Summary of product characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT
Diclac®
75 mg/3 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: Diclofenac sodium

One ampoule of 3 ml solution for injection contains 75 mg diclofenac sodium.

Other excipient(s) with known effect: 120 mg benzyl alcohol/3 ml

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection

Clear, colourless to yellowish solution

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Symptomatic treatment of severe acute pain due to
- acute arthritis (including gout attack)
- chronic arthritis, in particular with rheumatoid arthritis (chronic polyarthritis)
- ankylosing spondylitis (Bechterew's disease) and other inflammatory rheumatoid spinal conditions
- inflammatory conditions of degenerative joint and spinal disorders (osteoarthritis and spondylarthrosis)
- inflammatory soft-tissue rheumatoid diseases
- painful swelling or inflammation after injuries.

Note:
The solution for injection is only indicated when a particularly rapid onset of effect is required or when oral administration or use of suppositories is not possible. Treatment should usually only be administered in the form of a single injection for initial therapy.

4.2 Posology and method of administration
Adults
Treatment with Diclac should be administered as a single injection. If further therapy is deemed necessary, it should be administered orally or in the form of suppositories. The maximum daily dose of 150 mg diclofenac sodium must be adhered to at all times, including on the day of injection.

Method of administration
Diclac is administered by deep intragluteal injection. As anaphylactic reactions including shock may occur, an observation period of at least 1 hour following the injection of Diclac should be observed and a properly functioning emergency kit should be kept available. The patient must be informed about the purpose of this measure.

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.4).

Special patient groups
Elderly patients
No special dose adjustment is required. Because of the potential side effect profile, elderly patients should be monitored with particular care.

Impaired renal function
No dose reduction is required in patients with mild to moderate kidney function impairment (patients with severe kidney failure, see Section 4.3).

Impaired liver function
No dose reduction is required in patients with mild to moderate liver function impairment (patients with severe liver function impairment, see Section 4.3).

Children and adolescents
Diclac is not suited for children and adolescents under 18 years of age.

4.3 Contraindications
Diclac must not be used in case of
- hypersensitivity to the active ingredient diclofenac or one of the other ingredients listed in Section 6.1
- known reactions of bronchial spasm, asthma, rhinitis or urticaria after taking acetylsalicylic acid or other non-steroidal anti-rheumatic/anti-inflammatory drugs (NSAIDs) in the past
- unexplained haemopoietic disorders
- existing or a history of recurrent peptic ulcers or haemorrhages (at least 2 different episodes of proven ulceration or bleeding)
- history of gastrointestinal bleeding or perforation related to previous therapy with NSAIDs
- cerebrovascular or other active haemorrhages
- severe liver function impairment (see Section 4.4)
- severe kidney function impairment (see Section 4.4)
- known cardiac insufficiency (NYHA II-IV), ischaemic heart disease, peripheral arterial occlusive disease and/or cerebrovascular disease
- pregnancy, in the last trimester (see Section 4.6).

Diclac is not suited for children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use
Gastrointestinal effects
The use of Diclac in combination with NSAIDs, including selective cyclo-oxygenase-2 inhibitors, should be avoided (see Section 4.5).

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2 and gastrointestinal and cardiovascular risks below).

Elderly patients
In elderly patients, undesirable effects occur more frequently with NSAID therapy including diclofenac, most notably gastrointestinal bleeding and perforation, with fatal outcomes in some cases (see Section 4.2). It is recommended that the lowest effective dose be used in elderly patients who are frail or who have a low body weight.

Gastrointestinal bleeding, ulcers and perforation
Gastrointestinal bleeding, ulcers or perforations, sometimes with fatal outcome, have been reported for all NSAIDs including diclofenac. They occurred with or without previous warning symptoms or serious gastrointestinal events in the medical history, at any time during therapy.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with an increasing NSAID dose, in patients with ulcers in their medical history, in particular with complications of bleeding or perforation (see Section 4.3), and in elderly patients. These patients should start treatment with the lowest available dose.

For these patients, as well as for patients requiring concomitant therapy with low-dose acetylsalicylic acid (ASA) or other medicines that may increase the risk of gastrointestinal disease (see Section 4.5), combination therapy with gastrointestinal protection medicinal products (e.g., misoprostol or proton pump inhibitor) should be considered (see below and Section 4.5).

Patients with a history of gastrointestinal toxicity, especially the elderly, should report any unusual symptoms in the abdominal region (especially gastrointestinal bleeding), particularly at the start of therapy.

