PRODUCT MONOGRAPH

PrDICLOFENAC-K

(diclofenac potassium)

50 mg Tablets

Sanis Standard

Acetic Acid Derivatives and Related Substances

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[Pr]DICLOFENAC-K

(diclofenac potassium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Oral	tablets / 50 mg	calcium phosphate, corn starch, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, sodium starch glycolate. The film coating contains: hydroxypropyl methylcellulose, maltodextrin, polydextrose, polyethylene glycol, synthetic red iron oxide, synthetic yellow iron oxide, titanium dioxide, triacetin.

INDICATIONS AND CLINICAL USE

DICLOFENAC-K (diclofenac potassium) is indicated for:

the short-term (up to one week) treatment of acute, mild to moderately severe pain that may be accompanied by inflammation, in conditions such as: musculoskeletal and/or soft tissue trauma including sprains, post-operative pain following dental extraction, episiotomy, or dysmenorrhea.

Throughout this document, the term Nonsteroidal Anti-Inflammatory Drug (NSAID) refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

Diclofenac, particularly at higher doses, is associated with an increased risk of serious cardiovascular related adverse events that is comparable to COX-2 inhibitors. For patients with pre-existing risk factors for cardiovascular disease (including ischemic heart disease, cerebrovascular disease and/or congestive heart failure NYHA II-IV), other management strategies that do not include NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

For patients with increased risk of developing GI adverse events other management strategies that do not include NSAIDs should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of DICLOFENAC-K should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

DICLOFENAC-K, as a NSAID, does NOT treat clinical disease or prevent its progression.

DICLOFENAC-K, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Patient Subsets

Geriatrics
Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (<16 years of age)
Safety and efficacy have not been established in the pediatric population.

CONTRAINDICATIONS

DICLOFENAC-K is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although diclofenac potassium has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus, fetal renal impairment with subsequent oligohydramnios and prolonged parturition.
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants.
- severe uncontrolled heart failure.
- known hypersensitivity to DICLOFENAC-K or to any of the components/ excipients.
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions - *Anaphylactoid Reactions***).
- active gastric / duodenal / peptic ulcer, active GI bleeding or perforation, gastritis or ulcerative colitis, regional enteritis, recurrent ulceration (see **WARNINGS AND PRECAUTIONS** and **ADVERSE DRUG REACTIONS**).

- cerebrovascular bleeding or other bleeding disorders.
- inflammatory bowel disease.
- severe hepatic impairment or active liver disease.
- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS** - **Renal**).
- known hyperkalemia (see **WARNINGS AND PRECAUTIONS - Renal** - ***Fluid and Electrolyte Balance***).
- children and adolescents less than 16 years of age.

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Cardiovascular Disease (including ischemic heart disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV))
(See WARNINGS AND PRECAUTIONS - Cardiovascular).

Diclofenac is associated with an increased risk of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events, which can be fatal) that is comparable to COX-2 inhibitors. Meta-analyses of randomized clinical trials comparing several different NSAIDs suggest that diclofenac, particularly at higher doses, is associated with an increased risk of cardiovascular adverse events that is comparable to COX-2 inhibitors. Large population-based observational studies conducted in the general population also support these findings. The risk may increase with the dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Treatment with DICLOFENAC-K is not recommended in patients with pre-existing cardiovascular disease (congestive heart failure NYHA II-IV, ischemic heart disease, peripheral arterial disease) cerebrovascular disease, uncontrolled hypertension, or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). These patients should be treated with DICLOFENAC-K only after careful consideration.

Use of NSAIDs, such as DICLOFENAC-K, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS - Renal - *Fluid and Electrolyte Balance*).

Risk of Gastrointestinal (GI) Adverse Events (See WARNINGS AND PRECAUTIONS – Gastrointestinal).

Use of NSAIDs, such as DICLOFENAC-K is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

DICLOFENAC-K is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **DRUG INTERACTIONS - Drug/Drug Interactions -** ***Acetylsalicylic acid (ASA) or other NSAIDs)***.

Diclofenac potassium should not be used concomitantly with diclofenac sodium (e.g. DICLOFENAC EC or DICLOFENAC SR or DICLOFENAC) since both exist in plasma as the same active organic anion.

Carcinogenesis and Mutagenesis

(See **TOXICOLOGY**)

Cardiovascular

Diclofenac is associated with an increased risk of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events, which can be fatal) that is comparable to COX-2 inhibitors. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

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.

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.

Use of NSAIDs, such as diclofenac potassium, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described below. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing diclofenac potassium should hypertension either develop or worsen with its use.

Use of NSAIDs, such as DICLOFENAC-K**,** can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See **WARNINGS AND PRECAUTIONS - Renal - *Fluid and Electrolyte Balance***).

Caution should be exercised in prescribing DICLOFENAC-K to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA II-IV)**
- **Ischemic heart disease**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**
- **Acute myocardial infarction, history of myocardial infarction and/or angina**
- **Stroke, cerebrovascular accident, transient ischemic attacks, and/or amaurosis fugax**

If needed, these patients should be treated only after careful consideration (See **WARNINGS AND PRECAUTIONS BOX**).

Endocrine and Metabolism

Corticosteroids: DICLOFENAC-K (diclofenac Potassium) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see **DRUG INTERACTIONS – Drug-Drug Interactions - *Glucocorticoids***).

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, peritonitis, obstruction and gastrointestinal bleeding, gastrointestinal stenosis and ischemic colitis can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as DICLOFENAC-K. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with DICLOFENAC-K, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration**. For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see **WARNINGS AND PRECAUTIONS - Special Populations - *Geriatrics***).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using DICLOFENAC-K and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even a short-term therapy has its risks.

Caution should be taken if prescribing DICLOFENAC-K to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluotexine, paroxetine, sertraline)

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent or reduce the occurrence of gastrointestinal adverse events associated with the use of diclofenac potassium.

