



**BAADER SCHULZ LABORATORIES  
PRIVATE LIMITED**  
J-6, OI DC, M.G. UDYOG NAGAR, DABHEL,  
DAMAN - 396210. (U.T.)

**VIZIERIRORA PLUS**  
Diclofenac Sodium 50 mg &  
Paracetamol 500 mg Tablets

**PRODUCT INFORMATION**  
**SPC, LABELING & PACKAGE LEAFLET**  
SPC – SUMMARY OF THE PRODUCT CHARACTERISTICS

**SUMMARY OF PRODUCT CHARACTERISTICS**

**01. NAME OF THE MEDICINAL PRODUCT**

- a) **TRADE NAME** : **VIZIERIRORA PLUS**  
b) **GENERIC NAME** : Diclofenac Sodium 50 mg & Paracetamol 500 mg Tablets

**02. QUALITATIVE AND QUANTITATIVE COMPOSITION**

**COMPOSITION**

Each uncoated Tablet contains:

|                      |          |
|----------------------|----------|
| Diclofenac Sodium BP | : 50 mg  |
| Paracetamol BP       | : 500 mg |
| Excipients           | : Q.S.   |

**03. PHARMACEUTICAL FORM**

Tablets

**4. Clinical particulars**

**4.1 Therapeutic indications**

Musculoskeletal system inflammatory and degenerative affections such as: rheumatoid arthritis, ankylosing spondylitis, arthrosis (including spondylarthrosis, painful vertebral syndrome); abarticular inflammatory affections; acute gout; post-traumatic pains or postoperative inflammation; inflammation and oedema. Vizierirora Plus is indicated for symptomatic or add-on therapy.

**4.2 Posology and method of administration**

Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

Adults: 1 tablet 2-3 times daily.

If the symptoms are more important by night or in the morning, the tablets should be taken in the evening.

Children: the pharmaceutical form and dosage are not indicated for children.

Method of administration



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Vizierirora Plus tablets should be swallowed with a drink, preferably while eating.

Elderly patients: the dosage should be reduced and monitoring of biological parameters is recommended.

The daily dose of paracetamol cannot exceed 2 g in the following situations:

Liver failure

Gilbert's syndrome

Chronic alcoholism

Impaired renal function:.

#### **4.3 Contraindications**

Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. - Gastrointestinal ulcer - Known hypersensitivity to the active ingredients or any of the excipients - Severe hepatic failure - Moderate to severe renal failure - Due to cross-allergy, diclofenac should not be given to patients, especially asthmatics, who have experienced symptoms of asthma, urticaria or acute rhinitis after taking aspirin or other non-steroidal anti-inflammatory drugs (prostaglandin-synthetase inhibitors). - Severe heart failure - Third term of pregnancy.

#### **4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control the symptoms (see Section 4.2 and Gastrointestinal and cardiovascular risks, hereunder). Cardiovascular and cerebrovascular effects • As fluid retention and oedema have been reported in association with non-steroidal antiinflammatory drugs (NSAIDs) therapy, caution is required in patients with history of high blood pressure and/or heart failure. • Clinical studies and epidemiologic data suggest that diclofenac use, especially at high dose (150 mg daily) and prolonged use can be associated to a slight increase in arterial thrombotic events (such as cardiac infarction or stroke). • 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 reevaluated periodically. Gastrointestinal effects • Gastrointestinal (GI) bleeding, ulceration or perforation have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or in patients without any history of GI events. In elderly patients these events are usually more severe. • Should GI bleeding or ulceration occur in



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patients receiving diclofenac, treatment should be discontinued. • As with others anti-inflammatory drugs, allergic reactions including anaphylactic reactions can occur, even without prior exposure to the drug.