Caution is advised when patients are receiving concomitant medicinal products that can increase the risk of ulcers or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or platelet aggregation inhibitors such as ASA (see Section 4.5).

If gastrointestinal bleeding or ulcers occur in patients under Diclac, treatment must be discontinued.

NSAIDs, including Diclac, should be used with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's Disease), as their condition may worsen (see Section 4.8).

Cardiovascular and cerebrovascular effects
Adequate monitoring and counselling of patients with a history of hypertension and/or mild cardiac insufficiency (NYHA I) are required as fluid retention and oedema have been reported in conjunction with NSAID therapy including diclofenac.

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 (150 mg daily) and in long-term treatment (see Section 4.3).

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 use, the shortest duration possible and the lowest effective daily dose should be used. Regular monitoring should take place to see whether the patient still needs alleviation of symptoms and how he/she responds to treatment.

Patients should pay careful attention to signs and symptoms of severe arterial thrombotic events (e.g., chest pain, shortness of breath, weakness, slurred speech), which can occur without preceding warning symptoms. In these cases, instruct the patient to discontinue the medicine and see a doctor immediately.

Skin reactions
Serious skin reactions, some fatal, including exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis (Lyell Syndrome) have been very rarely reported under NSAID therapy, including diclofenac (see Section 4.8). The highest risk for such reactions appears to be at the beginning of therapy, as these reactions occurred in the majority of cases in the first month of treatment. Diclac should be discontinued at the first sign of rash, mucosal lesions or any other signs of a hypersensitivity reaction.

Hepatic effects
Patients with liver function impairment require careful medical supervision as their condition may worsen.
As with other NSAIDs, including diclofenac, the levels of one or more liver enzymes may increase. As a precautionary measure, regular liver function assessments should therefore be indicated for prolonged or repeated diclofenac treatment. Diclofenac should be discontinued immediately if any impairment in liver function persists or worsens, if clinical signs of liver disease are identified, or if other manifestations occur (e.g., eosinophilia, rash). Diclofenac may cause hepatitis without previous prodromal symptoms.
Caution must be taken with patients with hepatic porphyria, as an attack may be triggered.

Renal effects
Since fluid retention and oedema associated with NSAID therapy, including diclofenac, have been reported, special care should be taken in patients with impaired cardiac and renal functions, a history of hypertension, elderly patients, patients also on diuretics and other medicines that may significantly affect kidney function, and with patients who suffer from a significant reduction of extracellular fluid volume, for example before or after major surgery (see Section 4.3). For such patients we recommend precautionary supervision of the kidney function. After discontinuation of therapy, restoration of the condition to before the start of treatment usually follows.

Haematological effects
During prolonged treatment with NSAIDs, including diclofenac, monitoring of the blood count is recommended. Therapy with Diclac may cause, as with other NSAIDs, a temporary inhibition of platelet aggregation. Therefore, patients with haemostasis disorders should be carefully monitored.

Other instructions
Diclac should only be used under strict consideration of the risk-benefit ratio
- in congenital disorders of the porphyrin metabolism (e.g., acute intermittent porphyria)
- in systemic lupus erythematosus (SLE) and mixed collagenosis (mixed connective tissue disease) (see Section 4.8).

Particularly careful medical supervision is required
- in impaired renal function
- in liver function disorders
- directly after major surgical procedures (under conditions of increased bleeding propensity or worsening of the kidney function)
- in patients with allergic reactions to other substances as there is also an increased risk of hypersensitivity reactions for these patients when using Diclac.

Respiratory diseases
Patients suffering from asthma, hay fever, swollen nasal mucosa (e.g., nasal polyps), chronic obstructive respiratory diseases or chronic respiratory tract infections (particularly associated with symptoms as those occurring in the case of allergic rhinitis) have an increased risk of the occurrence of allergic reactions. These may be expressed as asthma attacks (so-called analgesic asthma), Quincke’s oedema or urticaria. Therefore, it is recommended that special precautions be taken in the case of such patients (emergency preparedness). This is also advisable for patients who experience allergic reactions to other substances, such as skin reaction, itching or urticaria.

Severe acute hypersensitivity reactions (e.g., anaphylactic shock) are very rarely observed during use of diclofenac. These may also occur with this medicine without prior exposure. At the first sign of a hypersensitivity reaction after administering Diclac, treatment must be discontinued. Medically necessary measures must be initiated by experts on the basis of the symptoms.

