Brand Name : AGODIC-50 TABLETS **Generic Name :** Diclofenac Tablets BP 50 mg	2021
Module 1 Administrative Information and Product Information **1.5** Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGODIC-50 TABLETS (Diclofenac Tablets BP 50 mg)

2. Qualitative and Quantitative Composition:

Each enteric coated tablet contains: Diclofenac Sodium BP 50 mg

3. Pharmaceutical form:

Brown coloured, round, biconvex, enteric coated tablet.

4. Clinical particulars:

4.1 Therapeutic Indications:

Rheumatoid arthritis

Diclofenac sodium has been shown to be effective and well tolerated in a number of open and double blind studies. It has similar efficacy to indomethacin, but is generally better tolerated. Typical doses were 75-100 mg daily in divided doses.

Suppositories administered at night were often helpful in the elderly or in other patients prone to upper gastrointestinal symptoms such as heartburn.

Osteoarthritis

Diclofenac sodium can often be used in lower doses in osteoarthritis as compared with rheumatoid arthritis, and in clinical trial it is also well tolerated and effective. In a long-term study, 50% of patients treated with diclofenac achieved a ‘good’ or ‘very good’ status over a 3-6 months period and the preparation was superior to indomethacin in this group patients.

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Low back, injuries and manifestations of soft tissue rheumatism

Studies have indicated that diclofenac is effective in various manifestations of soft tissue rheumatism including low back pain. Piroxicam and diclofenac were compared in 310 patients with a variety of musculoskeletal injuries with no statistically different response, both preparations having an equally rapid and effective onset of drug action.

Also diclofenac gel was found to be effective topically in doses of 4 g applied three times daily in soft tissue injures.

Ankylosing spondylitis

In a large number of non-comparative studies diclofenac 100-150 mg in divided doses daily or as suppositories has produced good to excellent response in 60-80% of patients with ankylosing spondylitis as has the 100 mg retard form given in the morning. A small number of double-blind studies have shown diclofenac is at least as effective as indomethacin.

Acute gout

Intramuscular injections of 75 mg diclofenac have been effective in relieving symptoms of acute gout given daily for 2 days, or occasionally twice daily. This dosage was as effective as phenylbutazone 600 mg daily given for a similar period. Oral administration of 150 mg daily was as effective as indomethacin 150 mg daily.

Control of pain and inflammation in orthopedic, dental and other minor surgery

Intramuscular diclofenac sodium in a dose of 1 $mg.kg^{-1}$ has been used to relieve pain for day case arthroscopy. In oral doses of 50-100 mg daily it has been found to be an effective analgesic for dental and minor surgical pain.

Juvenile rheumatoid arthritis

Diclofenac sodium has been compared aspirin in juvenile rheumatoid arthritis and found to be equally effective and clearly superior to placebo. No adverse effects were recorded in the diclofenac group whereas one third of patients on acetylsalicylic acid discontinued because of adverse effects.

Postoperative pain

Studies of postoperative pain relief have been performed with diclofenac daily following partial meniscectomy using both oral and intramuscular dosage forms. It was as effective as meperidine in the 6 h following administration but less so at 24 h.

After abdominal surgery diclofenac intramuscularly had significant morphine-sparing effects.

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Renal colic pain

Prostaglandin synthetase inhibition with diclofenac sodium has been used in the management or renal colic where ureteric obstruction caused increased synthesis and release of prostaglandins. In one study diclofenac sodium 75 mg intramuscularly was found to be more effective than 100 mg meperidine in the management of renal colic with fewer side effects.

Other uses

Diclofenac has been used for the relief of migraine and other types of headache, but is not recommended for this use.

4.2 Posology and Method of Administration:

Osteoarthritis

The recommended dosage is 100 to 150 mg/day q.d.

Rheumatoid Arthritis

The recommended dosage is 100 to 200 mg / day q.d.

Ankylosing Spondylitis

The recommended dosage is 100 to 125 mg / day.

Analgesia and primary Dysmenorrhea

The recommended starting dose of Diclofenac Tablet is 25 mg t.i.d. In some patients an initial dose of 100 mg of Diclofenac tablet 25 mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg.

Method of administration : Oral.

