Iron
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months (2 years)

6.4 Special precautions for storage

Store in dry place, below 30^0C. Protect from Light. Keep out of the reach of Children.

6.5 Nature and contents of container

Primary Packing: 10 Tablets Packed in Alu-PVC Blister.

Secondary Packing:10 Tablets are packed in one Alu-Pvc blister pack and such 1 blister is packed in a Printed Carton with a pack insert.

6.6 Special precautions for disposal <and other handling>

Not Applicable.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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