Like other NSAIDs, diclofenac can mask the signs and symptoms of an infection due to its pharmacodynamic properties.
If, during the use of Diclac, signs of infection recur or worsen, the patient is advised to consult a doctor immediately. It must be examined whether anti-infectious/antibiotic therapy is indicated.

Prolonged administration of Diclac requires regular monitoring of kidney function.

For more extended use of pain medication, headaches may occur, which may not be treated with increased doses of the medication.

Generally, the habitual intake of painkillers, especially when combining several pain-killing substances, can lead to permanent kidney damage with the risk of kidney failure (analgesic nephropathy).

The use of NSAIDs, including diclofenac, combined with alcohol consumption may increase the effect of active substance-related side effects, particularly those involving the gastrointestinal tract or the central nervous system.

For information regarding female fertility, see Section 4.6.

Instructions for intramuscular injection should be strictly followed to avoid adverse events at the injection site that may result in muscle weakness, muscle paralysis, hypoaesthesia and necrosis at the injection site.

Benzyl alcohol can cause toxic and anaphylactoid reactions in infants and children up to the age of 3 years.

4.5 Interactions with other medicinal products and other forms of interaction
Other NSAIDs including salicylates
Concomitant administration of multiple NSAIDs may increase the risk of gastrointestinal ulcers and haemorrhage due to a synergistic effect. Therefore, the concomitant use of diclofenac with other NSAIDs is not recommended (see Section 4.4).

Digoxin, phenytoin, lithium
The concomitant use of Diclac and digoxin, phenytoin or lithium can increase the concentration of these medicines in the blood. Monitoring the serum lithium level is required. Monitoring the serum digoxin and serum phenytoin level is recommended.

Diuretics, ACE inhibitors and angiotensin II antagonists
NSAIDs can weaken the effect of diuretics and antihypertensives. In patients with impaired renal function (e.g., dehydrated patients or elderly patients with impaired renal function), the concomitant intake of an ACE inhibitor or angiotensin-II antagonist with a medicinal product that inhibits cyclo-oxygenase may lead to further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, such a combination should only be used with caution, especially in elderly patients whose blood pressure should be regularly monitored. Patients must be prompted to ensure adequate fluid intake and regular monitoring of the kidney values should be considered after starting a combination therapy.

Medicines which are known to trigger hyperkalaemia
The concomitant administration of Diclac and potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may lead to hyperkalaemia. Therefore, potassium level monitoring is recommended for concomitant therapy (see Section 4.4).

Glucocorticoids

Increased risk of gastrointestinal side effects, such as, gastrointestinal ulcers or bleeding (see Section 4.4).

Platelet aggregation inhibitors such as, acetylsalicylic acid and selective serotonin reuptake inhibitors (SSRI)

Methotrexate
The administration of Diclac within 24 hours before or after administration of methotrexate may lead to an increased concentration of methotrexate in the blood and an increase in its toxic effect.

Cyclosporin
NSAIDs (such as diclofenac sodium) may increase the renal toxicity of cyclosporin.

Anticoagulants, platelet aggregation inhibitors such as acetylsalicylic acid and selective serotonin reuptake inhibitors (SSRIs)
Caution is required as concomitant administration can increase the risk of bleeding. Clinical investigations do not indicate that diclofenac influences the effect of anticoagulants although there are reports of an increased risk of bleeding in patients receiving concomitant diclofenac and anticoagulants. Close monitoring of these patients is therefore recommended.

NSAIDs can increase the effect of anticoagulants such as warfarin (see Section 4.4.). Increased risk of gastrointestinal bleeding and gastrointestinal side effects (see Section 4.4).
Antidiabetic agents
There have been isolated reports of an impact on the blood glucose level (e.g., hyperglycaemia or hypoglycaemia) after administration of diclofenac, which required a dose adjustment of the antidiabetic medication. Therefore, monitoring blood glucose levels is recommended as a precaution in the case of concomitant therapy.

Probenecid
Medicinal products containing probenecid may delay the elimination of diclofenac.

Potent CYP2C9 inhibitors
Caution is indicated during concomitant administration of diclofenac and potent CYP2C9 inhibitors (e.g. voriconazole). Since the metabolism of diclofenac is inhibited, there may be a significant increase in the exposure and the peak plasma concentration of diclofenac.