NSAIDs can mask the signs or symptoms of infection (due to antalgic and antipyretic effects) resulting in delayed diagnosis and treatment. • Patients with GI disorders or with a history ulcer as well as patients with ulcerous colitis, Crohn's disease, impaired hepatic function should be closely monitored. • During diclofenac treatment, increase in several hepatic enzymes levels can occur. • Hepatic function monitoring is recommended, as a preventive measure, during long term treatment. Vizierirora Plus treatment should be discontinued if hepatic function tests remain abnormal or worsen, if clinical symptoms of hepatic affections occur, or in case of other signs (such as eosinophilia, rash, ...). Hepatitis can appear without prodromal symptoms. Risk of hepatic toxicity significantly increases in case of chronic alcoholism. Dosage reduction is required in alcoholic patients. Special care is recommended in case of observed hepatic failure. The same recommendation is applicable for patients treated by hepatic enzymes inductors (alcohol, barbiturates and anti-epileptics). In those cases, paracetamol toxic metabolites accumulation may lead to or worse hepatic lesions. • In patient with hepatic porphyria, special care is recommended as diclofenac can induce an attack. • Due to the role of prostaglandins in maintaining renal blood flow, particular monitoring is required when diclofenac is used in patients with impaired heart, hepatic or renal function, in elderly patients, in patients treated by diuretics and in patients who have lost large extracellular volumes (for example during the peri-operative or post-operative phase of major surgical procedures). The effect is reversible upon discontinuation of the treatment. • In case of prolonged use, blood analysis, including haematocrit, transaminase levels, total proteins and serum albumin, should be performed regularly. • As with others NSAIDs, Vizierirora Plus may temporarily inhibit platelets aggregation. • Special care is required in patients with haemostasis disorders. • Special attention should be paid in elderly patients, especially regarding gastro-intestinal and renal undesirable effects. It is recommended to administer the lowest effective dose, particularly in debilitated patients. • Administration of Vizierirora Plus to patients with bronchial asthma should be carefully considered because of the risk of worsening symptoms. • As with others NSAIDs, increase in uraemia and creatininaemia can occur. • Prostaglandins synthesis inhibitors can modify the renal function especially if this function is already affected for example in case of sodium depletion, cardiac decompensation or severe liver affection. • As with others prostaglandins synthesis inhibitors, the following renal abnormalities can occur:



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glomerulonephritis, interstitial nephritis, papillary necrosis, nephrotic syndrome, acute renal failure.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Lithium: diclofenac may increase serum lithium levels. In case of NSAID and lithium concomitant use, special attention to signs of lithium intoxication should be paid and serum lithium levels should be closely monitored. • Digoxin: diclofenac may increase plasma levels of digoxin. Plasma digoxin levels should be monitored when initiating Vizierirora Plus (diclofenac) and when discontinuing treatment, since adjustment of the dose may be necessary. • Diuretics: diclofenac can lead to sodium retention, oedema and to a decrease in antihypertensive and diuretic treatment. Concomitant treatment with potassium-sparing diuretic can lead to hyperkalaemia. Kalaemia should therefore be closely monitored. • NSAIDs: concomitant administration of several NSAIDs (including salicylates and pyrazole compounds) should in general be avoided due to potential effect on bioavailability of these drugs, hence reduced activities, and to the increased risk of undesirable effects. • Anticoagulants: during clinical trials, diclofenac did not interfere with anticoagulants but isolated reports showed an increased risk of haemorrhage when diclofenac and anticoagulants are concomitantly administered. Close monitoring is therefore required. As with other NSAIDs, elevated doses of diclofenac can temporarily inhibit platelets aggregation. • As paracetamol is poorly linked to plasmatic proteins, the concomitant use of paracetamol and oral anticoagulants is allowed. However, concomitant use of paracetamol (at more than 2 g daily during a long period) with oral anticoagulants may lead to slight variations in INR values. In this case a regular monitoring of INR values is recommended. • Oral antidiabetics: clinical trials have shown that diclofenac does not influence the effect of antidiabetic agents, although there have been isolated reports of hypoglycaemia and hyperglycaemia that have required dose adjustment. • Methotrexate: caution should be exercised when NSAIDs are administered less than 24 hours before or after a methotrexate treatment because its plasma level and toxicity can be increased. • Cyclosporin: NSAIDs effects on renal prostaglandins may increase cyclosporin cytotoxicity.

#### **4.6 Fertility, pregnancy and lactation**

During pregnancy Vizierirora Plus should not be given unless clearly necessary and only at the lowest effective doses. As with others prostaglandins synthesis inhibitors, this rule should particularly be followed during the third trimester of pregnancy due to inhibition of uterine contractions resulting in delayed or prolonged labour and/or premature closure of the ductus arteriosus. Hemorrhagic risk is also increased in case of NSAIDs use at the end of pregnancy. At



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150 mg daily dose (50 mg every 8 hours), diclofenac is excreted in mother's milk at very low level. It is

unlikely that children be affected by therapeutic doses used by their mothers. Paracetamol can be administered during breastfeeding. Therefore, Vizierirora Plus can be prescribed to breastfeeding mothers.

#### **4.7 Effects on ability to drive and use machines**

Vertigo or central nervous system effects can occur during treatment with Vizierirora Plus. If these effects appear while using Vizierirora Plus, driving a car and using machines are not recommended.