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with DICLOFENAC-K should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from hemophilia or platelet disorders should be carefully observed when DICLOFENAC-K is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of DICLOFENAC-K with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

***Anti-platelet Effects**:* NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

Diclofenac Potassium and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see **DRUG INTERACTIONS - *Drug-Drug Interactions* - *Acetylsalicylic Acid (ASA) or other NSAIDs***).

Concomitant administration of DICLOFENAC-K with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias: Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including DICLOFENAC-K. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including DICLOFENAC-K, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic / Biliary / Pancreatic

As with other NSAIDs, including DICLOFENAC-K, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

In post-marketing 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. Post-marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should monitor hepatic function in patients receiving DICLOFENAC-K. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and «flu-like» symptoms), or if other manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued. Hepatotoxic effects may occur with use of diclofenac without prodromal symptoms.

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 and the appropriate action patients should take if these signs and symptoms appear. DICLOFENAC-K is contraindicated in severe liver impairment or active liver disease. If there is a need to prescribe this drug to other patients with liver impairment, it must be done under strict observation.

Caution is advised when using DICLOFENAC-K in patients with hepatic porphyria, since DICLOFENAC-K may trigger an attack.

Hypersensitivity Reactions

Anaphylactoid reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to diclofenac potassium. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving diclofenac potassium. DICLOFENAC-K should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **CONTRAINDICATIONS**).

***ASA-intolerance*:** DICLOFENAC-K should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **CONTRAINDICATIONS**).

***Cross Sensitivity*:** Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs as well.

***Serious Skin Reactions*:** (See **WARNINGS AND PRECAUTIONS - Skin**)

Immune

(See **WARNINGS AND PRECAUTIONS – Infection - *Aseptic Meningitis***)

Infection

DICLOFENAC-K, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

***Aseptic Meningitis*:** Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as DICLOFENAC-K. If patients experience such adverse reaction(s) they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs, which may be reversible with discontinuation. If such symptoms develop, DICLOFENAC-K should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving DICLOFENAC-K for an extended period of time.

Sun exposure in patients using DICLOFENAC-K might cause photosensitivity and vision changes. Patients should be advised to contact their physician for assessment and advice if this occurs.

Peri-Operative Considerations

(See **CONTRAINDICATIONS -** Coronary Artery Bypass Graft Surgery)

Psychiatric

(See **WARNINGS AND PRECAUTIONS – Neurologic**)

Renal

Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

During long-term therapy, kidney function should be monitored periodically (see **ACTION AND CLINICAL PHARMACOLOGY - Special Populations and Conditions - Renal Impairment**)

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR< 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporine, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis).

Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as DICLOFENAC-K, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

(See **WARNING AND PRECAUTIONS - Monitoring and Laboratory Tests - *Renal***)

Advanced Renal Disease: (See **CONTRAINDICATIONS**)

Fluid and Electrolyte Balance: Use of NSAIDs, such as DICLOFENAC-K, can promote sodium retention in a dose-dependant manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing DICLOFENAC-K in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS - Cardiovascular**).

Use of NSAIDs, such as DICLOFENAC-K, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporine, tacrolimus, trimethoprim or some diuretics. Electrolytes should be monitored periodically (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS-Drug-Drug Interactions**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

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 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.

Sexual Function / Reproduction

The use of DICLOFENAC-K, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of DICLOFENAC-K should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Use of DICLOFENAC-K may cause photosensitivity upon exposure to sunlight or UV light causing symptoms such as sunburn, skin rash, skin blisters, pruritus, erythema and discolouration.

Special Populations

Pregnant Women: **DICLOFENAC-K is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus, fetal renal impairment with subsequent oligohydramnios and the potential to prolong parturition (see TOXICOLOGY)**.

DICLOFENAC-K should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryofoetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Diclofenac potassium readily crosses the placental barrier.

Nursing Women: (See **CONTRAINDICATIONS**)

Pediatrics*:* (See **CONTRAINDICATIONS**)

Geriatrics: Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding.

For such patients, the dosage should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision, especially in frail elderly patients or those with a low body weight.

Monitoring and Laboratory Tests

Cardiovascular *(Hypertension)****:*** Blood pressure should be monitored regularly during therapy with DICLOFENAC-K.

Hematologic: Patients on long-term treatment with DICLOFENAC-K should have their hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC), and platelets checked if they exhibit any signs or symptoms of anemia or blood loss or blood dyscrasia.

Concurrent therapy of DICLOFENAC-K with warfarin requires close monitoring of the international normalized ratio (INR).

Hepatic: Hepatic function (e.g.serum transaminases, bilirubine) should be monitored regularly during therapy with DICLOFENAC-K.

Ophthalmologic: Patients on long-term treatment with DICLOFENAC-K should have an ophthalmologic examination performed periodically, and if they experience blurred and/or diminished vision.

Renal: Patients with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporine, diuretics, and the elderly should have their renal function monitored (e.g. urine output, serum creatinine, creatinine clearance and serum urea) during therapy with DICLOFENAC-K.

Electrolytes, including serum potassium, should be monitored periodically, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporine, tacrolimus, trimethoprim or some diuretics.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Although not all adverse drug reactions have been reported with diclofenac potassium, the types of adverse drug reactions are expected to be similar to those of diclofenac sodium since both formulations exist in the plasma as the same active organic anion.

Gastrointestinal, dermatological, CNS and hepatic adverse reactions are the most commonly seen with diclofenac. The most severe gastrointestinal adverse reactions observed were ulceration and bleeding, while the most severe dermatological, albeit rare, reactions observed with diclofenac were erythema multiforme (Stevens-Johnson Syndrome and Lyell Syndrome). Fatalities have occurred on occasion, particularly in the elderly.

