**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

# DICLOGESIC RR INJECTION

1. **Generic Name**
   Diclofenac Sodium Injection

## 2. Qualitative and quantitative composition

Each ampoule (2 ml) contains :
Diclofenac Sodium I.P. ..... 75 mg
Water for injection I.P. ..... Q.S. to 2 ml.

The excipients used are Hydroxypropyl Betadex, Monothioglycerol, Sodium Hydroxide and Hydrochloric Acid.

## 3. Dosage form and strength

Dosage Form: Injection
Strength: 75 mg

## 4. Clinical particulars

### 4.1 Therapeutic indication

For Intramuscular and intravenous Use:

- For acute painful conditions in post-operative pain, renal colic and acute exacerbation of gouty arthritis.

### 4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control.

**Adults**
Diclogesic RR injection (given IM or IV) should not be given for more than two days.

***Intramuscular Injection*:**
The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required, it is advised that the alternative buttock be used for the second injection.

Renal colic: One 75mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The recommended maximum daily dose of Diclogesic RR is 150mg.

***Intravenous Infusion*:**
Immediately before initiating an intravenous infusion, Diclogesic RR must be diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%). Only clear solutions should be used.

Two alternative regimens are recommended:

- For the *treatment* of moderate to severe post-operative pain, 75mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after 4-6 hours, not exceeding 150mg within any period of 24 hours.
- For the *prevention* of post-operative pain, a loading dose of 25mg-50mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of approx. 5mg per hour up to a maximum daily dosage of 150mg.

**Special populations**

**Elderly**
Although the pharmacokinetics of Diclogesic RR 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.

**Paediatric population**
Diclogesic RR is not recommended for use in children.

The recommended maximum daily dose of Diclogesic RR is 150mg.

## 4.3 Contraindications

- 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
- Hepatic failure
- Renal failure
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- 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.

***Specifically for IV use***.

- Concomitant NSAID or anticoagulant use (including low dose heparin).
- History of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding.
- Operations associated with a high risk of haemorrhage.
- A history of asthma.
- Moderate or severe renal impairment (serum creatinine >160μmol/l).
- Hypovolaemia or dehydration from any cause.

## 4.4 Special warnings 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 Diclogesic RR 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.

Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoesthesia and injection site necrosis.

**Gastrointestinal effects:**

Gastrointestinal bleeding (hematemesis, melena), 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.

As with all NSAIDs**,** including diclofenac**,** close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid.

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.

**Hepatic effects:**
Close medical surveillance is required when prescribing Diclogesic RR 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.

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclogesic RR should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

**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 Diclogesic RR. 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. Diclogesic RR should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

**SLE and mixed connective tissue disease:**
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

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

Reported clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

**Haematological effects:**
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclogesic RR may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

**Pre-existing asthma:**
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics / analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

**Female fertility:**
The use of Diclogesic RR 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 Diclogesic RR should be considered.

## 4.5 Drugs interactions

**Lithium:** If used concomitantly, Diclogesic RR may increase plasma concentrations of lithium Monitoring of the serum lithium level is recommended.

**Digoxin:** If used concomitantly, Diclogesic RR may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

**Diuretics and antihypertensive agents:** Like other NSAIDs, concomitant use of Diclogesic RR 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 hyperkalaemia**: Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored.

**Anticoagulants and anti-platelet agents:** Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. 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.

**Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids:** Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

**Selective serotonin reuptake inhibitors (SSRIs):** Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding.

**Antidiabetics:** Reported clinical studies have shown that Diclogesic RR can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

**Methotrexate:** Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

**Cyclosporine:** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporine due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving cyclosporine.

**Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

**Quinolone antibacterials:** 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. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

**Phenytoin:** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

**Colestipol and cholestyramine:** These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

**Cardiac glycosides:** Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

**Mifepristone:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

**Potent CYP2C9 inhibitors:** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

## 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

**Pregnancy**

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from reported 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 Diclogesic RR 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, Diclogesic RR 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.

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

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use.

**Table 1**

| | |
|---|---|
| **Infection and Infestations** | |
| Unknown | Injection site necrosis (Nicolau syndrome). |
| **Blood and lymphatic system disorders** | |
| Very rare | Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis. |
| **Immune system disorders** | |
| Rare<br>Very rare | Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).<br>Angioneurotic oedema (including face oedema). |
| **Psychiatric disorders** | |
| Very rare | Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder. |

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|---|---|
| **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** | |
| Uncommon* | Myocardial infarction, cardiac failure, palpitations, chest pain. |
| **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. |
| Unknown | Ischaemic colitis. |
| **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. |
| **Reproductive system and breast disorders** | |
| Very rare | Impotence |
| **General disorders and administration site conditions** | |
| Common<br>Rare | Injection site reaction, injection site pain, injection site induration<br>Oedema |

* The frequency reflects data from long-term treatment with a high dose (150 mg/day).