#### **4.8 Undesirable effects**

Associated with diclofenac • Gastrointestinal disorders Common: epigastric pain, other gastrointestinal disorders such as: nausea, vomiting, diarrhoea, abdominal cramp, dyspepsia, flatulence, anorexia. Uncommon: gastrointestinal bleeding (haematemesis, melena, haemorrhagic diarrhoea), peptic ulcer or intestinal ulcer with or without bleeding or perforation. Very rare: aphthous stomatitis, glossitis, oesophageal lesions, intestinal stenosis (diaphragm), large intestine reactions (unspecified haemorrhagic colitis and exacerbation of ulcerous colitis or of Crohn's disease), pancreatitis (unknown causal relationship), constipation. Attention should be paid on possible lesions of the gastroduodenal mucosa, especially erosions or ulcerations of the gastric mucosa, which sometimes occur without any symptoms but occult bleeding or melena. • Nervous system disorders Common: headache, dizziness or vertigo. Uncommon: drowsiness. Very rare: paraesthesia, memory disturbances, disorientation, sleeping difficulties, irritability, convulsions; depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis. • Sense organ Very rare: reduced hearing and disturbances of vision (blurred vision, double vision), tinnitus, changes in taste sensations. • Skin Common: rash. Uncommon: urticaria Very rare: eczema, erythema multiforme, bullous reactions including Stevens-Johnson syndrome and Lyell's Syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), hair loss, photosensitivity reactions, purpura (including allergic purpura). • Renal and urinary disorders Uncommon: oedema. Very rare: acute renal insufficiency, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis (mostly resulting from chronic use, renal complications are mainly more risky for elderly patients); • Hepato-biliary disorders Common: increased levels in transaminases (AST, ALT). Uncommon: liver function disorders, including hepatitis, with or without jaundice. Very rare: fulminant hepatitis.



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#### **4.9 Overdose**

**Diclofenac Symptoms:** Diclofenac overdose symptoms include headache, motor agitation, muscular spasm, irritability, ataxia, vertigo sensations, and convulsions especially in small children, epigastric pain, nausea, vomiting, haematemesis, diarrhoea, gastrointestinal ulcer, hepatic function disorders and oliguria. Therapeutic measure: NSAIDs acute intoxication treatment essentially consists in symptomatic treatment such as: - As early as possible after (within one hour) ingestion of potentially toxic amount, activated charcoal and gastric lavage should be considered. - Supportive and symptomatic treatment in case of complications such as hypotonia, renal failure, convulsions, gastrointestinal irritation and respiratory depression. As NSAIDs are highly bound to plasma proteins and mainly biotransformed, measures for NSAIDs elimination such as accelerated excretion, dialysis or hemoperfusion are ineffective. →

**Paracetamol** In adults with normal hepatic function, paracetamol toxic dose is 150 mg/kg (in one intake), i.e. around 10 grams for a 70kg adult. A risk of liver toxicity exists, in particular in elderly people, young children, in case of liver and kidney failure, chronic alcoholism, chronic malnutrition, enzyme inducing agents and very meagre adults (< 50 kg). It has to be kept in mind that a massive overdose with a glutathione depletion exceeding 70% (which theoretically requires that an adult absorb 15 g paracetamol and a child a dose equal or higher than 150 mg/kg body weight) leads to an increased quantity of reactive metabolite which, as it cannot be detoxified, causes hepatic cytolysis potentially leading to a complete and irreversible necrosis. Paracetamol accumulation due to metabolism impairment has not been observed at therapeutic doses. Glutathione depletion, which could increase the toxicity risk, does not usually occur.

#### **5. Pharmacological properties**

In postoperative pain treatment, the doses of morphinic analgesics can be significantly reduced when Vizierirora Plus is associated to the treatment.

##### **5.1 Pharmacodynamic properties**

Vizierirora Plus contains the following active substances: diclofenac and paracetamol.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Inhibition of prostaglandin synthesis has been shown experimentally to be an important component of the mechanism of action.

Prostaglandins synthesis reduction induces the following effects:



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- Inflammatory symptoms reduction by partial suppression of one of the main mediators of inflammation;
- Pain attenuation (by decrease of prostaglandins production, involved in sensitization of nociceptors to inflammatory mediators such as bradykinin) ;
- Dysmenorrhoea pain relief (dysmenorrhoea is due to increase in uterine activity and high prostaglandins levels in menstrual blood);
- Decrease in fever (prostaglandins acts on hypothalamic centre and thermoregulation)

Diclofenac exhibits anti-inflammatory and analgesic properties in clinical signs of rheumatic diseases, as relief of symptoms such as pain at rest or in motion, early morning stiffness and swollen joints. These properties are also manifested as improvement in function.

Diclofenac has been shown in clinical trials to significantly relieve non rheumatic moderate to severe pain.

Diclofenac relieves pain and reduces blood volumes in primary dysmenorrhoea.

In posttraumatic and postoperative pain, diclofenac relieves spontaneous pain, movement induced pain and reduces oedema.