4.3 Contraindications:

1. Active or suspected peptic ulcer or gastrointestinal bleeding

2. Previous sensitivity to diclofenac sodium

3. Asthmatic patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other NSAIDs possessing prostaglandin synthetase inhibiting activity

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4. Concomitant NSAID (intravenous use) or anticoagulant use (including low-dose heparin)

5. History of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding (intravenous use)

6. Operations associated with a high risk of hemorrhage (intravenous use)

7. A history of asthma (intravenous use)

8. Moderate or severe renal impairment (serum creatinine >160 $\mu mol.l^{-1}$), hypovolaemia or dehydration from any cause.

4.4 Special Warnings and Precautions for Use :

Deterioration in renal function has been attributed to the concomitant use of Diclofenac and triamterene1 and to the concomitant use of Diclofenac and cyclosporin.

Diclofenac sodium has been associated with clinical exacerbation of porphyria and is considered unsafe in porphyric patients.

4.5 Interaction with other medicinal products, and other forms of interaction:

Potentially hazardous interactions

Lithium

Diclofenac has been reported to increase plasma concentrations of lithium by impairing its renal excretion.

Digoxin

Diclofenac has been reported to increase plasma concentrations of digoxin, but no clinical signs of overdosage have been encountered.

Diuretics

Various non-steroidal anti-inflammatory agents are liable to inhibit the activity of diuretics and to potentiate the effects of potassium sparing diuretics, thus making its necessary to monitor serum potassium levels.

Methotrexate

Caution should be exercised if diclofenac and methotrexate are administered within 24 h of each other since NSAIDs may increase methotrexate plasma levels, resulting in increased toxicity.

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Other significant interactions

Diclofenac has been reported to lower salicylate concentrations and vice versa. The clinical significance of this is unclear. Several studies have shown that diclofenac has no significant effect on oral antidiabetic or anticoagulant drugs. As a precaution, however, the manufacturers recommend that when giving concomitant treatment with diclofenac and anticoagulants, laboratory tests (e.g. prothrombin time) should be performed in order to check the desired response to the anticoagulant is maintained.

Food has been shown to produce prolonged and variable delays in reaching maximum plasma concentrations of diclofenac. However, chronic dose studies in which the unchanged drug and its major metabolites were measured have shown that absorption is unaffected by food. Cases of nephroxicity have been reported in patients receiving concomitant cyclosporin and NSAIDs including diclofenac. 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. Co-administration of diclofenac with other systemic NSAIDs and steroids may increase the frequency of unwanted effects.

Potentially useful interactions

No interactions of this kind have been reported.

4.6 Pregnancy and Lactation:

Diclofenac sodium should not be prescribed during pregnancy unless there is some compelling reason to do so. As in the case of other prostaglandin-synthetase inhibitors, this applies particularly to the last 3 months of pregnancy (owing to the possibility of suppression of the uterine activity and/or premature closure of the ductus arteriosus).

Following oral doses of 50 mg administered every 8 h, the active substance passes into the breast milk, but in quantities so small that no undesirable effects are to be expected.

4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Diclofenac Tablets should refrain from driving or using machines.

4.8 Undesirable effects:

Potentially life-threatening effects

Perforation of peptic ulcers and gastrointestinal hemorrhage are real hazards and might be fatal in some cases. Blood dyscrasias and anaphylaxis might also be lethal in very rare instances.

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Severe or irreversible adverse effects

As already mentioned, peptic ulcer may occur rarely, and blood dyscrasias and isolated cases of anphylactoid reactions have been encountered. Lower gut disorders may also occur.

Symptomatic adverse effects

Initially, some patients may complain of epigastric pain, nausea, diarrhea, vomiting, abdominal cramps, dyspepsia, flatulence, anorexia, vertigo, headache and slight dizziness. These symptoms are often transient and disappear with continuation of medication. Elevation of ALT and AST, rashes or skin eruptions, drowsiness and tiredness urticaria, oedema, and liver function disorders with or without jaundice occur rarely and disturbance of sensation, vision, behavior and hearing, or convulsions, pancreatitis, constipation, parasthesia, memory disturbance, disorientation, insomnia, irritability, depression anxiety, nightmares, tremor, psychiatric reactions, aseptic meningitis, tinnitus, taste disturbances, acute renal insufficiency, urinary abnormalities, interstitial nephritis, nephrotic syndrome, papillary necorsis, vasculitis, pneumonitis, palpitations, chest pain, hypertension and congestive heart failure have only been reported in isolated cases. There have also only been isolated reports of severe skin reactions (erythema multiforme, Stevens- Johnson syndrome, Lyell's syndrome, bullous reactions, eczema, erythroderma and purpura), loss of hair and photosensitivity.