This section summarizes adverse drug reaction data pooled from clinical trials, published investigations and post-marketing experience with diclofenac potassium and diclofenac sodium

Frequency estimate:
Very common: ≥ 10%
Common: ≥1% and <10%
Uncommon: ≥0.01% and <1%
Very Rare <0.01%, including isolated reports.

Table 1 Most Common Adverse Drug Reactions (≥ 1%)

Gastrointestinal disorders	Very common	nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decrease appetite
Nervous system disorders	Common	dizziness, headache
Hepatic	Common	elevations (≥3 times the upper normal limit) of serum aminotransferase enzymes (SGOT or AST, SGPT or ALT).
Skin and subcutaneous disorders	Common	rash, pruritus
Ear and labyrinth disorders	Common	vertigo

Table 2 Less Common Adverse Drug Reactions (<1%)

Gastrointestinal disorders	Uncommon	gastritis, gastrointestinal hemorrhage, hemorrhagic diarrhea, melena, hematemesis, gastric and intestinal ulcerations (with or without bleeding or perforation).
	Very Rare	lower gut disorders (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), strictures intestinal diaphragm disease, hyperacidity, stomatitis, glossitis, coated tongue, esophageal lesions, constipation, pancreatitis

Nervous system disorders	Uncommon	somnolence, malaise, impaired concentration, tiredness.
	Very Rare	sensory disturbances including paresthesia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage), dysgeusia
Eye disorders	Very Rare	visual impairment (vision blurred, diplopia)
Ear and labyrinth disorders	Very rare	impaired hearing, tinnitus
Cardiac disorders	Uncommon	myocardial infarction, cardiac failure, palpitations, angina, arrhythmias, chest pain
Vascular disorders	Very rare	hypertension, vasculitis
Skin and subcutaneous disorders	Uncommon	urticarial
	Very Rare	bullous dermatitis , erythema, eczema, erythema multiforme, Stevens-Johnson Syndrome, Lyell Syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), alopecia, photosensitivity reactions, purpura, Henoch-Schonlein purpura
Renal and urinary disorders	Uncommon	edema (facial, general, peripheral).
	Very Rare	acute kidney injury (acute renal failure), nephrotic syndrome, urinary abnormalities (eg. hematuria and proteinuria), tubulointerstitial nephritis, renal papillary necrosis
Hematologic	Very Rare	thrombocytopenia, leukopenia, agranulocytosis, hemolytic anemia, aplastic anemia, anemia secondary to gastrointestinal bleeding
Hepatic	Uncommon	liver function disorders including hepatitis, hepatic necrosis, hepatic failure, jaundice
	Very Rare	hepatitis fulminant
Immune system disorders	Uncommon	hypersensitivity, anaphylactic / anaphylactoid systemic reactions (including hypotension and shock)
	Very Rare	angioedema, (including face edema)
Psychiatric	Very rare	disorientation, depression, insomnia, nightmare, irritability,

disorders		psychotic disorder
Respiratory disorders	Uncommon	asthma (including dyspnea)
	Very rare	pneumonitis

Post-Market Adverse Drug Reactions

Hepatic: Severe hepatic reactions including liver necrosis, fulminant hepatitis with and without jaundice, and liver failure, some of them with fatal outcome or requiring liver transplantation (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**).

Cardiovascular: Serious reactions including myocardial infarction, cardiac failure, palpitations, angina, arrhythmias, chest pain.

Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events associated with the use of diclofenac, particularly at a high dose (see **WARNINGS AND PRECAUTIONS** box).

Gastrointestinal Disorders: gastrointestinal stenosis, perforation which may lead to peritonitis, and ischemic colitis (which are sometimes fatal) (see **WARNINGS AND PRECAUTIONS – Gastrointestinal (GI))**.

DRUG INTERACTIONS

Drug-Drug Interactions

Overview

Effect of Other Drugs on the Metabolism of diclofenac: Co-prescribing diclofenac with CYP2C9 inhibitors could result in a significant increase in peak plasma concentrations and exposure to diclofenac. Although there are no clinical data available on the drug interaction between diclofenac potassium and CYP2C9 inducers, the possibility of decreased efficacy of diclofenac resulting from concomitant administration with a CYP2C9 inducer cannot be excluded. Dosage adjustment may be required.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus, trimethoprim, ACE inhibitors, angiotensin-II receptor antagonists or adrenergic blockers may be associated with increased serum potassium levels, which should therefore be monitored frequently (see **WARNINGS AND PRECAUTIONS** - Renal - *Fluid and Electrolyte Balance*).

Table 3 Established Potential Drug-Drug Interactions

Diclofenac Potassium	Clinical comment
Acetaminophen	There may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs.
Acetylsalicylic acid (ASA) or other NSAIDs	The use of DICLOFENAC-K in addition to any other NSAID, including over the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions. Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1 **Diclofenac potassium should not be used concomitantly with diclofenac sodium (e.g. DICLOFENAC) since both exist in plasma as the same active organic anion.** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.
Alcohol	There may be an increased risk of gastrointestinal side effects, including ulceration or hemorrhage, when administered concomitantly with NSAIDs.
Antacids	Concomitant administration of antacids with NSAIDs may affect the rate, but generally not the extent of the absorption of the NSAID
Anti-coagulants	(See **WARNINGS AND PRECAUTIONS – Hematologic - *Anti-coagulants***)
Anti-hypertensives	NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. Combinations of ACE inhibitors, angiotensin-II antagonists or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure (see **WARNINGS AND PRECAUTIONS – Renal**). Therefore the combination should be administered with caution especially in the elderly (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Anti-platelet Agents (including ASA)	There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as DICLOFENAC-K (see **WARNINGS AND PRECAUTIONS – Hematologic -** ***Anti-platelet Effects***).
Cyclosporine	Nephrotoxicity of cyclosporine may be increased because of the effect of NSAIDs on renal prostaglandins. Therefore, patients treated with cyclosporinee should receive doses of diclofenac lower than the regular doses.
CYP2C9 inducers	Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampin), which could result in a significant decrease in plasma concentration and exposure to diclofenac. Dosage adjustment may be required.
CYP2C9 inhibitors	Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole or sulfinpyrazone), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac. Dosage adjustment may be required.
Digoxin	Diclofenac may increase the plasma concentration of digoxin. Dosage adjustment may be required. Monitoring of serum digoxin level is recommended.
Diuretics	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics (see **WARNINGS AND PRECAUTIONS – Renal***)*. (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests – *Renal***)
Glucocorticoids	Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.
Lithium	Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur in patients taking lithium. Dosage adjustment of lithium may be required.
Methotrexate	Caution should be exercised when NSAIDs, including DICLOFENAC-K, are administered less than 24 hours before or after treatment with methotrexate.
Oral Contraceptives	No drug interaction data are available for DICLOFENAC-K co-administered with oral contraceptives.
Oral hypoglycemics	Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac; however, there are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac, which necessitated changes in the dosage of hypoglycemic agents. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy. There have also been reports of metabolic acidosis when diclofenac was co-administered with metformin, particularly in the context of renal impairment. Caution is recommended when co-prescribing diclofenac with metformin.

