SUMMARY OF PRODUCT CHARACTERISTICS

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1. Trade name of medicinal product

Diclomol SR Tablets 100 mg
(Sustained Release Diclofenac Tablets BP)

2. Qualitative and Quantitative Composition

Unit Composition:

Ingredients	Pharmacopoeial Standard	Quantity (mg / tablet)	Function
ACTIVE INGREDIENT			
Diclofenac Sodium	BP	100.00	NSAID
INACTIVE INGREDIENTS			
Colloidal Anhydrous Silica (Aerosil 200)	BP	2.57	Glidant
Cetyl Alcohol	BP	55.20	Granulating Agent
Magnesium Stearate	BP	4.57	Lubricant
Povidone K-30	BP	6.00	Lubricant
Stearyl Alcohol	USP/NF	2.51	Granulating Agent
Sucrose	BP	102.57	Diluent

Coating Composition

Ingredients	Pharmacopoeial Standard	Quantity (mg / tablet)	Function
Uncoated Tablet		273.42	
Instacoat Aqua Brown (A01D00121)*	In-house	8.58	Colouring Agent

*The target weight build-up for coating is about 3.0%. The given quantity contains the process losses also.

3. Pharmaceutical form

Sustained Release Tablets (Oral Dosage form)

4. Clinical Particulars

4.1 Therapeutic indications

Due to its anti-inflammatory and analgesic effects, Diclomol EC 50 Tablets is indicated for the treatment of:

- Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, cervical spondylosis, intervertebral disc syndrome and sciatica.
- Non-articular rheumatic conditions such as fibrositis, myositis, bursitis, low back pain, etc.
- Soft tissue injuries such as sprains, strain and sports injuries.
- Painful inflammatory conditions in gynaecology.
- Post-operative and post-traumatic inflammation and swelling.
- Pain and inflammation following dental surgery.
- Acute attacks of gout.

4.2 Posology and Method of Administration

Adults: 1 tablets of Diclomol SR daily.

Where the symptoms are more pronounced during the night or in the morning, Diclomol SR should preferably be taken in the evening. For milder cases, where a lower dosage is sufficient, other forms of Diclomol are available.

The tablet of Diclomol SR should neither be broken or chewed. They should be taken whole with liquid, preferably at mealtimes.

Children: Diclomol SR is not suitable for children because of difficulty in dosage titration.

4.3 Contraindications

- Hypersensitivity to Diclofenac Sodium
- Peptic ulcer
- In asthmatic patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetyl salicylic acid or by other drugs with prostaglandin synthesis inhibiting activity.

4.4 Special warnings and special precautions for use

- Gastrointestinal effects: Peptic ulceration and GI bleeding have been reported. It is recommended that patients be maintained on the lowest dose of Diclofenac possible, consistent with achieving a satisfactory therapeutic response.
- Hepatic Effects: Elevations of one or more liver tests may occur during Diclofenac therapy.
- Anaphylactoid reactions: These may occur in patients without prior exposure to Diclofenac.
- Advanced Renal Disease: In cases with advanced kidney disease, treatment with Diclofenac, as with NSAIDS, should only be initiated with close monitoring of the patient's kidney functions.

4.5 Interaction with other medicinal products and other forms of Interaction.

DICLOFENAC - DRUG INTERACTIONS			
Precipitant drug	**Object drug ***		**Description**
Diclofenac	Anti-coagulants	↑	Co-administration may prolong prothrombin time (PT). Also consider the effects; Diclofenac has on platelet function and gastric mucosa. Monitor PT and patients
Diclofenac	Cyclosporine	↓	Nephrotoxicity of both agents may be increased.
Diclofenac	Hydantoin	↑	Serum Phenytoin levels may be increased, resulting in an increase in pharmacologic and toxic effects of phenytoin.
Diclofenac	Loop diuretics	↓	Effects of loop diuretics may be decreased.
Diclofenac	Methotrexate	↑	The risks of methotrexate toxicity (e.g. stomatitis, bone marrow suppression, and nephrotoxicity) may be increased.
Cimetidine	Diclofenac	↔	NSAID plasma concentrations may be increased or decreased by Cimetidine; some studies report no effect.
Probenecid	Diclofenac	↑	Probenecid may increase the concentrations and possibly the toxicity of the NSAID.
Salicylates	Diclofenac	↓	Plasma concentrations of Diclofenac may be decreased by salicylates. Avoid concurrent administration as it offers no therapeutic advantage and may significantly increase the incidence of GI effects.

***Key:**

↑ = Object drug increased
↓ = Object drug decreased
↔ = Undetermined effect

4.6 Pregnancy and lactation

The use of Diclomol SR tablets during pregnancy should, if possible, be avoided.
Diclofenac sodium in oral doses of 150 mg daily passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

4.7 Effects on ability to drive and use machinery

Patients who experience central nervous system reactions should refrain from driving and operating hazardous machinery.

4.8 Undesirable effects

At recommended doses, Diclomol SR is generally well tolerated. At the start of treatment, however, patients may some times complain of epigastric pain, nausea, diarrhoea, dizziness or headache. These unwanted effects are usually of a mild nature. Peripheral oedema and skin reactions such as drug rash, urticaria and eczema, have also been observed.

The following side effects have seldom been reported with Diclofenac sodium although they have been observed in response to other non-steroidal, anti-inflammatory drugs. Central nervous system side-effects, such as tiredness, insomnia and irritability, have occurred in rare instances. There have been a few reports of gastro-intestinal ulceration or haemorrhage, hypersensitivity reactions (e.g. bronchospasm, anaphylactoid reactions), elevated transaminase levels, hepatitis, renal failure and nephrotic syndrome, isolated cases of leucopenia and thrombocytopenia have also been observed.

