EVANS BAROQUE LIMITED

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC) BAROFLAM 100MG SR

1. NAME OF THE MEDICINAL PRODUCT

(Baroflam 100 Sustained Release Tablets) Diclofenac 100mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: Diclofenac 100mg

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Orange coloured oval shape enteric coated tablet having plain on both sides. Packaging: Baroflam 100 SR-ALU/PVC blisters of 1 x 10's, 1 X 10 X 10 and 10 x 10's

4. Clinical particulars

4.1 Therapeutic indications

{Baroflam 100 SR, Diclofenac 100mg, tablet} is indicated in adults

In adults: Baroflam is used as an analgesic for Relief of all grades of pain and inflammation in a wide range of conditions, including:

(i) Arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,

(ii) Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,

(iii) other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery

Diclofenac Sodium 100mg SR tablets are not suitable for children.

4.2 Posology and method ofadministration

Posology

Pediatric population

Diclofenac sodium 100mg SR tablets are not suitable for children.

Posology and method of administration:

Dosage and administration

Adults: 1 tab daily.

The recommended maximum daily dose of diclofenac sodium is 100mg.

Special populations

Elderly:

Although the pharmacokinetics of Diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

Cardiovascular and significant cardiovascular risk factors

Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used and for the shortest duration possible.

Renal impairment: Diclofenac is contraindicated in patients with renal failure (see section 4.3 Contraindications). No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment.

Hepatic impairment: Diclofenac is contraindicated in patients with hepatic failure. No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment.

Paediatric population:

Diclofenac Sodium 100mg SR tablets are not suitable for children.

{Baroflam 100 SR, Diclofenac 100mg SR, tablet} is contraindicated in children (see Section 4.3).

Method of administration

For oral administration

To be taken whole with liquid, preferably with or after food

4.3 Contraindications

Diclofenac Sodium 100mg SR tablets are not suitable for children

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Active, or gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy Hepatic failure

- Renal failure
- Established congestive heart failure (NYHA-11-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angiodema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low bodyweight.

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/ anaphylactoid reactions, can also occur without earlier exposure to the drug.

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamics properties.

Gastrointestinal effects

Gastrointestinal bleeding (hematemesis, melena), ulceration or perforation, which can be fatal has been reported with all NSAIDs including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal (GI) events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin), or other medicinal products likely to increase gastrointestinal risk.

Renal impairment

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac,

particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, 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

Skin effects
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, including Diclofenac. Diclofenac sodium tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

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

Cardiovascular and cerebrovascular effects
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) 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.

Haematological effects
Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma
Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

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

4.5 Interaction with other medicinal products and other forms of interaction

Do not use different types of pain-relieving medicines at the same time unless directed by a doctor. Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharma¬ceutical forms of diclofenac.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum

digoxin level is recommended.

Diuretics and Anti-hypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Anticoagulants and anti-platelet agents: As with other nonsteroidal anti-inflammatory agents, diclofenac in high dose can reversibly inhibit platelet aggregation.

Other NSAIDS including cycfo-oxygenase-2selective inhibitors and corticosteroids: Co-administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration.

Selective serotonin reuptake inhibitors (SSR/s): Concomitant administration of SSRls may increase the risk of gastrointestinal bleeding.

Antidiabetics: 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 necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

Potent CYP2C9 inhibitors: "Caution is recommended when co¬prescribing diclofenac with potent CYP2C9 inhibitors

(such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

4.6 Pregnancy and Lactation

Pregnancy:
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 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-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. If diclofenac 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

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, diclofenac sodium tablets are contraindicated during the third trimester of pregnancy.

Breast-feeding:
Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2).
Female Fertility
As with other NSAIDs, the use of diclofenac 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 diclofenac should be considered (see also section 4.4 regarding female fertility).

4.7 Effects on ability to drive and use machines

{Baroflam 100 SR, Diclofenac 100mg SR, tablets} Patients who experience visual disturbances, dizziness, vertigo,

somnolence central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operate machinery.

4.8 Undesirable effects

The following undesirable effects include those reported with either short-term or long-term use.