Phenytoin	When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.
Probenecid	May decrease the excretion and increase serum concentrations of NSAIDs possibly enhancing effectiveness and/or increasing potential for toxicity. Concurrent therapy of NSAIDs with probenicid requires close monitoring to be certain that no change in dosage is necessary.
Quinolone antibacterials	There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.
Selective Serotonin Reuptake Inhibitors (SSRIs)	Concomitant administration of NSAIDs, including DICLOFENAC-K, and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS – Gastrointestinal (GI)**).
Sulfinpyrazone	Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as sulfinpyrazone), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac. Dosage adjustment may be required.
Tacrolimus	Nephrotoxicity of tacrolimus may be increased because of the effect of NSAIDs on renal prostaglandins. Therefore, patients treated with tacrolimus should receive doses of diclofenac lower than the regular doses.
Voriconazole	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. Dosage adjustment may be required.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, and are unlikely to be clinically important.

Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to therapy.

Drug-Lifestyle Interactions

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking DICLOFENAC-K should refrain from driving or using machines.

DOSAGE AND ADMINISTRATION

Dosing Consideration

Geriatrics*:** In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary. Caution is indicated, especially for frail elderly patients or those with a low body weight (See **WARNINGS AND PRECAUTIONS - Special Populations - *Geriatrics).

Cardiovascular disease or cardiovascular risk factors: Treatment with DICLOFENAC-K is not recommended in patients with pre-existing cardiovascular disease (congestive heart failure NYHA II-IV, ischemic heart disease, peripheral arterial disease), cerebrovascular disease, uncontrolled hypertension, or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). These patients should be treated with DICLOFENAC-K only after careful consideration (see **WARNINGS AND PRECAUTIONS** box).

Renal Impairment:
DICLOFENAC-K is contraindicated in patients with severe renal impairment or deteriorating renal disease (see **CONTRAINDICATIONS**). Lower doses of DICLOFENAC-K should be considered in patients with impaired renal function (See **WARNINGS AND PRECAUTIONS – Renal**).

Hepatic Impairment:
DICLOFENAC-K is contraindicated in patients with severe hepatic impairment or active liver disease (see **CONTRAINDICATIONS**). Lower doses of DICLOFENAC-K should be considered in patients with impaired hepatic function (see **WARNINGS AND PRECAUTIONS – *Hepatic/Biliary/Pancreatic***).

Recommended Dose and Dose Adjustment

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.

DICLOFENAC-K (diclofenac potassium) 50 mg tablets:

DICLOFENAC-K is indicated for short-term (up to one week) treatment only.

DICLOFENAC-K should be taken with food.

The recommended daily dose for DICLOFENAC-K is one 50 mg tablet, every 6-8 hours as required for a total daily maximum amount of 100 mg.

For primary dysmenorrhea, treatment may be initiated on the first day with a loading dose of 100 mg, followed by 50 mg every six to eight hours after the initial dose if needed, for a maximum dose of 200 mg only on the first day.

Patients should be maintained on the lowest effective dose.

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

Missed Dose

Patients who miss one or more doses of DICLOFENAC-K should not increase the dose of DICLOFENAC-K to compensate for the missed dose or doses, but should continue with their therapy as soon as possible.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center immediately.

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, including DICLOFENAC-K, 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, including DICLOFENAC-K, 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Diclofenac, the active substance of DICLOFENAC-K (diclofenac potassium), is a non- steroidal anti-inflammatory (NSAID) drug with analgesic properties. Diclofenac inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. This inhibitory effect may partially explain its actions. It is considered to be a peripherally acting analgesic.

Diclofenac potassium tablets have a rapid onset of action, making them particularly suitable for the treatment of acute painful inflammatory conditions.

Pharmacodynamics

The effects of DICLOFENAC-K are largely mediated by inhibition of cyclooxygenases (COXs, COX-1, COX-2). These enzymes are found throughout the body and produce prostaglandins, which are important mediators of pain, fever, and adaptive and protective reactions in many organs and (inflamed) tissues.

Pharmacokinetics

Absorption*:* In humans, diclofenac can be detected in the plasma within 10 minutes of oral administration of diclofenac potassium tablets. Absorption is virtually complete. The area under the plasma curve (AUC) is dose proportional. A 50 mg tablet produces a mean peak plasma concentration of 3.8 μmol/L, 20-60 min post dose. The amount of diclofenac absorbed from diclofenac potassium is the same as that obtained from an equivalent diclofenac sodium enteric-coated tablet dose. Since diclofenac undergoes extensive first pass metabolism, only half of an orally administered dose is systemically available. The rate and extent of absorption of diclofenac are insignificantly affected (slightly delayed) when diclofenac potassium tablets are taken with food. When given in a regimen of 50 mg TID for 8 days, diclofenac potassium did not produce plasma accumulation of diclofenac.

