Summary of Product Characteristics for Pharmaceutical Products

1. NAME OF THE MEDICINAL PRODUCT

Voltaren 75 mg/3 mL Solution for injection

Voltaren 25 mg gastro-resistant tablets

Voltaren 50 mg gastro-resistant tablets

Voltaren 75 mg prolonged-release tablets

Voltaren 100 mg prolonged-release tablets

Voltaren 12.5 mg suppositories

Voltaren 25 mg suppositories

Voltaren 50 mg suppositories

Voltaren 100 mg suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection

One Voltaren ampoule of 3 mL contains 75 mg of diclofenac sodium.

Excipients(s) with known effect Contains sugar: 18 mg Mannitol.

Preservative: 120 mg Benzyl alcohol

Antioxidant: 2 mg Sodium metabisulphite Voltaren ampoules contains 600 mg propylene glycol.

Gastro-resistant tablet (GRT)

Each gastro-resistant tablet contains 25 mg or 50 mg of diclofenac sodium.

Excipient(s) with known effect

Voltaren GRT 25 mg contains 16 mg lactose monohydrate and Voltaren GRT 50 mg contains 25 mg lactose monohydrate per dose.

Prolonged-release tablet (PRT)

Each prolonged-release tablet contains 75 mg or 100 mg of diclofenac sodium.

Excipient(s) with known effect

Voltaren PRT 75 mg contains 90.8 mg sucrose and Voltaren PRT 50 mg contains 119 mg sucrose per dose.

Suppositories

Each suppository contains 12.5 mg, 25 mg, 50 mg, or 100 mg of diclofenac sodium.

For a full list of excipients, see Section 6.1.

Not all strengths/formulations may be marketed.

3. PHARMACEUTICAL FORM

Solution for injection

Gastro-resistant tablets

Film-coated tablets

Suppositories

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Solution for injection Intramuscular injection Treatment of:

- Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Renal colic and biliary colic.
- Post-traumatic and post-operative pain, inflammation and swelling.
- Severe migraine attacks.

Intravenous infusion

Treatment or prevention of post-operative pain in a hospital setting.

GRT

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Post-traumatic and post-operative pain, inflammation and swelling, e.g., following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynecology, e.g., primary dysmenorrhea or adnexitis.
- As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g., pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

PRT

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Post-traumatic and post-operative pain, inflammation, and swelling, e.g., following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g., primary dysmenorrhoea or adnexitis.

Suppositories Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Post-traumatic and post-operative pain, inflammation and swelling, e.g., following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynecology, e.g., primary dysmenorrhea or adnexitis.

- Migraine attacks.
- As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g., pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

4.2 Posology and method of administration Posology

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults

Solution for injection

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

GRT

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.

The total daily dose should generally be divided into 2 to 3 separate doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

PRT

The recommended initial daily dose is 100 to 150 mg, administered as 1 tablet of Voltaren prolongedreleased 100 mg or as 2 tablets of Voltaren prolonged-released 75 mg.

In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.

Where the symptoms are most pronounced during the night or in the morning, Voltaren prolonged-release 75 mg and 100 mg should preferably be taken in the evening.

Suppositories

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.

The total daily dose should generally be divided into 2 to 3 separate doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Treatment of migraine attacks with Voltaren suppositories should be started with a dose of 100 mg at the first signs of an impending attack. Additional suppositories up to 100 mg may be taken on the same day if required. Should the patient require further therapy on the following days, the maximum daily dose should be limited to 150 mg in divided doses.

Special populations Renal impairment

Voltaren is contraindicated in patients with renal failure (GFR <15 mL/min/1.73 m^2) (see section 4.3).

No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren to patients with renal impairment (see section 4.4).

Hepatic impairment

Voltaren is contraindicated in patients with hepatic failure (see section 4.3).

No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Voltaren to patients with mild to moderate hepatic impairment (see section 4.4).

Pediatric patients (below 18 years)

Solution for injection

Because of their dosage strength, the ampoules of Voltaren solution for injection are not suitable for children and adolescents.

GRT

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily divided into 2 to 3 separate doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dose can be raised up to a maximum of 3 mg/kg daily, divided into 2 to 3 separate doses. The maximum daily dose of 150 mg should not be exceeded.