4.9 Overdose

Symptoms may include: Drowsiness; dizziness; mental confusion; disorientation; lethargy; paresthesia; numbness; vomiting; gastric irritation; nausea; abdominal pain; intense headache; tinnitus; sweating; convulsions; blurred vision; elevations in serum creatinine; and BUN; acute renal failure.

Treatment includes general supportive measures. Because these agents are acidic and are excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. NSAIDs are strongly bound to plasma proteins; hemodialysis and peritoneal dialysis may be of little value.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Diclomol SR Tablets for oral administration contain a non-steroidal compound with pronounced anti-inflammatory, analgesic and antipyretic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the causation of inflammation, pain and fever.

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclomol SR elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function. Diclomol SR is particularly suitable for patients in whom a daily dosage of 100 mg is appropriate to the clinical picture. The possibility of prescribing the drug in a single dose considerably simplifies long term treatment and helps to avoid the possibility of dosage errors. For milder cases, where a lower dosage is sufficient other forms of Diclomol are available.

5.2 Pharmacokinetic properties

Diclofenac is completely absorbed from the sustained-release tablets. As a result of delayed release of the active substance, the peak plasma concentrations attained are lower than those achieved following the administration of conventional dosage forms. On the other hand, concentrations remain measurable for some hours after attaining their peaks, Absorption sets in later following ingestion of a sustained-release tablet either with or after a meal than it does following administration on an empty stomach. The mean peak plasma concentration of 0.43 μg/ml (1.35μmol/litre) is attained on average about 5 hours after ingestion of a sustained-release tablet of 100mg.

Since about half the active substance is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) is about half as large following oral administration as it is, following a parenteral dose of equal size. Diclofenac becomes bound to serum proteins at a rate of 99.7%, chiefly to albumin. The total systemic clearance of Diclofenac in plasma is 263±56 l/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours.

Pharmacokinetic behavior remains unchanged following repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

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

The biotransformation of Diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation. About 60% of the administered dose is excreted as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 ,l/min, the theoretical steady-state plasma levels of metabolites are bout 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In the presence of impaired hepatic function (Chronic hepatitis, non decompensated cirrhosis), the kinetics and metabolism of Diclofenac are the same as the patients without liver disease.

5.3 Pre-clinical Safety data

A. Acute toxicity studies

Animal LD 50 values show a wide range of susceptibilities to acute over dosage, with primates being more resistant to acute toxicity than rodents (LD 50 in mg/ kg – rats, 55; dogs, 500; monkeys, 3200).

B. Sub-acute and chronic toxicity studies

Controlled studies in healthy subjects measuring faecal blood loss or during endoscopic examination show that Diclofenac causes less gastrointestinal damage than aspirin, feprazone or naproxen, but more than fenclofenac.

Two 1-week double blind crossover studies have used endoscopy to determine gastrointestinal damage induced by Diclofenac and naproxen. Osnes et al (1) found that Diclofenac 100 mg/day caused significantly ($p \leq 0.02$) less gastritis and haemorrhagic and erosive lesions of the gastro-duodenal mucosa than naproxen 500 mg/day in 14 subjects, and there were no significant changes in median scores for these parameters after Diclofenac compared with before treatment. Erosions tended to occur more frequently with naproxen, but too few subjects were enrolled for valid statistical analysis.

In a non-blind study 62 elderly patients with osteoarthritis received Diclofenac 75 mg/day or sulindac 400 mg/day for 12 weeks, mean blood urea increased ($p < 0.05$) from sulindac. Clinically, significant increases in blood urea nitrogen have been rarely reported during treatment with Diclofenac.

Diclofenac 150 mg/day had no adverse effect on blood glucose concentration or 24-hour urinary glucose excretion in 13 maturity onset diabetics treated with diet alone, or in another 14 maturity onset diabetics well controlled with diet and tolbutamide 500 to 2000 mg/day (2). Similarly, although Bongfiglioli et al (3). found that oral administration of Diclofenac 50 mg to 6 healthy subjects did not affect blood glucose concentrations, plasma free fatty acid concentrations increased from about 0.5 to 0.9 mmol/L ($p < 0.05$). At the same time there was no significant increase in serum cholesterol, triglycerides, β-lipoprotein or α,-lipoprotein, although pre-β-lipoprotein was increased from 1.08 to 1.3 g/L ($p < 0.005$).

6. Pharmaceutical Particulars

6.1 List of Excipients

S.No.	Name of the Ingredients
1	Diclofenac Sodium
2	Colloidal Anhydrous Silica (Aerosil 200)
3	Cetyl Alcohol
4	Magnesium Stearate
5	Povidone K-30
6	Stearyl Alcohol
7	Sucrose
8	Instacoat Aqua Brown (A01D00121)

6.2 Incompatibilities
None of the incompatibilities has been reported.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store protected from light and moisture at a temperature not exceeding 30^0C.

6.5 Nature and content of container
Box of 100 tablets (10 blisters x 10 tablets)

Blisters: Clear PVC rigid film and aluminum foil 0.25 mm

6.6 Instructions for use/handling
The tablets of Diclomol SR should neither be broken nor chewed. They should be taken whole with liquid, preferably at mealtimes.

7. Marketing authorization holder
Win-Medicare Pvt. Limited
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8. Marketing authorization number
Fresh Registration

9. Date of first authorization/renewal of the authorization
Fresh Registration

10. Date of revision of the text
May, 2019