ABITREN®
(diclofenac sodium)

SUSTAINED RELEASE TABLETS
SUPPOSITORIES

Physicians’ Prescribing Information

1 Trade name of the medicinal product
ABITREN Sustained Release Tablets
ABITREN Suppositories

2 Qualitative and quantitative composition
The active substance is sodium-\([2,6\text{-dichlorophenyl}]\text{-amino}]\text{-phenyl}\) –acetate (\(=\) diclofenac sodium).

One sustained release tablet contains 100 mg of diclofenac sodium.
One suppository contains 50 mg of diclofenac sodium.

For excipients, see section 6.1 List of excipients.

3 Pharmaceutical form
Tablets.
Suppositories

4 Clinical particulars
4.1 Therapeutic indications
Rheumatoid arthritis, osteoarthritis, low back pain and other acute musculoskeletal disorders such as periarthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocation, ankylosing spondylitis and acute gout.
Control of pain and inflammation in orthopedic, dental, and other minor surgery.

4.2. Posology and method of administration
As a general recommendation, the dose should be given for the shortest possible duration.
Because of their dosage strength, Abitren is not suitable for children and adolescents.

Abitren Sustained Release Tablets
The tablets should be swallowed whole with liquid, preferably with meals and must not be divided or chewed.
Generally 1 tablet daily is recommended. If gastrointestinal upset occurs, the dose may be taken with food, milk or antacids.

Where the symptoms are most pronounced during the night or in the morning, Abitren sustained release tablets should preferably be taken in the evening.

**Abitren Suppositories**
Generally 2 suppositories daily are recommended, usually administered at night. In more severe cases, combined therapy with tablets is recommended. The daily dose should not exceed 150 mg of diclofenac.

### 4.3. Contraindications
- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation).
- Severe hepatic and renal failure (see section 4.4 Special warnings and special precautions for use).
- Established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.

- Because of potential cross-sensitivity to other NSAIDs, diclofenac sodium should not be used in patients in whom aspirin or other NSAIDs have induced symptoms of asthma, acute rhinitis precipitated by ibuprofen, urticaria, nasal polyps, angioedema, bronchospasm and other symptoms of allergic reactions (anaphylactoid reactions have occurred in such patients).
- Patients with severe heart failure. The drug is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

### 4.4. Special warnings and special precautions for use

**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 diclofenac, 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 section 4.8 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. Diclofenac 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.
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 are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight 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.

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.

Each Abitren sustained release tablet contains 120 mg sucrose and therefore the tablets not recommended for patients with rare hereditary problems of fructose intolerance, glucose-galactose, malabsorption, or sucrase-isomaltase insufficiency.

Use of Abitren Suppositories may cause local reactions including itching, burning and increased frequency of bowel movement.
Abitren Suppositories should be used with caution in patients with painful or irritable anorectal conditions.

_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 or 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.

_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 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 Undesirable effects). The risk of GI bleeding is higher with increasing NSAIDs doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Posology and method of administration).
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 section 4.5 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 section 4.8 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 oedema 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 from any cause, e.g. before or after major surgery (see section 4.3 Contraindications). 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.

Haematological 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 haemostasis, 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.

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on NSAID therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, the possibility of its being related to ibuprofen should be considered.

Patients Who Require Surgery (Including Dental Surgery)
Caution is recommended in patients who require surgery. Most of the nonsteroidal anti-inflammatory agents inhibit platelet aggregation and may prolong bleeding time, which may increase intra-and postoperative bleeding. Consideration should therefore be given to discontinuing NSAIDAs treatment for an appropriate length of time prior to elective surgery, depending on the potency and duration of effect of the individual agent on platelet aggregability.

In case of patients requiring dental surgery, nonsteroidal anti-inflammatory agents may cause soreness, irritation, or ulceration of the oral mucosa. Most of the nonsteroidal anti-inflammatory agents may rarely cause leukopenia and/or thrombocytopenia, which may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts return to normal, and patients should be instructed in proper oral hygiene.

