SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DICLOTON 75 mg/3 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 25mg of diclofenac sodium.

Excipients with known effect: benzyl alcohol (52.35mg/ml), propylene glycol (0.63mg/ml), sodium metabisulphite (0.5mg/ml).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
DICLOTON is a sterile clear, colourless, or slightly yellow, solution for intramuscular injection or for preparing an intravenous infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ampoules for im use
The ampoules are effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.
Ampoules used in intravenous infusion
For treatment or prevention of post-operative pain in the hospital setting.

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 symptoms (see section 4.4).

Posology
Adults
DICLOTON ampoules (given im or iv) should not be given for more than two days; if necessary, treatment can be continued with DICLOTON tablets or suppositories.

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.

Alternatively, one ampoule of 75mg can be combined with other dosage forms of DICLOTON (tablets or suppositories) up to the maximum daily dosage of 150mg.

Renal colic:

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

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.

Paediatric population

DICLOTON ampoules are not recommended for use in children.

Elderly

Although the pharmacokinetics of diclofenac 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.

Cardiovascular and significant cardiovascular risk factors

Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.3).

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may

increase with dose and duration of exposure, the lowest effective daily dose should be used and for the shortest duration possible (see section 4.4).

Renal impairment
Diclofenac is contraindicated in patients with renal failure (see section 4.3).
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 (see section 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with hepatic failure (see section 4.3).
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 (see section 4.4).

The recommended maximum daily dose of DICLOTON is 150mg.

Method of administration
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.

Intravenous Infusion:
Immediately before initiating an intravenous infusion, DICLOTON 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.
DICLOTON must not be given as an intravenous bolus injection.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- 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 (see section 4.6)
- 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>160 μmol/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 (see section 4.2 and GI and cardiovascular risks below.)

The concomitant use of diclofenac 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 (see section 4.5).

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 (see section 4.2).

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the drug (see section 4.8).

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

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

The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

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, hypoaesthesia and injection site necrosis.

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena), 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 (see section 4.8). 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 has increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal (see section 4.2).

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. (See section 4.5).

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 (see section 4.5).

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8).

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic effects:

Close medical surveillance is required when prescribing diclofenac 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), diclofenac 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 (see section 4.3). 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 diclofenac (see section 4.8). 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.
Diclofenac 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 (see section 4.8).
Cardiovascular and cerebrovascular effects:
Patients with congestive heart failure (NYHA-I) or 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 re-evaluated periodically.
Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.
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 should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects:

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

Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5). 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 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 (see section 4.6).

DICLOTON contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium-free’.

DICLOTON contains benzyl alcohol. It must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

DICLOTON also contains propylene glycol and sodium metabisulphite.

Propylene glycol may cause alcohol-like symptoms.

Sodium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5. Interactions with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium and digoxin:

If used concomitantly, diclofenac may increase plasma concentrations of lithium or digoxin. Monitoring of the serum lithium level is recommended.

Anticoagulants and anti-platelet agents:

Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). 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 (see section 4.4). 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.

Antidiabetic agents:
Clinical studies have shown that diclofenac 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.

Ciclosporin:
Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin 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 ciclosporin.

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 antimicrobials:
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.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids:

Co-administration of diclofenac with aspirin or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4).

Selective serotonin reuptake inhibitors (SSRIs):
Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4).

Diuretics and antihypertensive agents:
Like other NSAIDs, concomitant use of diclofenac 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 hyperkalemia:
Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored (see section 4.4).

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 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from 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 diclofenac 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, diclofenac is contra-indicated during the third trimester of pregnancy.

Breast-feeding

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 (see section 5.2).

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. See also section 4.4.

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.

Infection and Infestations	
Not known	Injection site necrosis
Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare	Angioneurotic oedema (including face oedema)
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder
Nervous system disorders	
Common	Headache, dizziness
Rare	Somnolence, tiredness
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident
Not known	Confusion, hallucinations, disturbances of sensation, malaise
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia
Not known	Optic neuritis
Ear and labyrinth disorders	
Common	Vertigo
Very rare	Tinnitus, hearing impaired
Cardiac disorders	
Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain
Not known	Kounis syndrome
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
Not known	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	Injection site reaction, injection site pain, injection site induration
Rare	Oedema

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

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 (see sections 4.3 and 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system.

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.

Management

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. Pharmacodynamic properties

Pharmacotherapeutic group: Acetic acid derivatives and related substances, Antiinflammatory and antirheumatic products, Nonsteroids, ATC code: M01AB05.

Mechanism of action

Diclofenac is a non-steroidal 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, diclofenac often reduces the need for opioids.

5.2. Pharmacokinetic properties

Absorption

After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.558 ± 0.968 µg/ml (2.5 µg/mL ≡8 µmol/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 ± 0.436 µg/ml (1.9 µg/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 (see section 4.6).

Biotransformation
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.

Other special populations

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.

5.3. Preclinical safety data

No further relevant information.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol,
Sodium formaldehyde sulfoxylate,
Propylene glycol,
Sodium metabisulphite (E223),
Sodium hydroxide,
Water for injection.

6.2. Incompatibilities

The ampoules used im or iv as an infusion should not be mixed with other injection solutions.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25°C in the original package.
Do not refrigerate or freeze.

6.5. Nature and contents of container

DICLOTON is presented in single use amber type I glass ampoule containing 3 ml of diclofenac sodium 25 mg / ml, in packs of five, ten and one hundred ampoules.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

DICLOTON ampoules are single use ampoules. Open with aseptic precautions. Do not mix with other injection solutions.

For preparation of infusion solutions, DICLOTON should be used to freshly prepare the infusion solution, which should be used at once. Infusion solutions should not be stored after preparation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

Territory specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Territory specific

10. DATE OF REVISION OF THE TEXT

07/2020