1. NAME OF THE MEDICINAL PRODUCT: RECTONAC-100

Generic Name of Product : Diclofenac Sodium Suppositories 100 mg

Strength (formula) : Each Suppository contains:
Diclofenac Sodium BP 100 mg
Suppository Base q.s.
Not for Veterinary Use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative & Quantitative Composition Declaration:

Batch Size: 52,000 Suppositories

Sr. No.	Raw Materials	Specification	Mg/Supp.	Overages	Standard Qty. for Batch in Kg.
1.	Diclofenac Sodium	BP	100	---	05.20
2.	Water soluble Base D1.5	--	495.00	--	25.74
3.	Water soluble Base C_6	--	405.00	--	21.06
Theoretical Weight			**1.0 gm**		**52 kg.**

BP – British Pharmacopeia

3. PHARMACEUTICAL FORM:

Almost white colour bullet shaped Suppositories.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Indication:

RECTONAC-100 suppositories

Adults and Elderly:

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, orthopedic, dental and other minor surgery.
RECTONAC-100 suppositories are not indicated for use in children.

4.2 Posology and Method of Administration:

Not to be taken by mouth, as per rectal administration only.
The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools.

Adults:

75-150mg daily, in divided doses (50mg and 100mg suppositories only).
The recommended maximum daily dose of RECTONAC-100 is 150mg. This may be administered using a combination of dosage forms, e.g. tablets and suppositories. (50 mg and 100 mg suppositories only).
100 mg suppositories may also be given as a once daily treatment, usually at night. Where necessary, therapy may be combined with 25mg or 50mg tablets or suppositories up to the maximum dose of 150 mg per day.

Special populations

Elderly

Although the pharmacokinetics of RECTONAC-100 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.

Renal impairment

Diclofenac is contraindicated in patients with severe renal impairment. 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 severe hepatic impairment. 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.

4.3 Contraindication:

• Hypersensitivity to the active substance or any of the excipients.
• Active, gastric or intestinal ulcer, bleeding or perforation
• History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy
• Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
• Last trimester of pregnancy (see section 4.6 Pregnancy and lactation)
• Severe hepatic, renal or cardiac failure (see section 4.4 Special warnings and precautions for use).
• Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
• Proctitis
• Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special Warning 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 RECTONAC-100 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 body weight.

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

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena) 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 GI events. They generally have

more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

Hepatic effects:
Close medical surveillance is required when prescribing RECTONAC-100 to patients with impairment of hepatic function as their condition may be exacerbated.
As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure.

Renal effects:
As fluid retention and oedema have been reported in association with NSAIDs 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 those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery.

Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

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 RECTONAC-100. Patients appear to be at the 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. RECTONAC-100 should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Lithium: If used concomitantly, RECTONAC-100 may increase plasma concentrations of lithium Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, RECTONAC-100 may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of RECTONAC-100 with diuretics and 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.
Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that RECTONAC-100 has an influence on the effect of

anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly (see section 4.4 Special warnings and precautions for use). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

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 or 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 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 organogenetic period. If RECTONAC-100 is used by a woman attempting to conceive, or during the 1st 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 the 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, RECTONAC-100 is contra-indicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into 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 may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered. See also section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machine:

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

4.8 Undesirable effects

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.

Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	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.
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	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	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Application site irritation, oedema
Reproductive system and breast disorders	
Very rare	Impotence

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, 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

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 potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Mechanism of action

RECTONAC-100 is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, swelling of the joints and an improvement in function.

In post–traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

In clinical trials diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhoea, diclofenac is capable of relieving the pain and reducing the extent of bleeding. Diclofenac also has beneficial effects on the symptoms of migraine attacks.

5.2 Pharmacokinetic properties

Absorption

Absorption is rapid; although the rate of absorption is slower than from enteric-coated tablets administered orally. After the administration of 50mg suppositories, peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of enteric-coated tablets (1.95 ± 0.8µg/ml (1.9µg/ml ≡ 5.9µmol/l)).

Bioavailability

As with oral preparations the AUC is approximately a half of the value obtained from a parenteral dose.

Pharmacokinetic behavior does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

The plasma concentrations attained in children given equivalent doses (mg/kg, b.w.) are similar to those obtained in adults.

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.

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 (see section 4.6 Pregnancy and lactation).

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 (mean value ± SD). 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

Diclofenac is a well established drug substance whose pre-clinical profile has been thoroughly investigated and is established.

6. Pharmaceutical particulars

6.1 List of excipients

Water soluble Base D1.5, Water soluble Base $C_{6.}$

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from light, heat & moisture.

KEEP MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

6.5 Nature and contents of container

Strip of 05 suppositories and such 02 strip is packed in printed carton.

6.6 Special precautions for disposal and other handling

---

7. Marketing authorization holder

GALEN PHARMACEUTICAL LTD

334/5 GIDC ESTATE, WAGHODIA,
DIST. BARODA, GUJARAT 391760, INDIA

8. Marketing authorization number(s)
Not Applicable

9. Date of first authorization/renewal of the authorization
Not Applicable

10. Date of revision of the text
Not Applicable