Quinolone antibiotics
There have been isolated reports of cerebral convulsions which may be attributable to the concomitant use of quinolones and NSAIDs.

4.6 Fertility, pregnancy and lactation
Pregnancy
The inhibition of prostaglandin synthesis can negatively influence pregnancy and/or embryo-foetal development. Data from epidemiological studies indicate an increased risk of miscarriage as well as cardiac malformations and gastroschisis following the use of a prostaglandin synthesis inhibitor, including diclofenac, in early pregnancy. It is assumed that the risk increases with dose and therapy duration.

In animals, it has been proven that administration of a prostaglandin synthesis inhibitor, including diclofenac, leads to increased pre- and post-implantation loss and to embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals that received a prostaglandin synthesis inhibitor, including diclofenac, during the period of organogenesis.

During the first and second trimester of pregnancy, diclofenac should be given only when absolutely necessary. If diclofenac is used by a woman who is trying to become pregnant or if the medicine is used during the first or second trimester, the dose should be kept as low as possible and the duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors, including diclofenac,

- can expose the foetus to the following risks:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
  - renal impairment, which may progress to renal failure with oligohydramnios.
- expose the mother and child to the following risks at the end of pregnancy:
  - possible prolongation of bleeding time, a platelet aggregation inhibiting effect which can occur even at very low doses
  - inhibition of uterine contractions, resulting in delayed or prolonged labour.

Therefore, diclofenac is contraindicated during the third trimester of pregnancy.

Breast-feeding
The active ingredient Diclofenac and its decomposition products enter the breast milk in small quantities. As no disadvantageous consequences for the infant have become known up to now, interruption of breast-feeding is usually not necessary in cases of short-term use. However, if longer use or intake at higher doses for the treatment of rheumatic diseases is prescribed, early weaning should be considered.

Fertility
The use of diclofenac, and the use of other medicinal products known to inhibit cyclo-oxygenase/prostaglandin synthesis, may impair female fertility and is therefore not recommended in women who are attempting to conceive. In women who have difficulty becoming pregnant or on whom infertility tests are being carried out, discontinuation of Diclac should be considered.

4.7 Effects on ability to drive and use machines
Because central nervous system side effects such as fatigue, visual impairment and dizziness may occur when using Diclac, particularly in a higher dosage, it may in some cases affect reaction time as well as the ability to actively participate in road traffic and the operation of machines. This applies to a greater extent in combination with alcohol.

4.8 Side effects
The frequency of adverse events is defined using the following convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100
Rare (≥1/10,000 to <1/1,000
Very rare (<1/10,000)
Not known (frequency cannot be assessed based on available data)

The following adverse effects include those which were reported for Diclac and/or other pharmaceutical forms of diclofenac, for both short-term and long-term use.

With the following adverse effects, it be taken into account that they are mostly dose-dependent and vary among individuals.

The most commonly observed side effects are those that affect the digestive tract. Peptic ulcers, perforations or bleeding, sometimes fatal, can occur, especially in elderly patients (see Section

4.4). Nausea, vomiting, diarrhoea, bloating, constipation, digestive problems, abdominal pain, melena, haematemesis, ulcerative stomatitis, worsening of ulcerative colitis and Crohn's Disease (see Section 4.4) have been reported after use. Gastritis has been observed less commonly.

In particular, the risk of gastrointestinal bleeding depends on the dose range and duration of use.

Oedema, hypertension and cardiac insufficiency have been reported in connection of treatment with NSAIDs, including diclofenac.

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 (150 mg daily) and in long-term treatment (see Section 4.3 and 4.4).

Cardiac disorders
Uncommon:* heart attack, cardiac insufficiency, palpitations, chest pain
Very rare: Oedema
* The frequency reflects the data from long-term treatment with high doses (150 mg/day).

Blood and lymphatic system disorders
Very rare: Haematopoietic disorders (anaemia, leucopoenia, thrombocytopoenia, pancytopoenia, agranulocytosis), haemolytic anaemia, aplastic anaemia

First signs can be: fever, sore throat, superficial wounds in the mouth, flu-like symptoms, severe exhaustion, nose bleeds and skin bleeding.

With long-term therapy, the blood count should be checked regularly.