4.5. Interaction with other medicinal products and other forms of interaction
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 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 section 4.4 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 section 4.4 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 section 4.4 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 section 4.4 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 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:** 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 be increased.

**Ciclosporin and Tacrolimus:** 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. There is also a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

**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.

**Probenecid:** Probenecid may increase the plasma levels of some NSAIDs. The possibility of a drug interaction with diclofenac exists.

**Antacids:** Concomitant administration of diclofenac and an aluminium and magnesium hydroxide antacid may result in delayed diclofenac absorption; however, extent of absorption is not affected.

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

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 foetus. 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 section 4.3 Contraindications). Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3 Preclinical safety data).

Lactation
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 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 (>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 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.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

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

Very rare: Angioneurotic oedema (including face oedema).

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders
Common: Headache, dizziness.
Rare: Somnolence, tiredness, drowsiness.
Very rare: Paraesthesia, memory impairment, convulsion, dream abnormalities, anxiety, tremor, aseptic meningitis, taste disturbances, (dysgeusia), cerebrovascular accident.
Unknown: confusion, hallucinations, disturbances of sensation, malaise

Eye disorders
Very rare: Visual disturbance, vision blurred, diplopia.
Unknown: optic neuritis

Ear and labyrinth disorders
Common: Vertigo.
Very rare: Tinnitus, hearing impaired.

Cardiac disorders
Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

Vascular disorders
Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders
Rare: Asthma (including dyspnoea)
Very rare: Pneumonitis.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal 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, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, Henoch-Schönlein 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
Rare: Oedema.

Reproductive system and breast disorders
Very rare: Impotence.

4.9. Overdose
Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, 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. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

5 Pharmacological properties
5.1 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 fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever. Diclofenac in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised 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. In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. Abitren 100 mg sustained release tablets are particularly suitable for patients in whom a daily dose of 100 mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-term treatment and helps to avoid the possibility of dosage errors.
5.2 Pharmacokinetic properties

Absorption
Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micromol/L) are reached on average 4 hours after ingestion of the tablets. Food has no clinically relevant influence on the absorption and systemic availability of the sustained release tablets.

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of the sustained release tablets. The amount absorbed is linearly related to the dose strength. Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose. Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution
99.7% of diclofenac is bound 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 attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, 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'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination
Total systemic clearance of diclofenac from plasma is 263 ±56 mL/min (mean value ±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 faeces.

Characteristics in patients
No relevant age-dependent differences in the drug’s absorption, metabolism, or excretion have been observed.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of < 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3. Preclinical safety data
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.

6. Information for Patients
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

1. NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up.

2. NSAIDs, can cause GI discomfort and, rarely, more serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up.

3. NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS (Stevens Johnson Syndrome), and TEN (Toxic Epidermal Necrolysis), which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help.

7. In late pregnancy, NSAIDs, should be avoided because they will cause premature closure of the ductus arteriosus.
7. Pharmaceutical particulars
7.1. List of excipients
Abitren Sustained Release Tablets
Sucrose, cetyl alcohol, magnesium stearate, hydroxypropyl methylcellulose, talc, povidone, colloidal silicon dioxide, titanium dioxide, red ferric oxide.

Sucrose content: 120 mg per tablet
Sodium content: 7.23 mg per tablet.

Abitren Suppositories
Hard fat.

7.2. Incompatibilities
Not applicable.

7.3. Special precautions for storage
For Abitren Sustained Release Tablets
Store in a dry place below 25°C (protect from moisture).

For Abitren Suppositories
Store in a dry place below 25°C.

7.4. Instructions for use/handling
No special requirements.

8. Registration Numbers:
Abitren Sustained Release Tablets: 050 23 24117 00.
Abitren Suppositories: 015 72 24237 00.

9. Manufacturer
Teva Pharmaceutical Industries Ltd
P.O.Box 3190, Petach Tikva 49131

For
Abic Ltd
P.O.Box 8077, Kiryat Nordau, Netanya