Because of their dosage strength, Voltaren 50 mg gastro-resistant tablets are not recommended for use in children and adolescents below 14 years of age; Voltaren 25 mg gastro-resistant tablets could be used in these patients.

PRT

Because of their dosage strength, Voltaren prolonged-release tablets 75 mg and 100 mg are not suitable for children and adolescents.

Suppositories

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily divided into 2 to 3 separate doses, depending on the severity of the disorder.

For treatment of juvenile rheumatoid arthritis, the dose can be raised up to a maximum of 3 mg/kg daily, given in divided doses.

The maximum daily dose of 150 mg should not be exceeded.

Voltaren 12.5 mg or 25 mg suppositories are recommended for use in children and adolescents below 14 years of age. Because of their dosage strength, Voltaren 50 mg suppositories are not recommended for children and adolescents below 14 years of age.

Voltaren 100 mg suppositories are not suitable for children and adolescents.

Geriatric patients (65 years of age or above)

No adjustment of the starting dose is generally required for elderly patients. However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see section 4.4).

Established cardiovascular disease or significant cardiovascular risk factors

Treatment with Voltaren is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease should be treated with Voltaren only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section 4.4).

Method of administration

Solution for injection

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 (which may result in muscle weakness, muscle paralysis, hypoesthesia and Embolia cutis medicamentosa (Nicolau syndrome)).

The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant using aseptic technique. 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 Voltaren (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.

Intravenous infusion

Voltaren solution for injection must not be given as an intravenous bolus injection.

Immediately before starting an intravenous infusion, Voltaren solution for injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate according to the instructions given in section 14 Pharmaceutical Information (Instructions for use/handling).

Two alternative dosage regimens of Voltaren solution for injection are recommended.

For the *treatment* of moderate to severe post-operative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after a few hours, but the dose should not exceed 150 mg within any period of 24 hours.

For the *prevention* of post-operative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.

GRT

The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

PRT

The tablets should be swallowed whole with liquid, preferably with meals, and must not be divided or chewed.

Suppositories

The suppositories should be inserted well into the rectum. It is recommended to take the suppositories after passing stools.

Not to be taken by mouth, as for rectal use only.

4.3 Contraindications

- Known hypersensitivity to the active substance, sodium metabisulphite *(solution for injection only)* or to any of the other excipients listed in section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation (see sections 4.4 and 4.7).
- Last trimester of pregnancy (see section 4.5).
- Hepatic failure.

- Renal failure (GFR <15 mL/min/1.73 m^2).
- Severe cardiac failure (see section 4.4).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e., NSAID-induced cross-reactivity reactions) (see sections 4.4 and 4.7).
- Proctitis *(suppositories only).*

4.4 Special warnings and precautions for use

Gastrointestinal effects

Gastrointestinal bleeding ulceration or perforation, which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Voltaren, the treatment should be discontinued.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercized when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation, (see section 4.7). 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.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with hemorrhage 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 low-dose acetylsalicylic acid (ASA), or other drugs 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 4.4 Interactions) Close medical surveillance and caution should also be exercized in patients with ulcerative colitis or Crohn's disease, as their condition may by exacerbated (see section 4.4).

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

Cardiovascular effects

Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).

Treatment with Voltaren is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Voltaren only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

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.

Hematologic effects

During prolonged treatment with Voltaren, 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 should be carefully monitored.

Respiratory effects (pre-existing asthma)

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e., nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's edema or urticaria are more frequent than in other patients. Therefore, special caution 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 Voltaren is used parenterally in patients with bronchial asthma because symptoms may be exacerbated *(solution for injection only).*

Hepatobiliary effects

Close medical surveillance is required when prescribing Voltaren to patients with impaired he function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. Du prolonged treatment with Voltaren (e.g., in the form of tablets or suppositories), regular monitorin hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or wor if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (eosinophilia, rash), Voltaren should be discontinued. Hepatitis may occur with use of diclofenac wit prodromal symptoms.

Caution is called for when using Voltaren in patients with hepatic porphyria, since it may trigger an att

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Voltaren (see section 4.7). Patients appear to be at highest risk of these reactions early in the course therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Voltaren 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 with diclofenac without earlier exposure to the drug. **Renal effects**

As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal function, history of hypertension the elderly, patients receiving concomitant treatment with diuretics or medicinal products that significantly impact renal function, and in those patients with substantial extracellular volume depletion any cause, e.g., before or after major surgery (see section 4.5). Monitoring of renal function recommended as a precautionary measure when using Voltaren in such cases. Discontinuation of the is usually followed by recovery to the pre-treatment state.