Reported clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high doses (150mg daily) and in long term treatment.

- **Reporting of side effects**

  If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

### 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 Mechanism of Action

Pharmacotherapeutic group: Nonsteroidal anti-inflammatory drugs (NSAIDs).

Diclogesic RR is a nonsteroidal 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. When used concomitantly with opioids for the management of post-operative pain, Diclogesic RR often reduces the need for opioids.

## 5.2 Pharmacodynamic properties

In certain reported in-vitro studies it was reported that Diclogesic RR could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Diclogesic RR does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Diclogesic RR on HIV replication ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

## 5.3 Pharmacokinetic properties

### Absorption

After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.558 ± 0.968µg/ml (2.5µg/mL ≡ 8µmol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.

Intravenous infusion: When 75mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.875 ± 0.436µg/ml (1.9µg/mL ≡ 5.9µmol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. This is in contrast to the rapid decline in plasma concentrations seen after peak levels have been achieved with oral, rectal or IM administration.

### Bioavailability:

The area under the concentration curve (AUC) after intramuscular or intravenous administration is about twice as large as it is following oral or rectal administration as this route avoids "first-pass" metabolism.

### 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.

### 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**

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.

**Characteristics in patients**

***Elderly:*** No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed, other than the finding that in five elderly patients, a 15 minute IV infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

***Patients with renal impairment:*** 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 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

***Patients with hepatic disease:*** In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease

## 6. Nonclinical properties

### 6.1 Animal Toxicology or Pharmacology

No data available.

## 7. Description

Clear colorless to slight yellow mobile solution filled in 2ml flint glass ampoule USP Type-I with white band.

## 8. Pharmaceutical particulars

### 8.1 Incompatibilities

The ampoules used IM or IV as an infusion should not be mixed with other injection solutions

### 8.2 Shelf-life

Do not use later than the date of expiry

### 8.3 Packaging information

Diclogesic RR Injection is available in 10 blister strips of 5 ampoules of 2 ml.

### 8.4 Storage and handing instructions

Store at a temperature not exceeding 30$^{o}$C. Protect from light. Do not freeze.
Keep out of reach of children.
WARNING: 'NOT FOR VETERINARY USE'

## 9. Patient Counselling Information

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

**What is in this leaflet:**



### 9.1 What Diclogesic RR Injection is and what it is used for

Diclofenac sodium, the active ingredient in Diclogesic RR Injection, is one of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs reduce pain and inflammation.

The intramuscular injection is used to treat a number of painful conditions including:

- Acute painful conditions in post-operative pain
- Renal colic
- Acute exacerbation of gouty arthritis.

Diclogesic RR Injection can either be given as an injection into the muscle, or as a slow infusion into a vein. The intravenous infusion is used in hospitals to prevent or treat pain following an operation.

Diclogesic RR Injection is not suitable for children.

### 9.2 What you need to know before you use Diclogesic RR Injection

**Some people MUST NOT have this injection. Talk to your doctor if:**

- you think you may be allergic to diclofenac sodium, aspirin, ibuprofen or any other NSAID or to any of the other ingredients of Diclogesic RR Injection. (These are listed at the end of the leaflet.) Signs of a hypersensitivity reaction include swelling of the face and mouth (angioedema), breathing problems, runny nose, skin rash or any other allergic type reaction
- you have now, or have ever had, a stomach (gastric) or duodenal (peptic) ulcer, or bleeding in the digestive tract (this can include blood in vomit, bleeding when emptying bowels, fresh blood in faeces or black, tarry faeces)
- you have had stomach or bowel problems after you have taken other NSAIDs
- you have moderate or severe heart, kidney or liver failure
- if you have established heart disease and/or cerebrovascular disease e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear bypass blockages

- if you have or have had problems with your blood circulation (peripheral arterial
- disease)
- you are more than six months pregnant

**You should also ask yourself these questions before having a Diclogesic RR Injection or Infusion:**

- Do you suffer from any bowel disorders including ulcerative colitis or Crohn's disease?
- Do you have kidney or liver problems, or are you elderly?
- Do you suffer from any blood or bleeding disorder?
- Do you have a condition called porphyria?
- Have you ever had asthma?
- Are you breastfeeding?
- Do you have angina, blood clots, high blood pressure, raised cholesterol or raised
- triglycerides
- Do you have heart problems, or have you had a stroke, or do you think you might be at risk of these conditions (for example, if you have high blood pressure, diabetes or high cholesterol or are a smoker)?
- Do you have diabetes
- Do you smoke
- Do you have Lupus (SLE) or any similar condition?
- Could you be suffering from dehydration?
- Have you suffered any heavy loss of blood recently?