Distribution: Diclofenac sodium is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.12 to 0.17 L/kg. Single-dose (P.O. or I.M.) studies in rheumatoid patients with joint effusions have shown that diclofenac is distributed to the synovial fluid, where T_{max} occurs 2 to 4 hours after plasma T_{max}. Synovial fluid concentrations exceed plasma levels within 4 to 6 hours of administration. This elevation above plasma concentrations can be maintained for up to 12 hours. The synovial fluid elimination half-life is at least 3 times greater than that for plasma.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose (see **CONTRAINDICATIONS**).

Metabolism**:** The potassium salt of diclofenac in diclofenac potassium yields the same active organic anion produced by the sodium salt found in diclofenac sodium enteric coated tablets. Therefore, the fate of the systemically available anion is the same for both formulations.

Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3'-, 4'-, 5-hydroxy, 4'- 5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.

Excretion: Plasma clearance of diclofenac is 263±56 mL/min. The mean terminal drug half life in plasma is 1.8 hr after oral doses. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through the bile in the feces. About 1% of an oral dose is excreted unchanged in urine.

Special Populations and Conditions

***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 <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. Although no accumulation of pharmacologically active substance seem to occur, caution is advised while administering diclofenac potassium to patients with impaired kidney function (ie GFR < 60 mL/min or 1 mL/sec) (see **WARNINGS AND PRECAUTIONS - Renal**). DICLOFENAC-K is contraindicated in patients with severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min (0.5 mL/s) (see **CONTRAINDICATIONS**).

***Hepatic impairment*:** In a study of ten patients with impaired hepatic function (chronic hepatitis and non-decompensated cirrhosis) receiving a single 100 mg oral dose of diclofenac sodium, the kinetics and metabolism of diclofenac were similar to patients without liver disease.

Pediatrics: DICLOFENAC-K is contraindicated in children and adolescents less than 16 years of age (see **CONTRAINDICATIONS**).

Geriatrics: No relevant age-dependant differences in the absorption, metabolism, or excretion of diclofenac have been observed.

STORAGE AND STABILITY

Store bottles between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DICLOFENAC-K (diclofenac potassium) is available as:
50 mg round, biconvex, reddish-brown, film-coated tablets engraved N on one side and 50 on the other.

Each 50 mg tablet contains: calcium phosphate, corn starch, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, sodium starch glycolate.

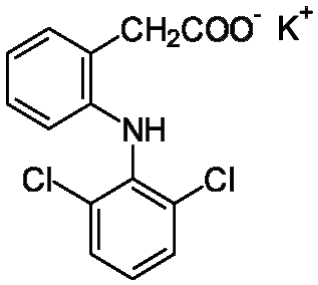
The film coating contains: hydroxypropyl methylcellulose, maltodextrin, polydextrose, polyethylene glycol, synthetic red iron oxide, synthetic yellow iron oxide, titanium dioxide, triacetin.

Supplied: Bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name:	Diclofenac potassium
Chemical name:	Potassium [*o*-(2,6-dichloroanilino)-phenyl]acetate
Molecular formula:	$C_{14}H_{10}Cl_2KNO_2$
Molecular mass:	334.25 g/mol
Structural formula	
Physicochemical properties:	Diclofenac potassium is an odourless pale yellowish or beige crystalline powder. At 25°C diclofenac potassium is 5% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative, two way single dose bioavailability study was performed in fed volunteers on two diclofenac potassium 50 mg tablet formulations, DICLOFENAC-K and Voltaren Rapide®. The pharmacokinetic data calculated for diclofenac in the DICLOFENAC-K and Voltaren Rapide® tablet formulation is tabulated below:

DICLOFENAC-K (2 x 50 mg) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	DICLOFENAC-K*	Voltaren Rapide®†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	1692 1716 (18)	1661 1691 (19)	102	96% – 106%
AUC_I (ng*h/mL)	1720 1746 (19)	1721 1750 (19)	100	95% - 107%
C_{max} (ng/mL)	999.2 1107 (47)	1072 1149 (37)	93	81% - 106%
T_{max} § (h)	1.85 (0.62)	1.84 (0.77)		
$T_{½}$ § (h)	1.57 (0.54)	1.81 (0.88)		

* Diclofenac-K 50 mg Tablets (Sanis Health Inc., Canada)
† Voltaren Rapide® 50 mg Tablets (Geigy Pharmaceuticals, Ciba Geigy, Canada) Purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

Randomized clinical trials with diclofenac potassium have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

However, large population-based observational studies, meta-analyses and systematic reviews suggest that diclofenac use is associated with an increased risk of cardiovascular thrombotic events, including myocardial infarction and ischemic stroke. Results of some studies suggest that the CV risk is related to the dose and duration of diclofenac exposure and is greater in patients with risk factors for CV disease.

Large meta-analyses of randomized clinical trials show that diclofenac is associated with an increased risk of stroke, cardiovascular death, and death from any cause when compared with placebo. Data also suggest that diclofenac, particularly when used at a high dose (150 mg daily) may have a higher risk of thrombotic CV events than other NSAIDs.

The information provided below supported the original registration and its subsequent amendments. These studies were conducted in accordance with the standards and regulations in force at the time of conduct of these studies.

Although the rate of absorption of diclofenac from immediate release tablets containing the potassium salt is faster than that from the enteric coated tablet containing the sodium salt, the extent of absorption is comparable. The extent of absorption of diclofenac potassium whether given with a phosphate buffer or a fat-protein breakfast is equivalent. However, the rate of absorption in the presence of food is slightly reduced, resulting in lower maximum concentrations in plasma.

Several controlled, double blind clinical studies have compared the safety and efficacy of diclofenac potassium to that of ASA or naproxen for the relief of pain following dental surgery, episiotomy and dysmenorrhea.