Injection site reactions

Injection site reactions have been reported after the administration of Voltaren intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during i.m. administration of Voltaren

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

This medicine contains less than 1mmol sodium (23 mg) per 3 ml ampoule, that is to say essentially 'sodium-free'.

GRT

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

PRT

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Voltaren solution for injection, gastro-resistant tablets, prolonged-released tablets, suppositories, and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered

CYP2C9 inhibitors

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

Lithium

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

Digoxin

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

Diuretics and antihypertensive agents

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g., betablockers, 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 (see section 4.4).

Ciclosporin and tacrolimus

Diclofenac, like other NSAIDs may increase the nephrotoxicity of ciclosporin and tacrolimus 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 or tacrolimus.

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 (see section 4.4).

Quinolone antibacterials

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

Anticipated interactions to be considered Other NSAIDs and corticosteroids
Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4).

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

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.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

Phenytoin

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

Methotrexate

Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

CYP2C9 inducers

Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive. Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the fetal ductus arteriosus and fetal renal impairment leading to oligohydramnios.

Because of these risks, Voltaren should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

In addition, Voltaren should not be used during the third trimester of pregnancy (see section 4.3).

In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, or rabbits given diclofenac daily during the period of organogenesis at doses up to approximately 0.41, 0.41, and 0.81 times, respectively, the maximum recommended human dose (MRHD) of Voltaren, despite the presence of maternal and fetal toxicity (see Animal data).

Clinical considerations Fetal Adverse Drug Reactions

Premature Closure of Fetal Ductus Arteriosus

As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of premature closure of the fetal ductus arteriosus (see section 4.5).

Oligohydramnios/Fetal Renal Impairment

Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.

If an NSAID is necessary from the 20th week gestation to the end of the 2nd trimester, limit the use to the lowest effective dose and shortest duration possible (see section 4.2). If Voltaren treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Voltaren and follow up according to clinical practice.

Labor or Delivery

There are no studies on the effects of Voltaren during labor or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia (see section 4.5). In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Human Data

Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus**.**

Oligohydramnios/Fetal Renal Impairment

Published studies and post-marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal impairment leading to oligohydramnios. These adverse outcomes are seen, on

average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug.

Animal Data

Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of Voltaren, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison).

In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.08 and 0.16 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal mortality (caused by gastrointestinal ulceration and peritonitis) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, intrauterine growth retardation, and decreased fetal survival. Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the fetal ductus arteriosus.

Lactation

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

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother treated orally with a diclofenac salt of 150 mg/day. The estimated dose ingested by an infant consuming breast milk is equivalent to 0.03 mg/kg/day.

Fertility

<u>Female fertility</u>

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

Male fertility

There is no human data on the effect of Voltaren on male fertility.

Diclofenac administered to male and female rats at 4 mg/kg/day (approximately 0.16 times the MRHD based on BSA comparison) did not affect fertility.

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 VOLTAREN, should refrain from driving or using machines.

4.8 Undesirable effects

Tabulated summary of adverse drug reactions

Adverse drug reactions from clinical trials and/or spontaneous or literature reports (Table 7-1) 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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

The following undesirable effects include those reported with Voltaren solution for injection/gastroresistant tablets/prolonged-released tablets/suppositories and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 7-1 Adverse drug reactions

Infections and infestations *(solution for injection only)*

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:	Angioedema (including face edema).
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia.
Ear and labyrinth disorder	**s**
Common:	Vertigo.
Very rare:	Tinnitus, impaired hearing.
Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain
Frequency not known	Kounis syndrome
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, decreased appetite.

Rare: Gastritis, gastrointestinal hemorrhage, hematemesis, hemorrhagic diarrhea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis), proctitis ***(suppositories only)***.

Very rare: Colitis (including hemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis, hemorrhoids ***(suppositories only)***.

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 dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schoenlein purpura, pruritus.

