TOLERAN

Tablet

Composition
Each tablet contains 50 mg of diclofenac potassium

Action
Non-steroidal anti-inflammatory drug (NSAID)

Mechanism of Action
Toleran tablets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced analgesic, anti-inflammatory, and antipyretic properties.

Toleran tablets have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever.

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

Pharmacodynamics
Diclofenac potassium has been found to exert a pronounced analgesic effect in moderate and severe pain. In the presence of inflammation, e.g. due to trauma or following surgical interventions, it rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound oedema. Clinical studies have also revealed that in primary dysmenorrhea the active substance is capable of relieving the pain and reducing the extent of bleeding. In migraine attacks Diclofenac potassium has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting.

Pharmacokinetics
Absorption
Diclofenac is rapidly and completely absorbed from diclofenac potassium tablets. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium gastro-resistant tablets. Mean peak plasma concentrations of 3.8 µmol/L are attained after 20 - 60 minutes after ingestion of one tablet of 50 mg. Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

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

Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size.

Pharmacokinetic behavior does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

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

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

Biotransformation
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination
Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 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 less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

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

Indications
Short-term treatment in the following acute conditions:

- post-traumatic pain, inflammation and swelling, e.g. due to sprains;
- post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery;
- painful and/or inflammatory conditions in gynecology, e.g. primary dysmenorrhea or adnexitis;
- migraine attacks;
- painful syndromes of the vertebral column;
- non-articular rheumatism;
- 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.

Contraindications

- Gastric or intestinal ulcer.
- Known hypersensitivity to the active substance or the excipients.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other drugs with prostaglandin-synthetase inhibiting activity.

Adverse Reactions
In patients taking Diclofenac Potassium tablets or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1% to 10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

Body as a Whole: fever, infection, sepsis

Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope

Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomtatitis, thrombocytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System: asthma, dyspnea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure.

Other adverse reactions, which occur rarely, are:
Body as a Whole: anaphylactic reactions, appetite changes, death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, eructation, liver failure, pancreatitis

Hemic and Lymphatic System: agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Metabolic and Nutritional: hyperglycemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment

Warnings and Precautions

Warnings

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to the drug. Like other NSAIDs, Diclofenac potassium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Cardiovascular Thrombotic Events
Observational studies have indicated that non-selective NSAIDs may be associated with a n increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimize 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.

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.

Gastrointestinal Events
All NSAIDS can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk. Gastrointestinal bleeding or ulceration/perforation can occur at any time during treatment, with or without warning symptoms or a previous history.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal events.
In the rare cases where gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac potassium, the drug should be withdrawn.

Severe Skin Reactions
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 potassium. 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 legion or any other sign of hypersensitivity, and Diclofenac potassium should be discontinued.

Precautions
Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders or a history suggestive of gastric or intestinal ulcer, patients with ulcerative colitis or Crohn's disease, and in patients suffering from impaired hepatic function.

As with other NSAIDs, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac potassium monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash, etc.), Diclofenac potassium should be discontinued. Hepatitis may occur without prodromal symptoms.

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

Owing to the importance of prostaglandins in maintaining renal blood flow, particular caution is called for in patients with impaired cardiac or renal function, the elderly, patients being treated with diuretics, and patients with substantial extracellular volume depletion of any cause, e.g. before and after major surgery. Monitoring of renal function is recommended as a precautionary measure when using Diclofenac potassium in such cases. Discontinuation of therapy is normally followed by a return to the pretreatment state.

Treatment with Diclofenac potassium in the aforementioned indications usually proves necessary only for a few days. But if, contrary to the recommendations for its use, Diclofenac potassium is administered over a more prolonged period, it is advisable - as with other NSAIDs - to perform blood counts.

Like other NSAIDs, Diclofenac potassium may temporarily inhibit platelet aggregation. Patients with haemostatic disorders should be carefully monitored.

Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dosage should be used in frail elderly patients or those with a low body-weight.

Pregnancy
Category C
Because of the known effects of non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

Drug Interactions
(Including interactions observed with diclofenac sodium)

Lithium, digoxin: Diclofenac potassium may raise plasma concentrations of lithium or digoxin.

Diuretics: Like other NSAIDs, Diclofenac potassium may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored.

NSAIDs: Concomitant administration of systemic NSAIDs may increase the frequency of side effects.

Anticoagulants: Although clinical investigations do not appear to indicate that Diclofenac potassium affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving Diclofenac potassium and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Antidiabetic: Clinical studies have shown that Diclofenac potassium can be given together with oral antidiabetic agents without influencing their clinical effect. However, isolated cases have been reported of both hypoglycemic and hyperglycemic effects necessitating changes in the dosage of hypoglycemic agents during treatment with Diclofenac potassium.

Methotrexate: Caution is called for if 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.

Cyclosporin: The effects of NSAIDs on renal prostaglandins may increase the nephrotoxicity of cyclosporin.

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

Dosage and Administration

For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Toleran tablets, followed by 50 mg doses, will provide better relief.

For the relief of osteoarthritis the recommended dosage is 100 to 150 mg/day in divided doses, 50 mg b.i.d. or t.i.d.

For the relief of rheumatoid arthritis the recommended dosage is 150 to 200 mg/day in divided doses, 50 mg t.i.d. or q.i.d.

For treatment of Migraine an initial loading dose of 50mg, then if necessary a further 50mg after 2 hours. The maximum daily dose is 150mg.

Overdosage

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Storage

Protect from moisture and heat (store below 30°C). Medicines should be kept out of the reach of children.

Presentation

Box of 10 tablets