Administration of the suppository may produce local reactions such as itching, burning, or increased frequency of bowel movement and, in isolation, exacerbation of hemorrhoids. Following injection of the intramuscular preparation, there may be some pain or burning sensation and in isolated cases abscesses and local necrosis.

In a Japanese study of diclofenac tolerability involving over 18 000 patients, the incidence of 'serious' gastrointestinal effects was 0.01%. Other studies have also been published.

Other effects

In a 3-month study involving over 800 patients, minor changes in liver function were reported in 241 instances but only 19 were related to drug use. Changes in blood urea nitrogen have been recorded and also decreased hemoglobin; no patients had diclofenac withdrawn because of abnormalities in laboratory tests.

4.9 Overdose:

There is no published report of any death caused by overdosage with diclofenac sodium. However, a case has been reported of an adult consuming 750 mg together with a large quantity of red wine. The presenting symptom was drunkenness and recovery was uneventful. A 19-year-old female consumed 325 mg and presented 2 h

later with discomfort in the upper abdomen, hiccup, dizziness and somnolence. She was treated with gastric lavage and made a complete recovery within 48 h.

Because of the paucity of information at present on overdosage, the symptomatology is still ill-defined; the following, however, may serve as a guide to what might be expected: dizziness, headache, myoclonic encephalopathy, impairment of consciousness, nausea, vomiting, pain in the upper abdomen, gastrointestinal hemorrhage with subsequent hematemesis or melena, ulceration of the stomach or intestine, perforation in patients with peptic or duodenal ulcers, hepatopathy, jaundice, oliguria or anuria, increased serum transaminases and/or bilirubin.

Treatment is by removal or inactivation of the drug by inducing vomiting or washing out the stomach and giving activated charcoal. In severe manifestations of overdose, hemodialysis or hemoperfusion may have to be considered.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Diclofenac is an effective anti-inflammatory and analgesic drug in clinical practice and is widely used in the treatment of rheumatoid arthritis and osteoarthritis. It is as effective as Indomethacin or aspirin with perhaps fewer side effects than these two agents. Diclofenac is as effective at inhibiting cycloxygenase as Indomethacin in therapeutic usage. The duration of inhibition is such that twice-daily dosage is appropriate. Diclofenac reduces joint swelling and relieves pain in patients with rheumatoid arthritis but has no long-term effects on the disease process. Diclofenac is effective in the treatment of postoperative pain and is available as a parenteral preparation. Diclofenac inhibits platelet adhesiveness and prolongs the bleeding time. By inhibiting prostaglandin synthesis in the uterus of pregnant women it may delay the onset of labor.

Diclofenac has no effect on renal function in normal individuals but can worsen renal function in patients whose renal blood flow is dependent on the vasodilatory prostaglandin E_2 (e.g. in hypertension, diabetes, cirrhosis of the liver and other conditions). Diclofenac may cause gastric erosions, partly by directly irritating the gastric mucosa and partly by inhibiting the synthesis of cytoprotective prostaglandins.

5.2 Pharmacokinetic Properties:

The method of choice for the analysis of diclofenac in biological fluids has been capillary gas chromatography with electron-capture detection; in this method diclofenac must be converted to the lactam before being measured, or extractive alkylation can be used. Concentrations as low as 2 $\mu g.l^{-1}$ in plasma could be detected.

Diclofenac is well absorbed following oral dosing but, with administration of the enteric-coated preparation, the time to peak plasma concentration can be variable.

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There is some presystemic elimination but about 60% of the oral dose reaches the systemic circulation. A linear increase in AUC with dose has been reported over the range 25 – 150 mg In humans. Like many other NSAIDs, diclofenac is highly bound to plasma protein, mainly albumin, and the degree of binding has been shown to be >99.5%.