Nervous system disorders
Common: central nervous system disorders such as headaches, dizziness, drowsiness, agitation, irritability or exhaustion
Very rare: sensitivity disorders, disorders of the sense of taste, memory disorders, disorientation, seizures, trembling, stroke

Eye disorders
Very rare: Visual disorders (blurred and double vision)

Ear and labyrinth disorders
Common: Dizziness
Very rare: Tinnitus, temporary hearing disorders

Gastrointestinal disorders
Very common: Gastrointestinal problems such as nausea, vomiting and diarrhoea; insignificant gastrointestinal blood losses which may cause anaemia in exceptional cases
Common: dyspepsia, flatulence, abdominal pain, abdominal cramps, loss of appetite and gastrointestinal ulcers (under certain circumstances with bleeding and perforation).
Uncommon: haematemesis, melaena or bloody diarrhoea
Rare: gastritis
Very rare: stomatitis (including ulcerative stomatitis), glossitis, oesophageal lesions, lower abdominal pain (e.g., colitis, bleeding colitis or worsening of ulcerative colitis or Crohn's Disease), obstipation, pancreatitis, diaphragm-like intestinal strictures
Not known: ischaemic colitis

The patient must be instructed to discontinue use of the medicinal product in case of severe pain in the upper abdomen, melaena or haematemesis, and to consult a doctor immediately.

Renal and urinary disorders
Uncommon: Oedema, especially in patients with arterial hypertension or renal insufficiency
Very rare: damage to renal tissue (interstitial nephritis, papillary necrosis) which may be associated with acute renal failure, proteinuria and/or haematuria, nephrotic syndrome, acute renal failure.

Renal function should therefore be checked regularly.

Skin and subcutaneous tissue disorders
Common: inflammatory skin change
Uncommon: alopecia
Very rare: exanthema, eczema, erythema, photo sensitisation, purpura (also allergic purpura) and bullous skin reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis (Lyell's Syndrome), exfoliative dermatitis, erythroderma

Infections and infestations
Very rarely has an aggravation of infection-related inflammations (e.g., development of necrotising fasciitis) been described in temporal correlation with the systemic use of NSAIDs. This is possibly related to the mechanism of action of NSAIDs.

If, during the use of Diclac, signs of infection occur or worsen, the patient is advised to consult a doctor immediately. It must be checked whether anti-infectious/antibiotic therapy is indicated.

Very rarely have symptoms of aseptic meningitis with rigid neck, headache, nausea, vomiting, fever or impaired consciousness been observed with the use of diclofenac. Patients with autoimmune diseases (SLE, mixed connective tissue disease) seem to be predisposed.

Not known: necrosis at the injection site

Vascular disorders
Very rare: hypertension, vasculitis

General disorders and injection site conditions
When administered intramuscularly, local side effects (burning sensation) or tissue damage such as sterile abscess formation, fatty tissue and skin necrosis (embolia cutis medicamentosa) can often occur at the injection site.

Immune system disorders
Common: hypersensitivity reactions such as skin rash and itching of the skin
Uncommon: Urticaria

In such a case, instruct the patient to inform the doctor immediately and discontinue using Diclac.

Rare: anaphylactic and anaphylactoid reactions (including hypotension and shock)

Very rare: severe general hypersensitivity reactions. These can manifest themselves as: angioedema including facial oedema, tongue swelling, internal laryngeal swelling with airway constriction, shortness of breath, tachycardia, low blood pressure up to life-threatening shock.

If any of these occur, which may already appear at first use, Diclac should be discontinued and immediate medical assistance is required.

Very rare: allergic vasculitis and pneumonitis

Hepatobiliary disorders
Common: elevation of serum transaminases
Uncommon: liver damage, particularly in the case of long-term therapy, acute hepatitis with or without icterus (very rarely fulminant, also without prodromal symptoms)
Very rare: liver cell necrosis, liver failure

Liver values should therefore be checked regularly during long-term therapy.

Psychiatric disorders
Very rare: psychotic reactions, depression, anxiety, nightmares, insomnia

Respiratory, thoracic and mediastinal disorders
Rare: asthma (including dyspnoea)
Very rare: pneumonitis

Hypersensitivity reactions may occur rarely with benzyl alcohol.