**If the answer to any of these questions is YES, discuss your treatment with your doctor or pharmacist because Diclogesic RR Injection might not be the right medicine for you.**

**Are you taking other medicines?**

Some medicines can interfere with your treatment. Tell your doctor or pharmacist if you are taking any of the following:

- Medicines to treat diabetes
- Anticoagulants (blood thinning tablets like warfarin)
- Diuretics (water tablets)
- Lithium (used to treat some mental problems)
- Methotrexate (for some inflammatory diseases and some cancers)
- Ciclosporin and tacrolimus (used to treat some inflammatory diseases and after
- transplants)
- Trimethoprim (a medicine used to prevent or treat urinary tract infections)
- Quinolone antibiotics (for infections)
- Any other NSAID or COX-2 (cyclo-oxgenase-2) inhibitor, for example aspirin or ibuprofen
- Mifepristone (a medicine used to terminate pregnancy)
- Cardiac glycosides (for example digoxin), used to treat heart problems
- Medicines known as SSRIs used to treat depression
- Oral steroids (an anti-inflammatory drug)
- Medicines used to treat heart conditions or high blood pressure, for example beta-blockers or ACE inhibitors.
- Voriconazole (a medicine used to treat fungal infections).

- Phenytoin (a medicine used to treat seizures)
- Colestipol/cholestyramine (used to lower cholesterol)

Always tell your doctor or pharmacist about all the medicines you are taking. This means medicines you have bought yourself as well as medicines on prescription from your doctor.

**Pregnancy**

- Are you pregnant or planning to become pregnant? Although not common, abnormalities have been reported in babies whose mothers have taken NSAIDs during pregnancy. You should not have a Diclogesic RR Injection during the last 3 months of pregnancy as it may affect the baby's circulation.
- Are you trying for a baby? Having Diclogesic RR Injections may make it more difficult to conceive. You should talk to your doctor if you are planning to become pregnant, or if you have problems getting pregnant.

**Will there be any problems with driving or using machinery?**

Very occasionally people have reported that Diclogesic RR Injections have made them feel dizzy, tired or sleepy. Problems with eyesight have also been reported. If you are affected in this way, you should not drive or operate machinery.

**Other special warnings**

- You should take the lowest dose of Diclogesic RR Injection for the shortest possible time, particularly if you are underweight or elderly.
- There is a small increased risk of heart attack or stroke when you are taking any medicine like Diclogesic RR Injection. The risk is higher if you are taking high doses for a long time. Always follow the doctor's instructions on how much to take and how long to take it for.
- Whilst you are taking these medicines, your doctor may want to give you a check-up from time to time.
- If you have a history of stomach problems when you are taking NSAIDs, particularly if you are elderly, you must tell your doctor straight away if you notice any unusual symptoms.
- Because it is an anti-inflammatory medicine, Diclogesic RR Injection may reduce the symptoms of infection, for example, headache and high temperature. If you feel unwell and need to see a doctor, remember to tell him or her that you are taking Diclogesic RR Injection.
- Diclogesic RR Injection should not be used in children.

## 9.3 How to use Diclogesic RR Injection

Your doctor will decide when and how to treat you with Diclogesic RR Injection. You will either be given an intravenous infusion (a drip into a vein) or an intramuscular injection (an injection into a muscle). The intramuscular injection is usually injected into the buttocks.

The usual dose is:

*Adults*

One or two ampoules (75 to 150 mg) each day for one or two days.

*Elderly*

Your doctor may give you a dose that is lower than the usual adult dose if you are elderly.

*Children*

Not suitable for children.

A doctor, nurse or pharmacist will prepare the injection for you.
If you have had an operation and are in hospital, the ampoule contents may be diluted and put into a drip bag before being given to you. A nurse or doctor will usually then give you the injection or infusion. You would not usually have to give the injection to yourself.

The doctor may also prescribe another drug to protect the stomach to be taken at the same time, particularly if you have had stomach problems before, or if you are elderly, or taking certain other drugs as well.

**What if you have had too much Diclogesic RR Injection? (Overdose)**
If you think, you have been given too much Diclogesic RR, tell your doctor or nurse straight away.

### 9.4 Possible Side Effects

Diclogesic RR injection is suitable for most people, but, like all medicines, they can sometimes cause side effects. Side effects may be minimised by using the lowest effective dose for the shortest duration necessary.