Data on tissue penetration in man are scare, but in mice the highest concentrations were found in liver, bile and kidney with only a small amount in the brain and spinal cord. Diclofenac sodium has been measured in the synovial fluid of 12 patients with effusions 2 – 7 h after the administration of 75 mg intramuscularly. Diclofenac entered the synovial fluid quickly, since the mean 2 h synovial concentration was approximately 2/3 that in plasma (197 and 293 $\mu g.1^{-1}$, respectively) and diclofenac persisted in the synovial fluid much longer (mean 7 h concentration 205 $\mu g.1^{-1}$) compared with plasma (52 $\mu g.1^{-1}$). In study of six mothers treated for 1 week with 100 mg diclofenac sodium daily, none of the 59 milk samples contained detectable amounts of unchanged drug (limit of detection 10 $\mu g.1^{-1}$).

A comparison of diclofenac pharmacokinetics in young volunteers with rheumatoid patients showed a reduction in the peak plasma concentration in the latter group but no significant change in AUC or elimination half-life.

Oral absorption	>90%
Presystemic metabolism	40%
Plasma half-life	1 – 2 h
Volume of distribution	0.12 $l.kg^{-1}$
Plasma protein binding	99.5%

Concentration-effect relationship

In common with other NSAIDs, clinical efficacy is probably not directly related to plasma concentrations of diclofenac.

Metabolism

Diclofenac is extensively metabolized by animals and humans to a range of phenolic compounds, excreted as their glucuronide or sulfate conjugates. In humans the major metabolite is the 4'-hydroxy compound and 20-30% of an oral dose is excreted in this form in the urine with a further 10-20% in the bile. Free diclofenac accounts for <1% of the dose in urine.

Following intravenous administration, the elimination profile of diclofenac has been fitted by a tri-exponential function. The mean terminal elimination half-life in humans is 1-2 h. Some of the metabolites show anti-inflammatory, analgesic and antipyretic activity. There is no evidence of enterohepatic circulation in man. Methods have been published for the determination of the metabolites.

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5.3 Pre-clinical safety data:

Diclofenac sodium exhibited no teratogenic effects in the mouse at doses up to 20 $mg.kg^{-1}$ orally throughout the entire gestational period. In rats, the fertility of both males and females was unaffected although some embryotoxicity was noted in dams on 2-4 $mg.kg^{-1}$ daily. This manifested itself in increased intracuterine reabsorption and/or deceased number of offspring in a full-term litter together with a decreased average neonate, weight subsequent growth and survival was, however, comparable with controls. In rats given doses of diclofenac sodium up to 10 $mg.kg^{-1}$ throughout gestation, no teratogenic effect were observed.

In the high-dose studies, many of the animals died from ulceration of the stomach and intestines.

In rabbit studies no teratogenic effects were observed and feral development was satisfactory in animals given 10 mg daily on days 7-16 post-coitus.

In acute toxicity tests in rats, the LD_{50} was shown to be 226-240 $mg.kg^{-1}$ while chronic toxicity studies demonstrated a dose-depended gastrointestinal hemorrhage, ulceration and, sometimes, perforation. No toxic changes other than these gastrointestinal lesions were observed.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose	BP
Maize starch	BP
Sodium methyl paraben	BP
Sodium propyl paraben	BP
Magnesium stearate	BP
Purified talc	BP
Colloidal anhydrous silica	BP
Sodium lauryl sulphate	BP
Sodium starch glycolate	BP
Croscarmellose sodium	BP
Cross Povidone	USP

COATING

Colour instacoat sol brown IC-EN-695	Inhouse
Dichloromethane	BP
Isopropyl alcohol	BP

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6.2 Incompatibilities:

None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store below 30°C in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:
10 tablets packed in one blister. Such blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:

AGOG PHARMA LTD.
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8. Manufacturer:

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India.

9. Marketing Authorisation Number: Rwanda FDA-HMP-MA-1358

10. Date of revision of the text: July 2024

AGOG PHARMA LTD. VASAI

Date:
Director of the manufacturer
(Signature, Full name, Stamp)

AGOG PHARMA LTD. VASAI

Date:
Director of applicant company
(Signature, Full name, Stamp)