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 ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse events via

Bundesinstitut für Arzneimittel und Medizinprodukte [Federal Institute for Drugs and Medical Devices]
Abt. Pharmakovigilanz [Office of Pharmacovigilance]
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

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4.9 Overdose
a) Symptoms of an overdose
Central nervous system disorders such as headache, dizziness, light-headedness, tinnitus, seizures, hyperventilation, impaired consciousness and unconsciousness (in children also myoclonic seizures) as well as abdominal pain, nausea, vomiting and diarrhoea may occur as symptoms of an overdose. In addition, gastrointestinal bleeding and functional disorders of the liver and kidneys are possible. Hypotension, respiratory depression and cyanosis may also occur. In the event of significant intoxication, acute renal failure and liver damage are possible.

b) Overdose therapy measures
The treatment of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic therapy. A specific antidote does not exist. Treatment of complications such as hypotension, renal failure, seizures, gastrointestinal irritation and respiratory depression is supportive and also symptomatic.
Specific measures such as forced diuresis, dialysis or haemoperfusion are unlikely to be helpful in the elimination of NSAIDs, including diclofenac, because of their high protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:

Non-steroidal anti-inflammatory medicines and anti-rheumatic medicines; acetic acid derivatives and related substances

ATC Code: M01AB05

Diclofenac is a non-steroidal anti-inflammatory/analgesic medicine that has been shown to be effective in the usual animal experimental models of inflammation through the inhibition of prostaglandin synthesis. In humans, diclofenac reduces pain, swelling and fever caused by inflammation. In addition, diclofenac inhibits ADP- and collagen-induced platelet aggregation.

5.2 Pharmacokinetic properties
After oral application of the usual gastro-resistant pharmaceutical forms, diclofenac is completely absorbed distally by the stomach. Maximum plasma levels are reached based on the duration of passage through the stomach after 1-16 hours, on average after 2-3 hours. After intramuscular administration, maximum plasma levels are reached after 10-20 minutes; after rectal administration, after approx. 30 minutes. Orally administered diclofenac is subject to a first-pass effect; only 35-70% of the absorbed drug continues to reach the posthepatic circulation. Approximately 30% of the active substance is excreted with the faeces in metabolised form.
About 70% is eliminated via the kidneys after hepatic metabolism (hydroxylation and conjugation) in the form of pharmacologically inactive metabolites. The elimination half-life is approx. 2 hours largely irrespective of hepatic or renal function. Plasma protein binding is approximately 99%.
Diclofenac was detected in low concentrations (100 ng/ml) in the breast milk of a lactating woman. The calculated quantity that an infant consumes with breast milk is equivalent to a daily dose of 0.03 mg/kg body weight.

5.3 Preclinical safety data
Based on conventional studies on safety pharmacology, genotoxicity and carcinogenic potential, the preclinical data do not indicate any particular risks for humans beyond those risks already described in other sections of the Summary of Product Characteristics. Chronic toxicity of diclofenac was seen in animal studies particularly in the form of lesions and ulcers in the gastrointestinal tract. In a 2-year toxicity study, a dose-dependent increase of thrombotic vascular occlusions of the heart was observed in rats treated with diclofenac.

In animal experiment studies on reproductive toxicity, diclofenac led to an inhibition of ovulation in rabbits as well as implantation disorders and early embryonal development in rats. Gestation and duration of labour/delivery were prolonged by diclofenac. The embryotoxic potential of diclofenac was studied in three animal species (rat, mouse, rabbit). Foetal death and growth retardation occurred at doses in the maternal-toxic range. Based on the available data, diclofenac is considered to be non-teratogenic. Doses below the maternal-toxic limit did not influence postnatal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Acetylcysteine
- Benzyl alcohol
- Mannitol (Ph.Eur.)
- Sodium hydroxide
- Propylene glycol
- Water for injection

6.2 Incompatibilities
Diclac should not be mixed with other solutions for injection.

6.3 Shelf life
4 years

Discard remainder after opening.

This medicine should not be used after the expiry date.

6.4 Special precautions for storage
Do not store above 25 °C.

Store in the original package to protect contents from light!

6.5 Nature and contents of container
Pack of 1 and 5 ampoules, each containing 3 mL of solution for injection

6.6 Special precautions for disposal and other handling
No special requirements

Unused medicinal product or waste material should be disposed of according to national regulations.

7. MARKETING AUTHORISATION HOLDER
Hexal AG
Industriestraße 25
83607 Holzkirchen
Tel.: (08024) 908-0
Fax: (08024) 908-1290
E-mail: medwiss@hexal.com

8. MARKETING AUTHORISATION NUMBER
6360.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 04/06/1985
Date of latest renewal: 02/04/2002

10. DATE OF REVISION OF THE TEXT
September 2016

11. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription