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Physician's Package Insert

עלון לרופא

ABITREN®
AMPOULES

אביטרן®

SOLUTION FOR INJECTION

תמיסה להזרקה תוך שרירית בלבד

Name of the medicinal product

ABITREN® ampoules 75 mg/3 ml solution for injection.

Qualitative and quantitative composition

Each ampoule of 3 ml contains:

Active Ingredient

Diclofenac sodium 75 mg

Other Ingredients

Propylene glycol, benzyl alcohol, mannitol, sodium metabisulfite, sodium hydroxide, water for injection.

Sodium content per 3 ml ampoule: 8.13 mg

Pharmaceutical form

Solution for injection.

Clinical particulars

Therapeutic indications

- Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, non-articular rheumatism.
- Treatment of painful conditions due to inflammation of non rheumatic origin.
- Renal colic and biliary colic.
- Post-traumatic and post-operative pain, inflammation and swelling.

Posology and method of administration

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

Adults

Abitren solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with the tablets or suppositories.

Intramuscular Injection

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of Abitren (e.g. tablets, suppositories) up to a total maximum daily dose of 150 mg.

In migraine attacks, clinical experience is limited to initial use of one ampoule of 75 mg administered as soon as possible, followed by suppositories up to 100 mg on the same day if required. The total dose should not exceed 175 mg on the first day.

Children and adolescents

Because of their dosage strength, the Abitren solution for injection is not suitable for children and adolescents.

Contraindications

- Known hypersensitivity to the active substance, sodium metabisulfite or any of the other excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see Pregnancy and lactation).
- Severe hepatic and renal failure (see Special warnings and special precautions for use).
- Established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Abitren is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs

Special warnings and special precautions for use

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1) as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see also Precautions under *Arterial thrombotic events*)

Patients with congestive heart failure (NYHA-1) and 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.

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.

Warnings

Gastrointestinal bleeding ulceration or perforation, which can be fatal, have been reported with all NSAIDs 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 the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Abitren, the medicinal product should be withdrawn.

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 Undesirable effects). Patients appear to be at 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. Abitren should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to diclofenac. The sodium metabisulfite in the solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

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

Special populations
(see also *Precautions*)

Elderly

Although the pharmacokinetics of Abitren is 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 and the patient should be monitored for GI bleeding during NSAID therapy.

Renal impairment

Diclofenac is contraindicated in patients with severe renal impairment (see Contraindications). No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment.

Hepatic impairment

Diclofenac is contraindicated in patients with severe hepatic impairment (see Contraindications). 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.

Children and adolescents

(see Posology and method of administration).

Precautions

General

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

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.

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.

Arterial thrombotic events)

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.

Patients with cardiovascular disease or with significant risk for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) may also be at greater risk and should only be treated with diclofenac after careful consideration. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension)

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure)

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

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/analgesic-asthma), Quincke's edema 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 Abitren injection is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

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, close medical surveillance is imperative and particular caution should be exercised when prescribing Abitren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation, (see Undesirable effects). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation and in the elderly.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal (see Posology and method of administration).

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. proton pump inhibitors or misoprostol) 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 the 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, anti-platelet agents or selective serotonin-reuptake inhibitors (see Interaction with other medicinal products and other forms of interaction).

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 Undesirable effects)

Hepatic effects

Close medical surveillance is required when prescribing diclofenac to patients with impairment of hepatic function as their condition may be exacerbated.

Elevations of one or more liver tests may occur during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN [ULN = the upper limit of normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients.

In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (> 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulfillment hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac sodium should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with diclofenac sodium, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

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 edema have been reported in association with NSAID therapy, 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 in those patients with substantial extracellular volume depletion of any cause, e.g. before or after major surgery (see Contraindications). Monitoring of renal function is recommended as a precautionary measure when using Abitren in such cases. Discontinuation of therapy is normally followed by recovery to the pre-treatment state.

Hematological effects

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 hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs, including diclofenac. These serious adverse events are idiosyncratic and are independent of dose or duration of use.

Patients appear to be at 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, and Abitren should be discontinued.

Systemic lupus erythematosus and mixed connective tissue disease

In patients with systemic lupus erythematosus and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Abitren for injection and/or other pharmaceutical forms of diclofenac.

Potent CYP2C9 inhibitors

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

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 diclofenac 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 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 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 Special warnings and special precautions for use).

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids:

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects. Avoid concomitant use of 2 or more NSAIDs (see Special warnings and special precautions for use).

Anticoagulants and anti-platelet agents:

Caution is recommended since concomitant administration could increase the risk of bleeding (see Special warnings and special precautions for use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated 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 and SSRIs may increase the risk of gastrointestinal bleeding (see Special warnings and special precautions for use).

Antidiabetics:

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 both hypoglycemic and hyperglycemic 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:

Caution is recommended when NSAIDs 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 may 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 antibacterials:

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

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 frequently.

Phenytoin

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

Tacrolimus

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

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.

Mifepristone

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

Pregnancy, lactation and fertility**Pregnancy**

The use of diclofenac in pregnant women has not been studied. Therefore, Abitren should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the fetus. As with other NSAIDs, use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see Contraindications).

Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/fetal development, parturition or postnatal development (see Preclinical safety data).

Lactation

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

Fertility

As with other NSAIDs, the use of Abitren 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 Abitren should be considered.

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.

Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature reports are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known: cannot be estimated from available data. The following adverse effects include those reported with diclofenac solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Infections and infestations

Very rare: Injection site abscess.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.

Immune system disorders

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioneurotic edema (including face edema).

Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders

Common: Headache, dizziness.

Rare: Somnolence, tiredness.

Very rare: Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances (dysgeusia), cerebrovascular accident.

Unknown: confusion, hallucinations, disturbances of sensation, malaise

Eye disorders

Very rare: Visual disturbances, vision blurred, diplopia.

Unknown: optic neuritis

Ear and labyrinth disorders

Common: Vertigo.

Very rare: Tinnitus, hearing impaired.

Cardiac disorders

*Uncommon**: cardiac failure, myocardial infarction, palpitations, chest pain.

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

Vascular disorders

Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders

Rare: Asthma (including dyspnea).

Very rare: Pneumonitis.

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhea hemorrhagic, melena, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

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 (dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, Henoch-Schonlein purpura, allergic purpura, pruritus.

Renal and urinary disorders

Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions

Common: Injection site reaction, injection site pain, injection site induration

Rare: Edema, injection site necrosis.

Reproductive system and breast disorders

Very rare: impotence.

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 (150 mg daily) and in long term treatment (see sections Contraindications and Special warnings and special precautions for use).

Overdose**Symptoms**

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs 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 haemoperfusion are probably of no help in eliminating NSAIDs due to the high protein binding and extensive metabolism.

Pharmacological properties**Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non steroids, acetic acid derivatives and related substances (ATC code: M01A B05).

Mechanism of action

Diclofenac is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action. Prostaglandins play an important role in causing inflammation, pain and fever.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

Diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes.

Diclofenac has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.

When used concomitantly with opioids for the management of post-operative pain, diclofenac significantly reduces the need for opioids.

Abitren injection is particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

Pharmacokinetic properties**Absorption**

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

When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL (5.9 micromol/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. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of tablets or suppositories.

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, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes. Pharmacokinetic behavior does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution

99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

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 (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and 3'- methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination

Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value \pm SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy- 4'-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as 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 feces.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed. However, in a few elderly patients a 15-minute intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.

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 less than 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.

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

Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac, revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

Incompatibilities

As a rule, Abitren solution for injection should not be mixed with other injection solutions.

Storage

Store below 25°C

Store in the original container in order to protect from light.

Drug Registration Number:

015 57 24238 21

Manufactured by

Teva Pharmaceutical Works Private Limited Company,
Hungary

License Holder

Abic Ltd.,
P.O.Box 8077, Netanya.