The efficacy of diclofenac potassium and ASA were compared following impacted molar extraction. Dosages of 50 mg diclofenac potassium and 650 mg ASA were statistically significantly more effective than was placebo in relieving pain following this dental procedure. In one study (04) a 50 mg dose of diclofenac potassium was also statistically superior to ASA 650 mg for "total pain relief at 8 hours", "sum of pain intensity difference at 8 hours" and time to remedication.

Table 4 Summary of clinical studies in moderate or severe pain following removal of one or more impacted third molar teeth

Study no.	Study design	Patients	Treatment Duration	Medication dose/day	Efficacy variables
02	Double-blind, parallel study	255	Up to 8 hours after study medication administration	-Diclofenac Potassium 50 mg -Aspirin 650 mg -Placebo	-Total Pain relief at 8 and 4 hours -Pain relief for each time points from ½ to 8 hours -Sums of Pain Intensity Differences - Time to re-medication - Overall patient evaluation
04	Double-blind, parallel study	208	Up to 8 hours after study medication administration	Diclofenac Potassium 50 mg -Aspirin 650 mg -Placebo	Total Pain relief at 8 and 4 hours -Pain relief for each time points from ½ to 8 hours -Sums of Pain Intensity Differences - Time to re-medication - Overall patient evaluation

The safety and efficacy of diclofenac potassium for pain relief following episiotomy was demonstrated in a trial using 50 mg diclofenac potassium and 650 mg of ASA.

Female patients with a history of regular menses accompanied by dysmenorrhea were enrolled into two double blind, randomized clinical studies in which they received a three day t.i.d. treatment with either diclofenac potassium 50 mg (100 mg loading dose) or naproxen 275 mg (loading dose of 550 mg). Both treatments were efficacious for the treatment of moderate to severe dysmenorrhea.

DETAILED PHARMACOLOGY

Diclofenac potassium contains the same active principle, diclofenac, as diclofenac sodium; therefore, the two salts have similar pharmacological profiles. Diclofenac is a phenyl-acetic acid derivative possessing anti-inflammatory, analgesic activities as shown in various pharmacological models.

Anti-inflammatory Activity in Rats

The anti-inflammatory potency of diclofenac was assessed by testing inhibition of paw edema (carrageenin solution and kaolin suspension) and reduction of adjuvant arthritis (Freund's adjuvant).

	Inhibition of edema induced by	
Preparation	Carrageenin (ED_{50}mg/kg) P.O.*	Kaolin (ED_{50} mg/kg) P.O.*
Diclofenac potassium (ED_{40})	3	--
Diclofenac sodium (ED_{50})	2.0	1.2

* determined by graphic interpolation from 3 or more doses.

Analgesic Activity in Mice and Rats

The antinociceptive effect of diclofenac was assessed by established tests with results as tabulated.

	Analgesic potency		
Preparation	Phenyl-p-benzoquinone writhing test, mouse [ED_{50} mg/kg (15 min) P.O.]	Acetic acid test, rat (ED_{50} mg/kg P.O.)	Ethacrynic acid test, rat (ED_{50}mg/kg P.O.)
Diclofenac potassium (ED_{40})	0.3	--	--
Diclofenac sodium (ED_{50})	4.3	2.5	1.4

Inhibition of Prostaglandin

A close correlation exists between certain febrile reactions and increased prostaglandin levels in the brain. Diclofenac (0.5 mg/mL) reduces prostaglandin E_2 formation. The inhibition of prostaglandin synthesis *in-vitro* (IC_{50} mM/L) is 1.6.

Platelet Adhesiveness

At 15 mg/mL, diclofenac reduces collagen-induced aggregation in rabbit platelets by 50%. ADP-induced adhesiveness at the same dosage is similarly affected. At 10 mg/kg P.O., diclofenac protected rabbits against the lethal action of thrombokinase without untoward effects.

Gastrointestinal Tolerability

In rats, a 10-day treatment with oral doses of 5 mg/kg diclofenac sodium and diclofenac potassium caused a cumulative blood loss of 360 µL and 410 µL, respectively, as measured by the administration of ^{51}Cr-labelled erythrocytes.

TOXICOLOGY

Since the same active principle, diclofenac, is absorbed from the potassium and sodium salts, toxicological findings with diclofenac sodium are representative of systemic toxicities with diclofenac potassium:

Acute Toxicity

Species	Route	LD_{50} mg/kg	95% Confidence Limits (mg/kg)
Mouse	P.O. I.V.	389 133	197 - 595 126 - 140
Rat	P.O. I.V.	173 106	133 - 213 80 - 132
Guinea-pig	P.O. I.V.	1110 127	950 - 1270 123 - 132
Rabbit	P.O.	194	151 - 259

The symptoms included bradycardia and convulsions.

The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequelae.

Long-term Toxicity Studies

SPECIES	PERIOD	DAILY DOSE mg/kg/P.O.		
		No signs of intoxication	Reversible signs of toxicity, mainly GI Tract	Minimum lethal dose
Rat	3 months 6 months 98 weeks	2 1 0.25	- 2 -	6 4 1
Dog	3 months	-	0.5	2
Rhesus Monkey	6 months	-	5-15	75
Baboon	12 months	-	5	10

Diclofenac sodium was given orally to male and female rats in doses of 0.25, 1.0 and 2.0 mg/kg/day from 59 weeks (high-dose groups) to 98 weeks (low- and intermediate-dose groups). High dose-related mortality rates resulted in termination of the high-dose administration after 59 weeks; the high mortality rate was caused by severe dose-dependent ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and sequelae. Body-weight gains and food consumption of the treated groups were close to the controls. Hematologic patterns showing neutrophilic leucocytosis and anemia were seen in the high- and intermediate-dose groups, particularly females at weeks 52 and 98, respectively. Female animals tended to develop enlarged adrenals and eventually experienced depressed glucose and elevated alkaline phosphatase levels. Histology studies carried out on the tissues of the control-, low- and intermediate-dose groups showed drug-related changes including mucosal ulceration of the small intestine, lymphangiectasis, lymphoid hypoplasia, and plasma cell hypoplasia of the mesenteric lymph nodes, foci of hepatocytic hyperplasia, adrenal cortical atrophy and prostatitis. No increase in tumour incidence was observed in the drug-treated groups as compared to the control group.