Renal and urinary disorders

Very rare: Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

General disorders and adm	**inistration site conditions**	
		Injection site reaction, injection site pain, injection site induration ***(solution for injection only)***.
	Common:	Application site irritation ***(suppositories only)***
	Rare:	Edema, injection site necrosis ***(solution for injection only)***.

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

Adverse drug reactions from spontaneous reports and literature cases (frequency not known) The following adverse drug reaction has been derived from post-marketing experience with Voltaren. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known.

Table 7-2 Adverse drug reaction from spontaneous reports and literature cases (frequency not known) Injection site reactions

~~Embolia cutis medicamentosa (Nicolau syndrome) *(solution for injection only*~~).

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section 4.4).

Visual effects

Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, 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, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

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

GRT and PRT

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).

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.

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

Solution for injection

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

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

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

Voltaren ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

GRT

In clinical trials Voltaren has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhea, Voltaren is capable of relieving the pain and reducing the extent of bleeding.

PRT

Voltaren 75 mg and 100 mg prolonged-release tablets are particularly suitable for patients in whom a daily dose of 75 mg or 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. Voltaren 75 mg prolonged-release tablets also allow the maximum daily dose of 150 mg to be given in a balanced b.i.d. schedule.

Suppositories

In clinical trials Voltaren has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhea, Voltaren is capable of relieving the pain and reducing the extent of bleeding.

Voltaren also has beneficial effects on the symptoms of migraine attacks.

Mechanism of action (MOA)

Voltaren contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, antiinflammatory, 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 sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans

5.2 Phamacokinetic properties

Absorption

Solution for injection

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 [78]. 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) [207-212]. 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 gastro-resistant 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 metabolized during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes.

GRT

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet.

Mean peak plasma concentrations of 1.5 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg.

The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same.

Since about half of diclofenac is metabolized 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.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

PRT

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from Voltaren prolonged-release tablets as from gastro-resistant tablets. However, the systemic availability of diclofenac from Voltaren prolonged-release tablets is on average about 82% of that achieved with the same dose of Voltaren administered in the form of gastroresistant tablets (possibly due to release-rate dependent "first-pass" metabolism). As a result of a slower release of the active substance from Voltaren prolonged-release tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

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 a prolonged-release tablet of 100 mg or 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of Voltaren prolonged-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 Voltaren prolonged-release tablets 100 mg (75 mg).

Since about half of diclofenac is metabolized 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.

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with Voltaren prolonged-release tablets 100 mg once daily or 75 mg twice daily.

Suppositories

Diclofenac shows a rapid onset of absorption from suppositories, although the rate of absorption is slower than from gastro-resistant tablets administered

orally. After the administration of 50 mg suppositories, peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of gastroresistant tablets.

Since about half of diclofenac is metabolized 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.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

For all formulations

Pharmacokinetic behaviour 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/metabolism

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'-methoxydiclofenac), 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 ± 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.

Linearity/non-linearity Solution for injection

The amount absorbed is in linear proportion to the size of the dose.

GRT

The amount absorbed is linearly related to the size of the dose [78].

PRT

The amount absorbed is linearly related to the dose strength [189].

Suppositories

The amount absorbed is linearly related to the size of the dose

Special populations

Geriatric patients

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed [7,172,173,225]. 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

Renal impairment

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of 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.

Hepatic impairment

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 (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solution for injection

Mannitol; sodium metabisulphite (E223); benzyl alcohol; propylene glycol; water for injection; sodium hydroxide.

GRT

- **Core for 25 mg and 50 mg**: Cellulose microcrystalline; lactose monohydrate; magnesium stearate; maize starch; povidone; silica, colloidal anhydrous; sodium starch glycolate (type A).
- **Coating for 25 mg:** hypromellose; iron oxide yellow (E172); macrogoglycerol hydroxystearate; Methacrylic acid – ethyl acrylate copolymer; macrogol 8000; talc; titanium dioxide (E171); Simeticone; alpha-octadecyl-omega-hydroxy-polyglykolether; sorbic acid.

- **Coating for 50 mg:** hypromellose; iron oxide red (E172); iron oxide yellow (E172); macrogoglycerol hydroxystearate; Methacrylic acid – ethyl acrylate copolymer; macrogol 8000; talc; titanium dioxide (E171); Simeticone; alpha-octadecyl-omega-hydroxy-polyglykolether; sorbic acid.

