SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Econac 75 mg/3 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains 75 mg Diclofenac sodium in 3 ml injectable solution.

Excipient(s) with known effect

Sodium metabisulphite (E223)- 2 mg per 3 ml
Benzyl alcohol-120 mg per 3 ml

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection Clear colourless or almost colourless sterile aqueous solution presented in 3 ml glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For Intramuscular use
Diclofenac ampoules are indicated in
- acute forms of pain, including renal colic
- exacerbations of osteo- and rheumatoid arthritis
- acute back pain
- acute gout
- acute trauma and fractures
- post-operative pain

For Intravenous use-

For the treatment or prevention of post-operative pain in the hospital setting.

It is indicated in adults

4.2 Posology and method of administration

Posology

Adults:

Ampoules for Intramuscular use:
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 alternate buttock be used for the second injection. Econac injection 75 mg/3 ml should not be given for more than 2 days; if necessary, treatment can be continued with tablets or suppositories.

Econac injection 75 mg / 3 ml should not be administered by intravenous injection.
Combinations with other dosage forms of Diclofenac (tablets or suppositories) can be used up to the maximum daily dosage of 150mg.

Renal colic: One 75 mg ampoule intramuscularly.
A further ampoule may be administered after 30 minutes if necessary.
The recommended maximum daily dose of 150 mg in any combination of the three formulations of Econac should not be exceeded.

“Econac 75 mg/3 ml Solution for Injection can also be given by an intravenous infusion, never as a bolus.”

Ampoules for intravenous use:
Prior to infusion it 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%).

For the treatment of moderate to severe post-operative pain, 75mg should be infused over a period of 30 minutes to 2 hours. This can be repeated after 4-6 hours, without exceeding 150mg within any 24-hour period.

For the prevention of post-operative pain, a loading dose of 25mg-50mg should be infused after surgery over 15 minutes to an hour, followed by a continuous infusion of around 5mg per hour up to a maximum of 150mg daily.

Elderly
Although the pharmacokinetics of Diclofenac are not impaired to any clinically relevant extent in older patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients as older patients are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dosage be used and for the shortest possible duration The patient should be monitored regularly for GI bleeding during NSAID therapy (see section 4.4)

Paediatric population
Econac 75 mg / 3 ml Solution for Injection is not suitable for children.

Method of administration:
For IM (intramuscular) and IV (intravenous) infusion use only.
For instructions on dilution of the medicinal product before administration, see section 6.6

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).

• Severe hepatic, renal or cardiac failure (see section 4.4).

• 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, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

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

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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (GI and cardiovascular risks below).

The concomitant use of Econac 75mg / 3ml Solution for Injection 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 older patients on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail older patients or those with a low body weight.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with Diclofenac without earlier exposure to the drug. 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, Econac 75mg / 3ml Solution for Injection may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Gastro-intestinal **effect**: Gastrointestinal bleeding–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 gastrointestinal events.

They generally have more serious consequences in older patients. If gastrointestinal bleeding or ulceration occurs in patients receiving Econac 75mg / 3ml Solution for Injection the medicinal product 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 (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (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.

The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. Older patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal 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 older patients, 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 other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly older patients, 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, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5).

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

Hepatic impairment:
Close medical surveillance required when prescribing Diclofenac to patients with impaired 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, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), Diclofenac should be discontinued. Hepatitis may occur with use of Diclofenac without prodromal symptoms.

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

Renal impairment:
As fluid retention and oedema have been reported in association with NSAID therapy, including Diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, older patients, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in 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 of therapy is usually followed by recovery to the pre-treatment state.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery.

Effects on renal function are usually reversible on withdrawal of Econac 75 mg/3 ml Solution for Injection.

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 (see section 4.8).

Patients appear to be at highest risk for 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. Econac 75 mg/3 ml Solution for Injection should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular effects:
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/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of Diclofenac, particularly at a high dose (150mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

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. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

***Haematological effect*:** Use of Econac 75 mg / 3 ml Solution for Injection is recommended only for short term treatment. During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis 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.

Special caution is recommended when Diclofenac is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

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).

Impaired female fertility
The use of Econac 75 mg/3 ml Solution for Injection may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Econac 75 mg/3 ml Solution for Injection should be considered.

Pediatric population
Econac 75mg / 3ml Solution for Injection must not be given to premature babies or neonates. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.

This drug contains the following excipients:

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

Benzyl alcohol:
High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction 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: If used concomitantly, Diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

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

Diuretics and antihypertensive agents: Like other NSAIDS, concomitant use of

Econac 75 mg / 3 ml Solution for Injection with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially older patients, 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 and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels; which should therefore be monitored frequently(see section 4.4).

Other NSAIDs and corticosteroids: Concomitant administration of Diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4).

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 affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving Diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including Diclofenac and SSRI may increase the risk of gastrointestinal bleeding (see section 4.4)

Antidiabetics:
Clinical studies have shown that Econac 75 mg/3 ml Solution for Injection can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of both 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 or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

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.

Quinolone antibiotics:
There have been isolated reports of convulsions which may have been due to concomitant use of 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 a NSAIDs.

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.

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

Cardiac glycosides:
Concomitant use of cardiac glycosides and NSAIDs 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.

Tacrolimus:
Possible increased risk of nephrotoxicity when NSAlDs are given with tacrolimus. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and calcineurin inhibitor.

Zidovudine:
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine.

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 of 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 been 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 the organogenetic period. During the first and second trimester of pregnancy, Diclofenac sodium should not be given unless clearly necessary. If Diclofenac sodium is used by a woman attempting to conceive, or during the first and second 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 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 sodium is contraindicated during the third trimester of pregnancy.

Breast-feeding:

Like other NSAIDs, Diclofenac passes into the breast milk in small amounts. Therefore, Diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

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 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 experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Diclofenac, should refrain from

driving or using machines.

4.8 Undesirable effects

Adverse reactions are ranked under 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, <1/1,000); very rare (<1/10,000); Not known: cannot be estimated from the available data.
The following undesirable effects include those reported with either short-term or long-term use.

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Not known	Injection site necrosis
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioedema, face oedema).
Psychiatric disorders	Very rare Not known	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, anxiety, Confusion, hallucination
Nervous system disorders	Common Rare Very rare Not known	Headache, dizziness. Somnolence. Paraesthesia, memory impairment, convulsion, tremor, meningitis aseptic*, dysgeusia, cerebrovascular accident. disturbances of sensation
Eye disorders	Very rare Not known	Visual impairment, vision blurred, diplopia. Optic neuritis
Ear and labyrinth disorders	Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.

	Not Known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Rare Very rare	Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	Common Rare Very rare Not known	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer** Colitis***, constipation, stomatitis, glossitis, Crohn's disease, mouth ulceration, oesophageal disorder, large intestinal stricture, pancreatitis. Ischaemic colitis
Hepatobiliary disorders	Common Rare Very rare	Transaminases increased. Hepatitis, jaundice, liver disorder. hepatitis fulminant, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	Common Rare Very rare	Rash. Urticaria. Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis**** dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	Very rare	Renal failure acute, haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	Not known	Erectile dysfunction.

General disorders and administration site conditions	Common	Injection site reaction, injection site pain, injection site induration, Generalised oedema
	Very Rare	Injection site abscess.
	Not known	Malaise.

*Meningitis aseptic (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation
** Gastrointestinal ulcer could be with or without bleeding or perforation sometime fatal in older people
*** Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis),
****Toxic epidermal necrolysis includes Lyell's syndrome

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 dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 haemorrhage, diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting or convulsions. In the event of significant poisoning acute renal failure and liver damage are possible.

Management

Management of acute poisoning with NSAIDs, including Diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and

symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including Diclofenac, due to the high protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Econac injection 75 mg/3 ml contain Diclofenac. Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties.

ATC code: M01AB05

Mechanism of action
It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Clinical efficacy and safety
Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is absorbed after all forms of administration. The plasma concentrations of the agent is linearly proportional to the administered dose.

After intramuscular injection of 75 mg Diclofenac a plasma maximum of 2,5 µg/ml (8µmol/l) will be achieved after approximately 20 minutes. The area under the plasma concentration curve (AUC) after i.m. injection is approximately the double of that after oral or rectal administration of the same dose, because approximately half of the active substance is metabolized (first pass effect) in the first passage in the liver.

Distribution

Diclofenac is 99.7 % bound to serum proteins mainly albumin (99.4 %).

Diclofenac passes into the synovial fluid. Here maximum concentrations are measured 2 - 4 hours after maximal plasma values have been reached. The elimination half-life of the synovial fluid is 3 - 6 hours. Therefore the concentrations of the active substance are higher 4 - 6 hours after administration than in the plasma and remain at

this level for up to 12 hours after administration.

Biotransformation

The metabolism of Diclofenac occurs quickly and almost completely. The metabolites are known. The biotransformation occurs for a small part by glucuronidation of the unchanged molecule, by mainly a simple or multiple hydroxylation which leads to a formation of several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5'-hydroxy-, 4',5'-dihydroxy- and 3'-hydroxy-4'-methoxydiclofenac), which are then extensively conjugated to glucuronic acid.

Elimination

The elimination of the active substance out of the plasma occurs with a systemic clearance of 263 ± 56 ml/min.

The terminal half-life is 1 - 2 hours.

Less than 1 % of the active substance is renally eliminated in its unchanged form. 60 % of the administered amount are renally eliminated as metabolites, the rest is eliminated with the feces.

The pharmacokinetics of Diclofenac also remain unchanged after repeated administration.

No cumulation is to be expected, if the recommended dosage is observed. No relevant differences of absorption, metabolism and elimination caused by the age of the patients have been observed.

In patients with impaired renal function, no accumulation of Diclofenac has been reported.

Elimination rates in renally impaired patients are comparable to those in other patients. The steady state concentrations of the total metabolites in patients with severe renal impairment are four times higher than in subjects with normal renal function, but exert no additional pharmacological effects.

Bioavailability

Bioavailability studies are not necessary because it is an injection solution.

5.3 Preclinical safety data

Acute Toxicity

The study of acute toxicity in various animal models did not reveal any special sensitivity.

Chronic Toxicity

The chronic toxicity was examined in rats, dogs and monkeys. Ulceration in the gastrointestinal tract was observed and produced complications, i.e. peritonitis, anemia and leucocytosis.

Mutagenic and Cancerogenic Potential

A mutagenic effect of Diclofenac seems to be excluded by the results of in-vitro and in-vivo tests. Studies on carcinogenicity in rats did not show any evidence of tumour-developing activities.

Reproduction Toxicology

The embryotoxic potential of Diclofenac was studied in 3 animal models (rat, mouse and rabbit). Fetal death and retardation of growth resulted in doses in the toxic range. Malformations have not been observed. The gestation period and duration of parturition were prolonged by Diclofenac. The effect on fertility was not examined. Doses below the maternal-toxic range did not reveal any influence on the postnatal development of the descendants.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, propylene glycol, benzyl alcohol, sodium metabisulphite, sodium hydroxide, water for injections.

6.2 Incompatibilities

Diclofenac ampoules for intramuscular use should not be mixed with other solutions for injections.

6.3 Shelf Life

2 years.

6.4 Special Precautions for Storage

Do not store above 25°C.
Store in the original outer carton.

6.5 Nature and Contents of Container

3 ml Type I glass ampoules.
10 ampoules per carton.

6.6 Special precautions for disposal and other handling

When used intravenously, Econac 75 mg/3 ml Solution for Injection should be given as an intravenous infusion, never as bolus. Prior to infusion it 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%). Intravenous infusions should be freshly made up and used immediately. Only clear solution should be used.

If only part of an ampoule is used, discard the remaining solution.

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Mercury Pharma Group Ltd
Capital House, 85 King William Street,
London EC4N 7BL, UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 10972/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

27/09/2019