Diclofenac sodium was administered orally in gelatin capsules once daily to baboons (*Papio spp*.) at dose levels of 0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day for up to 52 weeks. At all dose levels studied, diclofenac caused ulceration of the gastrointestinal tract. Ulceration was confined to the colon in the low-dose group but was present in the stomach and small intestine also in the other two groups. Body weights were below controls. Constipation, with occasional episodes of diarrhea, was a marked feature. In all treated groups, there was a dose-related fall in serum albumin levels. Anemia and an increased erythrocyte sedimentation rate were observed in the high-dose group. In the recovery groups (control, low, and intermediate), no intestinal lesions were present. Food consumption and body-weight gains were within normal limits. Hematology parameters were comparable to controls and serum albumin levels returned towards normal values.

Reproduction Studies

Rats: Doses of 2 and 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryotoxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated animals were comparable to those of controls except for slightly retarded growth at the higher dose.

Mice and Rats: Teratology studies at oral doses of 2, 3, 10, and 20 mg/kg/day showed no teratogenic effects on fetuses. At the higher doses, pronounced gastrointestinal effects were observed in the dams and a marked toxic effect noted in fetuses (reduced birth weights and increased fetal deaths).

Rabbits: Pregnant females treated with total oral doses of 5 or 10 mg/day throughout the gestation period showed a dose-dependent increase in resorption rates, diminished fetus weights, and abnormal skeletal findings. Definite embryotoxicity was observed at the highest dose although there was no evidence to suggest teratogenicity.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased

fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS-Special Populations**).

Mutagenicity Studies

Mutagenicity studies were carried out *in-vitro* using bacteria with, and without microsomal activation, and in mammalian cells. Studies *in-vivo* were also performed. Diclofenac sodium was not mutagenic in any of these test systems.

Carcinogenicity Studies

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day have revealed no significant increases in tumour incidence. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats. In a 2-year mouse study, only controls and animals at the two lower daily doses of 0.1 and 0.3 mg/kg showed survival sufficient for assessment of carcinogenic potential. The two higher daily doses of 1 and 2 mg/kg resulted in a shortening of lifespan, particularly in males, as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to non-steroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. Diclofenac sodium was not carcinogenic to mice under the conditions of this study.

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PART III: CONSUMER INFORMATION

[Pr]DICLOFENAC-K
(diclofenac potassium)

Read this information each time you refill your prescription in case new information has been added.

This leaflet is Part III of a three-part "Product Monograph" published when DICLOFENAC-K was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DICLOFENAC-K. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the Medication is used for:

Your healthcare provider has prescribed DICLOFENAC-K for short term treatment of acute, mild to moderately severe pain that may be accompanied with swelling (inflammation) in conditions such as sprains, tooth extraction, episiotomy (a surgical cut made just before delivery to enlarge vaginal opening), and dysmenorhea (painful menstrual periods).

What it does:

DICLOFENAC-K (diclofenac potassium), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals prostaglandins produced by your body which cause pain and swelling.

DICLOFENAC-K, as a nonsteroidal anti-inflammatory drug (NSAID) does NOT cure your illness or prevent it from getting worse. DICLOFENAC-K can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:

***DO NOT TAKE DICLOFENAC-K* if you have any of the following conditions:**

- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Bleeding in the brain or other bleeding disorders**
- **Current pregnancy (after 28 weeks of pregnancy)**
- **Currently breastfeeding (or planning to breastfeed)**
- **Allergy (hypersensitivity) to diclofenac potassium, or ASA (Acetylsalicylic Acid), or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs), or any of the nonmedicinal ingredients in DICLOFENAC-K**
- **Ulcer (active)**
- **Bleeding or perforation from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**

Patients who took a drug in the same class as DICLOFENAC-K after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

DICLOFENAC-K should NOT be used in patients under 16 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:

DICLOFENAC-K contains the active ingredient diclofenac potassium.

What the non-medicinal ingredients are:

Each DICLOFENAC-K tablet contains the following inactive ingredients: calcium phosphate, corn starch, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, sodium starch glycolate
The film coating contains: hydroxypropyl methylcellulose, maltodextrin, polydextrose, polyethylene glycol, synthetic red iron oxide, synthetic yellow iron oxide, titanium dioxide, triacetin.

What dosage forms it comes in:
DICLOFENAC-K 50 mg tablet: reddish brown, round, biconvex.

Check with your pharmacist if the identifying markings or colour appear different.

WARNINGS AND PRECAUTIONS

If you have, or previously had, any of the following conditions, see your health care provider to discuss treatment options other than DICLOFENAC-K .

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**
- **High blood pressure**
- **Diabetes**
- **High levels of fats in your blood**
- **Smoking**

It is important to take the lowest dose of DICLOFENAC-K that relieves your pain and/or swelling and for the shortest time possible in order to keep your risk of side effects on the heart and blood vessels as small as possible.

Use of NSAIDS, such as DICLOFENAC-K can result in increased blood pressure and /or worsening of congestive heart failure

Use of NSAIDs, such as DICLOFENAC-K may cause stomach and bowel problems (such as ulceration, perforation, obstruction and bleeding).