Blood and lymphatic system disorders: Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis

Immune system disorders: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock), Angioneurotic oedema (including face oedema)

Psychiatric disorders: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders: Headache, dizziness, somnolence, tiredness, paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders: Visual disturbance, vision blurred, diplopia. Optic neuritis.

Ear and labyrinth disorders: Vertigo, Tinnitus, hearing impaired

Cardiac disorders: Myocardial infarction, cardiac failure, palpitations, chest pain.

Vascular disorders: Hypertension, hypotension, vasculitis.

Respiratory, thoracic and mediastinal disorder: Asthma (including dyspnoea), Pneumonitis

Gastrointestinal disorders: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly),Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, Ischaemic colitis.

Hepatobiliary disorders: Transaminases increased, Hepatitis, jaundice, liver disorder, Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders: Rash. Urticaria.

Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

Renal and urinary disorders: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis

Reproductive system and breast disorders: Impotence General disorders and administration site conditions: Oedema.

4.9 Overdose

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures

and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose

If you have taken more Baroflam tablets than you should, or if children have taken this medicine by accident always contact a doctor or nearest hospital to get an opinion of the risk and advice on action to be taken

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Non-steroidal anti-inflammatory drugs (NSAIDs)

Pharmacotherapeutic group: {Analgesic}, ATC code:{N02}

Mechanism of action

Diclofenac sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase). It works by non-selectively inhibiting the enzyme called cyclooxygenase (COX), which is required for the synthesis of prostaglandins via the arachidonic acid pathway. COX converts arachidonic acid to prostaglandin H2 (PGH2) in the body. PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation, leading to the formation of blood clots).

Pharmacodynamic effects

Diclofenac sodium works by blocking the production of prostaglandins, substances that the body releases in response to illness and injury. Prostaglandins cause pain and swelling, or inflammation.

Clinical efficacy and safety

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Paediatric population

Not for use by children

5.2 Pharmacokinetic properties

Absorption:

Absorption is complete but onset is delayed until passage through the stomach, which may be affected by food which delays stomach emptying. The mean peak plasma diclofenac concentration reached at about 2 hours

Bioavailability:

About half of the administered diclofenac is metabolised during its first passage through the liver ("first-pass" effect),

the area under the concentrations curve (AU) following oral administration is about half that following an equivalent parenteral dose.

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%). Diclofenac was detected in a low concentration (100 ng/ml) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose

Metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination

The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min. The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

5.3 Preclinical safety data

None stated.

TERATOGENICITY

Pregnancy, breast-feeding and fertility:

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. If diclofenac 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
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, diclofenac sodium tablets are contraindicated during the third trimester of pregnancy.

Breast-feeding:

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Female Fertility

As with other NSAIDs, the use of diclofenac 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 diclofenac should be considered.

TOXICOLOGICAL DATA

The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low bodyweight.

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/ anaphylactoid reactions, can also occur without earlier exposure to the drug.

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamics properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NAME AND FUNCTION OF EACH INGREDIENT

Raw Material	**Function**
Diclofenac Sodium	Active
Calcium Hydrogen Phosphate	Diluent
Maize Starch	Binder
Maize Starch	Binder
Sodium Metabisulphite	Antioxidant
Diclofenac Sodium	Active
Purified Talc	Lubricant
Magnesium Stearate	Lubricant
Sodium Starch Glycolate	Disintegrant
Croscarmellose Sodium	Disintegrant
Microcrystalline Cellulose Granules 200 CPS 5	Diluent/Disintegrant
Colorcoat SC4S-H	Seal coat
Colorcoat EC4W-F	Film coat
Isopropyl Alcohol	Solvent
Methylene Chloride	Solvent

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep all medicines out of the reach of children. Do not store above 30°C.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Each film-coated tablet contains: Baroflam 100 SR-ALU/PVC blisters of 1 x 10's , 1 X 10 X 10 and 10x 10's

6.6 Special precautions for disposal <and other handling>

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

Evans Baroque Nigeria Limited

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