# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. Trade Name of Medicinal Product

Diclomol EC 50 Tablets
(Diclofenac Tablets BP)

## 2. Qualitative and Quantitative Composition

| Ingredients | Pharmacopoeial Standard | Quantity (mg / tablet) | Function |
|---|---|---|---|
| **ACTIVE INGREDIENT** | | | |
| Diclofenac Sodium | BP | 50.00 | NSAID |
| **INACTIVE INGREDIENTS** | | | |
| **UNCOATED TABLET** | | | |
| Croscarmellose Sodium (Ac-Di-Sol) | BP | 8.00 | Disintegrant |
| Colloidal Anhydrous Silica (Aerosil -200) | BP | 1.00 | Diluent |
| Magnesium Stearate | BP | 1.00 | Lubricant |
| Microcrystalline Cellulose | BP | 45.00 | Diluent |
| Sodium Starch Glycollate | BP | 2.00 | Disintegrant |
| Starch | BP | 13.00 | Diluent |
| Talc | USP | 2.00 | Glidant |
| **ENTERIC COATED TABLET** | | | |
| Acryl Eze 93 O 56798 Brown | BP | 10.00 | Film former |
| Hydroxypropyl Methyl Cellulose 15 cps | USP | 3.65 | Film former |
| Polyethylene Glycol 400 | USP/NF | 0.35 | Plasticizer |
| Purified Water* | BP | q.s. | Vehicle |

*Lost during manufacturing process

## 3. Pharmaceutical Form

Enteric coated tablets
Description: Brown coloured, round, biconvex, enteric-coated tablets

## 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

The tablet should be taken orally. As a rule the initial daily dosage for adults is 1 tablet, 2 or 3 times a day. The drug should be taken with or after meals. For long term therapy, 1 tablet, 2 times a day is sufficient.

The tablets of Diclomol EC 50 should neither be broken nor chewed. They should be taken whole with liquid, preferably at mealtimes.

The recommended dosage of Diclofenac sodium for children (1 year and older) is 0.5-3mg/kg/day in divided doses. Since, the Diclomol EC tablets cannot be sub-divided; it is not a suitable dosage form for children below 14 years.

### 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

Close medical surveillance is required in patients with symptoms indicative of gastro-intestinal disease, a history of dyspepsia, Crohn's disease, ulcerative colitis, etc. and in patients with blood coagulation disorders and those with severe cardiac, hepatitis or renal disease.

Caution should be exercised in elderly patients, who are generally more likely to experience side effects.

In patients receiving long term treatment, it is advisable to check blood counts at intervals and monitor hepatic and renal function.

When given along with oral anticoagulants or oral antidiabetics, as a precaution the dosage of these drugs should be carefully adjusted in accordance with prothrombin time and blood glucose levels respectively.

### 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 EC during pregnancy should, if possible, be avoided.
Diclofenac has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Diclofenac is not recommended for use in nursing women.

### 4.7 Effects on Ability to Drive and Use Machines

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

### 4.8 Undesirable Effects

At recommended doses, Diclomol EC is generally well tolerated. At the start of treatment, however, patients may sometimes complain of epigastric pain, nausea, diarrhoea, dizziness or headache. These unwanted effects are usually of a mild nature.

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. Peripheral oedema and skin reactions, such as drug rash, urticaria and eczema. 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 Mode of Action

Diclomol EC 50 Tablets contains diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and anti-pyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammation and primary dysmenorrhoea. With regard to its analgesic effect, diclofenac is not a narcotic.

In rheumatic disease, the anti-inflammatory & analgesic properties of Diclomol EC 50 elicit a clinical response characterized by marked relief from signs & symptoms such as pain at rest or on movement, morning stiffness and swelling of the joints, as well as by an improvement in joint function.

### 5.2 Pharmacokinetic Properties

Diclofenac Sodium is well absorbed after oral administration and peak plasma levels are usually attained in 2 -3 hours. Absorption occurs more rapidly when ingested on an empty stomach than when administered during or after a meal. Plasma concentrations show a linear relationship to the size of the dose administered. However, concentrations shown are maintained at higher levels in the synovial fluid than in plasma.

A large proportion of diclofenac sodium is metabolized in the liver and about 30% of the ingested dose undergoes first pass metabolism. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Plasma concentration of diclofenac decline from peak levels in a biexponetial fashion, with the terminal phase having a half-life of approximately 2 hrs. However, the elimination half-life from the synovial fluid is about three times longer than that from plasma.

Pharmacokinetic behavior remains unchanged following repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

More than 99% is protein bound.

## 5.3 Pre Clinical Safety Data

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

- **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 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. Similarly, although Bongfiglioli et al. 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 ($p < 0.005$).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies in rats given diclofenac up to 2 mg/kg/day (or 12-mg/ $m^2$/ day, approximately the human dose) have revealed no significant increase in tumour incidence. There was a slight increase in benign mammary fibroadenomas in mid-dose treated (0.5 mg/ kg/ day or 3 mg/ $m^2$ / day) in males and in 3 mg/ kg/ day) female rats (high dose females had excessive mortality), but the increase was not significant for this common rat tumour. A two-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/ kg/ day (0.9 mg/ $m^2$/ day) in males and 1 mg/ kg/ day (3 mg/ $m^2$ /day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in *in-vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was non-mutagenic in several mammalian *in-vitro* and *in-vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/$m^2$ /day) did not affect fertility.

**Teratogenic Effects**

Reproduction studies have been performed in mice given diclofenac Sodium (up to 20 mg/kg/day or 60 mg/m2/day) and in rats and rabbits given diclofenac sodium (upto 10mg/kg/day or 60 mg/m2/day for rats, and 80 mg/m2/day for rabbits) and have revealed no evidence of Teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

## 6. Pharmaceutical Particulars

### 6.1 List of Excipients

| S. No. | Name of the Excipients |
|---|---|
| 1. | Croscarmellose Sodium (Ac-Di-Sol) |
| 2. | Colloidal Anhydrous Silica (Aerosil - 200) |
| 3. | Magnesium Stearate |
| 4. | Microcrystalline Cellulose |
| 5. | Sodium Starch Glycollate |
| 6. | Starch |
| 7. | Talc |
| 8. | Acryl Eze 93 O 56798 Brown |
| 9. | Hydroxypropyl Methyl Cellulose 15 cps |
| 10. | Polyethylene Glycol 400 |
| 11. | Purified Water |

### 6.2 Incompatibilities
None Reported

### 6.3 Shelf life
36 months from the date of manufacturing

### 6.4 Special Precautions for Storage
Store protected from light and moisture at a temperature not exceeding 30$^{o}$C

### 6.5 Nature and Content of Container
Diclomol EC 50 Tablets are packed in aluminium blister strips comprising of PVC film (width 152 mm × thickness 0.25 mm) backed with printed aluminium foil (width 148 mm × thickness 0.025 mm).

Blister of 10's; Box of 10x10's

### 6.6 Instructions for use/handling
The tablets of Diclomol EC 50 should neither be broken nor chewed. They should be taken whole with liquid, preferably at mealtimes.

7. **Marketing authorization holder**
   Win-Medicare Pvt. Limited
   1311, Modi Tower,
   98, Nehru Place, New Delhi – 110 019, India
   Telephone: +91-11-42504555
   Fax:+91-11-26480115

8. **Marketing authorization number**
   Fresh Registration

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

10. **Date of revision of the text**
    April 2022