Paracetamol is an antalgic and antipyretic.

It might exercise its peripheral analgesic activity by elevating the pain sensation thresholds.

Its antipyretic activity might be due to an action on the hypothalamic centre

## **5.2 Pharmacokinetic properties**

### **Absorption**

Diclofenac is rapidly and completely absorbed from diclofenac tablets. Absorption started immediately following the administration. Food intake does not affect the quantity absorbed but can delay and reduce the absorption.

Both oral and rectal paracetamol are rapidly and totally absorbed; however rectal resorption may change according to exposure time with rectal membrane.

Peak plasma concentration from diclofenac tablets is reached within 2 hours.

### **Distribution :**

Diclofenac plasma concentrations are dose proportional.

Almost half of diclofenac is metabolized by the liver (first –pass metabolism), in comparison to parenteral administration, 50% of diclofenac reaches the systemic circulation after oral administration.

The pharmacokinetic is not affected by repeated doses. Repeated diclofenac oral administration, at recommended interval dose, does not lead to accumulation of diclofenac in plasma.



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Diclofenac is highly bound to plasma proteins (99.7%), mainly to albumin (99.4%). This should be taken into consideration when others plasma proteins highly bounded drugs are coadministered.

Distribution volume is about 0.12 to 0.17 l/kg.

Diclofenac penetrates synovial fluids where the concentrations are maximal 2 – 4 hours after peak plasma concentration. The concentration in synovial fluid remains higher than in plasma for a 12 hours period. Half life in synovial fluid is about 3 – 6 hours.

Paracetamol is weakly bound to plasmatic proteins (20 to 50%) and its diffusion is rapid.

Metabolism and elimination:

The biotransformation of diclofenac is partly performed by glucuroconjugation of the intact molecule but mainly by single and multiple hydroxylation and methoxylation which lead to different phenol metabolites eliminated by glucuroconjugation. Two of those phenol metabolites are active but significantly less active than diclofenac.

The total systemic clearance of diclofenac in plasma is  $263 \pm 56$  ml/min (mean  $\pm$  SD).

The terminal half-life in plasma is 1-2 hours.

Four metabolites, two of which are active, have also a brief terminal half-life in plasma (1-3 hours). Another metabolite, inactive, has a long terminal half-life in plasma.

Approximately 60% of the dose administered is excreted in the urine in the form of glucuroconjugates of unchanged diclofenac or of its metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in faeces.

Paracetamol is metabolised in the liver and follows two major metabolic routes. It is excreted via the urine under glucuroconjugated (60 to 80 %) and sulfoconjugated (20 to 40%) forms. A small fraction (less than 4%) is transformed with the intervention of cytochrome P450 into a metabolite formed by oxidative process and which would have been involved in the hepatotoxicity of paracetamol at high doses; indeed, at therapeutic doses, this metabolite is eliminated by conjugation with glutathione. The conjugation ability is not changed in elderly patients and the kinetics is linear for doses until 7 g. In case of massive intoxication, the conjugation ability is exceeded, and the hepatotoxic metabolite quantity is increased.

At therapeutic doses, the paracetamol half-life is about 3 hours.





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### 5.3 Preclinical safety data

None stated

## 6. Pharmaceutical particulars

### 6.1 List of excipients

| SR. NO. | EXCIPIENTS                          |
|---------|-------------------------------------|
| 1       | Lactose                             |
| 2       | Maize Starch                        |
| 3       | Sodium Methyl Paraben               |
| 4       | Sodium Propyl Paraben               |
| 5       | Magnesium Stearate                  |
| 6       | Talcum Powder                       |
| 7       | Sodium Starch Glycolate             |
| 8       | Colloidal Silicon Dioxide (Aerosil) |
| 9       | Crosspovidone                       |
| 10      | Sodium Lauryl Sulphate              |
| 11      | Gelatin                             |
| 12      | Purified Water                      |

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 30°C .Protect from light

### 6.5 Nature and contents of container

Alu/PVC blister of 1 x 10 tablets packed in a carton with a packaging insert

### 6.6 Special precautions for disposal and other handling

No special requirements.



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**7. Marketing authorisation holder**

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**8. Marketing authorisation number(s)**

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**9. Date of first authorisation/renewal of the authorisation**

Date of first authorisation:

Date of first renewal:

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

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**11. REGISTRANT/OPERATOR:**

**12. MANUFACTURED BY :**

**BAADER SCHULZ LABORATORIES PRIVATE LIMITED**  
J-6, OI DC, M.G. UDYOG NAGAR, DABHEL, DAMAN - 396210. (U.T.)

**13. DATE OF FIRST AUTHORISATION**

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**14. DATE OF REVISION OF TEXT**