**Some side effects can be serious**

Tell the doctor straight away if you notice:

- Stomach pain, indigestion, heartburn, wind, nausea (feeling sick) or vomiting (being sick)
- Any sign of bleeding in the stomach or intestine, for example, when emptying your bowels, blood in vomit or black, tarry faeces
- Allergic reactions which can include skin rash, itching, bruising, painful red areas, peeling or blistering
- Wheezing or shortness of breath (bronchospasm)
- Swollen, face, lips, hands or fingers
- Yellowing of your skin or the whites of your eyes
- Persistent sore throat or high temperature
- An unexpected change in the amount of urine produced and/or its appearance.
- Mild cramping and tenderness of the abdomen, starting shortly after the start of the treatment with Diclogesic RR Injection and followed by rectal bleeding or bloody diarrhoea usually within 24 hours of the onset of abdominal pain.

If you notice that you are bruising more easily than usual or have frequent sore throats or infections, tell your doctor.

**The side effects listed below have also been reported:**

**Common side effects (These may affect between 1 and 10 in every 100 patients):**
Stomach pain, heartburn, nausea, vomiting, diarrhoea, indigestion, wind, loss of appetite
Headache, dizziness, vertigo
Skin rash or spots
Raised levels of liver enzymes in the blood
Injection site reactions, symptoms include redness, swelling, change in the skin colour, inflammation, pain, and hypersensitivity

**Rare side effects (These may affect between 1 in every 1000 to 1 in every 10,000 patients):**
Stomach ulcers or bleeding (there have been very rare reported cases resulting in death, particularly in the elderly)

Gastritis (inflammation, irritation or swelling of the stomach lining)
Vomiting blood
Diarrhoea with blood in it or bleeding from the back passage
Black, tarry faeces or stools
Drowsiness, tiredness
Hypotension (low blood pressure, symptoms of which may include faintness, giddiness or light-headedness)
Skin rash and itching
Fluid retention, symptoms of which include swollen ankles
Liver function disorders, including hepatitis and jaundice
Injection site necrosis (dead skin and tissue around the injection site)

**Very rare side effects (These may affect less than 1 in every 10,000 patients):**
Effects on the nervous system:
Tingling or numbness in the fingers, tremor, visual disturbances such as blurred or double vision, hearing loss or impairment, tinnitus (ringing in the ears), sleeplessness, nightmares, mood changes, depression, anxiety, mental disorders, disorientation and loss of memory, fits, headaches together with a dislike of bright lights, fever and a stiff neck, disturbances in sensation.

Effects on the stomach and digestive system:

Constipation, inflammation of the tongue, mouth ulcers, inflammation of the inside of the mouth or lips, taste changes, lower gut disorders (including inflammation of the colon, or worsening of colitis or Crohn's disease).

Effects on the heart, chest or blood:

Palpitations (fast or irregular heart beat), chest pain, hypertension (high blood pressure), inflammation of blood vessels (vasculitis), inflammation of the lung (pneumonitis), heart disorders, including congestive heart failure or heart attack, blood disorders (including anaemia).

Effects on the liver or kidneys:

Kidney or severe liver disorders including liver failure, presence of blood or protein in the urine.

Effects on skin or hair:

Serious skin rashes including Stevens-Johnson syndrome, Lyell's syndrome and other skin rashes which may be made worse by exposure to sunlight.

Hair loss.

Other side effects that have also been reported include:
Inflammation of the pancreas, impotence. Facial swelling, inflammation of the lining of the brain (meningitis), stroke, throat disorders, confusion, hallucinations, malaise (general feeling of discomfort), inflammation of the nerves in the eye, tissue damage at the injection site.

**Do not be alarmed by this list - most people have an injection of Diclogesic RR without any problems.**

**If any of the symptoms become troublesome, or if you notice anything else not mentioned here, please go and see your doctor. He/she may want to give you a different medicine.**

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

**9.5 How to store Diclogesic RR Injection**

Keep out of the sight and reach of children. Do not take this medicine after the expiry date shown on the strip and carton after EXP. The expiry date refers to the last day of that month. Store at a temperature not exceeding 30°C. Protect from light. Do not freeze. Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

**9.6 Contents of the pack and other information**

**What Diclogesic RR Injectioncontains:**

The active substance in this product is Diclofenac Sodium.

The other ingredients are Hydroxypropyl Betadex, Monothioglycerol, Sodium Hydroxide, Hydrochloric Acid.

**10. Details of manufacturer**

Manufactured by:
Torrent Pharmaceuticals Ltd.
Indrad-382 721, Dist.Mehsana, INDIA
At : Plot no. J-174 , J-168/1, MIDC,
Tarapur, Dist.Thane- 401 506

**11. Details of permission or licence number with date**

Mfg.Lic.No. : KD-2035-A

12. **Date of revision**

Aug 2019

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/DICLOGESIC RR 75mg/Aug-2019/02/PI**