Before taking this medication, tell your health care provider if you have any of the following:

- Disease of the heart or blood vessels (also called cardiovascular disease, including uncontrolled high blood pressure, congestive heart failure, established ischemic heart disease, or peripheral arterial disease), as treatment with DICLOFENAC-K in these cases is not recommended.
- Risk factors for cardiovascular disease (see above) such as high blood pressure, abnormally high levels of fat (cholesterol, triglycerides) in your blood, diabetes, or if you smoke,
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- Any other medical problem such as alcohol abuse
- Any side effects from medicines for arthritis, rheumatism or sore joints that you have taken in the past
- A history of stomach upset
- Are on any special diet, such as a low-sodium diet

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

While taking this medication:

- Tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- Do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- Fertility may be decreased. The use of DICLOFENAC-K is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping DICLOFENAC-K should be considered.
- If you have cardiovascular disease or risks for cardiovascular disease, your doctor will periodically re-evaluate whether you should continue treatment with DICLOFENAC-K.
- Your doctor will monitor your kidney function, your liver function and your blood count to decide if DICLOFENAC-K needs to be discontinued.

If, at any time while taking DICLOFENAC-K you experience any signs or symptoms of problems with your heart or blood vessels such as chest pain, shortness of breath, weakness, or slurring of speech, contact your doctor immediately.

Long-term use of DICLOFENAC-K might increase the risk of heart attacks or strokes

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or

non-prescription) such as any of the following (NOT a complete list):

- Acetaminophen
- Acetylsalicylic Acid (ASA) or other NSAIDs e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Alcohol
- Antacids
- Anti-depressants
    - Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
    - ACE (angiotensin converting enzymes) inhibitors e.g. enalapril, lisinopril, perindopril, ramipril
    - ARBs (angiotensin II receptor blockers) e.g. candesartan, irbesartan, losartan, valsartan o Beta-blockers e.g. metoprolol
- Blood thinners (medicines used to prevent blood clotting) e.g. warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids) (medicines used to provide relief for inflamed areas of the body) e.g. prednisone
- Cyclosporine (a medicine primarily used in patients who have received organ transplants)
- Digoxin (a medicine used for heart problems)
- Diuretics (medicines used to increase the amount of urine) e.g. furosemide, hydrochlorothiazide
- Lithium
- Methotrexate (a medicine used to treat some kinds of cancer or arthritis)
- Oral hypoglycemics (diabetes medications such as metformin)
- Phenytoin (a medicine used to treat seizures)
- Probenecid
- Quinolone antibacterials (medicines used against infection)
- Rifampin (an antibiotic medicine used to treat bacterial infections)
- Sulfinpyrazone (a medicine used to treat gout)
- Tacrolimus (a medicine primarily used in patients who have received organ transplants)
- Trimethoprim (a medicine used to prevent or treat urinary tract infection)
- Voriconazole (a medicine used to treat fungal infections).

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking DICLOFENAC-K. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both DICLOFENAC-K and ASA than if you took DICLOFENAC-K alone.

PROPER USE OF THIS MEDICATION

Usual dose:

Medical Condition	Usual Dose	Maximum Dose (per day)	Maximum Duration of Treatment
Pain and Swelling	50 mg every 6-8 hours (if needed)	100 mg	One week
Painful menstrual cramps	First dose of 50 mg or (if needed) 100 mg followed by 50 mg every 6-8 hours after initial dose (if needed)	100 mg. First day may be increased to 200 mg	when required

Take DICLOFENAC-K as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much DICLOFENAC-K may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly and frail or if you have a low body weight,, have other diseases or take other medications.

If you are not getting adequate relief from your medication, speak to your doctor before you stop taking it.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

DICLOFENAC-K is NOT recommended for use in patients under 16 years of age since safety and effectiveness have NOT been established.

Take DICLOFENAC-K with a meal or food to reduce the possibility of stomach upset.

DICLOFENAC-K: DICLOFENAC-K are immediate release tablets. The tablets should be swallowed whole with water, and must not be divided or chewed.

Missed dose:

If you forget to take one or more doses of DICLOFENAC-K (diclofenac potassium), you should not increase the dose of DICLOFENAC-K to make up for the missed dose or doses, but you should continue taking your tablet at the next prescribed or regular time.

Overdose:

If you have accidentally taken more than the prescribed dose of DICLOFENAC-K **contact your doctor, pharmacist or poison control centre immediately or go to the hospital emergency unit at once.** You may require medical attention.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

DICLOFENAC-K may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

DICLOFENAC-K may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking DICLOFENAC-K, do NOT drive or operate machinery.

DICLOFENAC-K may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first sign of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM		
Symptom	**STOP taking DICLOFENAC-K and get emergency medical attention IMMEDIATELY**	**STOP taking DICLOFENAC-K and talk to your physician or pharmacist**
Bloody or black tarry stools, vomiting blood	√	
Spontaneous bleeding or bruising (signs of thrombo-cytopenia)	√	
Shortness of breath, wheezing, any trouble breathing or chest tightness	√	
Skin rash, hives, swelling or itching	√	
Skin rash with flacking or peeling (signs of dermatitis exfoliative).	√	
Purple skin patches (signs of purpura or Henoch-Schonlein purpura if caused by an allergy).	√	
Blurred vision, or any visual disturbance	√	
Any change in the amount or colour of your urine (red or brown)	√	
Any pain or difficulty experienced while urinating		√
Swelling of the feet, lower legs; weight gain		√

Swelling mainly of the face and throat (signs of angioedema)		√
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		√
Yellow discolouration of the skin or eyes (signs of liver failure), with or without itchy skin		√
Malaise, fatigue, loss of appetite or « flu-like » symptoms		√
Headaches, stiff neck, fever, nausea, vomiting (signs of aseptic meningitis)		√
Mental confusion, depression		√
Dizziness, lightheadedness		√
Hearing problems		√
Right upper abdominal discomfort or pain		√

This is NOT a complete list of side effects. If you develop any other symptoms while taking DICLOFENAC-K see your health care provider.

HOW TO STORE IT

Store between 15°C to 30°C.

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Sanis Health Inc., at:

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