PRT

- **Tablet core for 75 mg and 100 mg**: Cetyl alcohol; magnesium stearate; povidone; silica; colloidal anhydrous; sucrose.
- **Tablet coating for 75 mg:** hypromellose; iron oxide red (E172); macrogol 8000; polysorbate 80; sucrose; talc; titanium dioxide (E171).
- **Tablet coating for 100 mg:** hypromellose; iron oxide red (E172); macrogol 8000; polysorbate 80; sucrose; talc; titanium dioxide (E171).

Suppositories Hard fat.

6.2 Incompatibilities

Solution for injection

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

Infusion solutions of sodium chloride 0.9% or glucose 5% without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading to formation of crystals or precipitates. Infusion solutions other than those recommended should not be used.

GRT

Not applicable.

PRT

Not applicable.

Suppositories Not applicable.

6.3 Shelf Life

Solution for Injection

2 years

GRT

5 years

PRT

3 years

Suppositories

3 years

6.4 Special precautions for storage

Solution for Injection

Do not store above 30°C.

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

Protect from heat.

Keep out of the reach and sight of children

GRT

Do not store above 30°C.

Store in the original package

Keep out of the reach and sight of children

PRT

Do not store above 30°C.

Store in the original package.

Keep out of the reach and sight of children

Suppositories

Do not store above 30°C.

Store in the original package

Keep out of the reach and sight of children

6.5 Nature and contents of container

Solution for Injection

Ampoule, Glass type I, colourless with one point cut

GRT

Blister Foil (formed side), PVC/PE/PVDC, transparent, colourless

Blister Foil (lidding) Aluminium (AL)

PRT

Blister Foil (formed side), PVC/PE/PVDC, transparent, colourless

Blister Foil (lidding) Aluminium (AL)

Suppositories

PVC/LD-PE foil

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling of the product

No special requirements.

Solution for 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.

To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant using aseptic technique, or intravenously by slow infusion after dilution in accordance with the following instructions. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded.

Appropriate injection technique and length of the needle (considering the thickness of the patient's gluteal fat) should be used to avoid inadvertent subcutaneous administration of Voltaren injection.

Depending on the intended duration of infusion (see section 4 Dosage regimen and administration), mix 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% solution with the contents of one Voltaren ampoule. Both solutions should be buffered with sodium bicarbonate injectable solution (0.5 mL of 8.4% or 1 mL of 4.2% or a corresponding volume of a different concentration) taken from a freshly opened container. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma AG Lichtstrasse 35

4056 Basel

Switzerland

Manufacturer

Solution for injection

Novartis Pharma Stein AG

Schaffhauserstrasse,

4332 Stein,

Switzerland

GR tablets

Novartis Saglik, Gida ve Tarim Urunleri San.Ve Tic. A.S

Yenisehir Mahallesi Ihlara Vadisi

Sokak No. 2 Pendik

Istanbul TR 34912 Turkey

PR tablets Novartis Farma S.p.A.

Via Provinciale Schito 131,

80058 Torre Annunziata,

Italy

Suppositories Delpharm Huningue S.A.S.

26, rue de la Chapelle,

68330 Huningue,

France

9. MARKETING AUTHORISATION NUMBER

Prescription only medication.

Voltaren 75 mg/3 ml solution for injection Kenya: 2002

Voltaren 75 mg PRT

Kenya: 8014

Voltaren 100 mg PRT

Kenya: 2005

Voltaren 12.5 mg suppositories

Kenya: 16764

Voltaren 25 mg suppositories

Kenya: 16798

Voltaren 50 mg suppositories

Kenya: 16799

Voltaren 100 mg suppositories

Kenya: 16763

10. DATE OF FIRST AUTHORISATION

Voltaren 75 mg/3 ml solution for injection

Kenya: 19 April 1983

Voltaren prolonged-release tablets 75mg

Kenya: 23 March 1984

Voltaren prolonged-release tablets 100 mg

Kenya: 19 April 1983

Voltaren 12.5 mg suppositories

Kenya: 25 November 2005

Voltaren 25 mg suppositories Kenya: 25 November 2005

Voltaren 50 mg suppositories Kenya: 25 November 2005

Voltaren 100 mg suppositories

Kenya: 25 November 2005

11. DATE OF REVISION OF THE TEXT

September 2024 (CDS)