PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-DICLO
Diclofenac Sodium Delayed-Release Tablets
Delayed-Release Tablets, 25 mg and 50 mg, for oral use
USP

PrAPO-DICLO SR
Diclofenac Sodium Slow-Release Tablets
Slow Release Tablets, 75 mg and 100 mg, for oral use
Apotex Standard

Non-Steroidal Anti-Inflammatory Drug (NSAID)

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX- Risk in Pregnancy	09/2022
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, *Pregnancy*	09/2022
7 WARNINGS AND PRECAUTIONS, Skin, *Serious skin reactions*	09/2022
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	09/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-DICLO (diclofenac sodium delayed-release tablets) and APO-DICLO SR (diclofenac sodium slow release tablets) are indicated for:

- the symptomatic treatment of rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

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.

APO-DICLO and APO-DICLO SR, particularly at higher doses, are 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 2 CONTRAINDICATIONS and 7 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Use of APO-DICLO or APO-DICLO SR 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

APO-DICLO and APO-DICLO SR, as NSAIDs, do NOT treat clinical disease or prevent its progression.

APO-DICLO and APO-DICLO SR, as NSAIDs, only relieve symptoms and decrease inflammation for as long as the patient continues to take them.

1.1 Pediatrics

Pediatrics (< 16 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. (see 2 CONTRAINDICATIONS).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and post-market experience

suggests that use in the geriatric population is associated with differences in safety (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

APO-DICLO and APO-DICLO SR are contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although APO-DICLO and APO-DICLO SR have 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 risks of premature closure of the ductus arteriosus, and prolonged parturition.
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants.
- severe uncontrolled heart failure.
- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 7 WARNINGS AND PRECAUTIONS —Sensitivity/Resistance - Anaphylactoid Reactions).
- active gastric/duodenal/peptic ulcer, active GI bleeding or perforation, regional ulcer, gastritis or ulcerative colitis (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE 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 7 WARNINGS AND PRECAUTIONS - Renal).
- known hyperkalemia (see 7 WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).
- children and adolescents less than 16 years of age.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

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 APO-DICLO or APO-DICLO SR 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 APO-DICLO or APO-DICLO SR only after careful consideration. See 7 WARNINGS AND PRECAUTIONS - Cardiovascular

Use of NSAIDs, such as APO-DICLO and APO-DICLO SR, 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 7 WARNINGS AND PRECAUTIONS - Renal - *Fluid and Electrolyte Balance*.

Risk of Gastrointestinal (GI) Adverse Events:
Use of NSAIDs, such as APO-DICLO and APO-DICLO SR, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding). See 7 WARNINGS AND PRECAUTIONS –Gastrointestinal (GI).

Risk in Pregnancy:

Caution should be exercised in prescribing APO-DICLO and APO-DICLO SR during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7.1.1 Pregnant Women). APO-DICLO and APO-DICLO SR are contraindicated for use during the third trimester because of risks of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (See 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use of APO-DICLO and APO-DICLO SR 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Cardiovascular disease or cardiovascular risk factors: Treatment with APO-DICLO or APO-DICLO SR 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 APO-DICLO or APO-DICLO SR only after careful consideration (see 3 SERIOUS WARNINGS AND PRECAUTIONS box).

4.2 Recommended Dose and Dosage Adjustment

APO-DICLO and APO-DICLO SR are to be used for maintenance therapy only.

APO-DICLO Tablets 25 mg and 50 mg (delayed-release)

Rheumatoid arthritis and osteoarthritis patients may use APO-DICLO (diclofenac sodium) delayed-release tablets if:

- They were previously initiated at the lowest dose of 75 mg (delayed-release) per day in 3 divided doses and required up-titration because they did not respond to that dose.
- The maximum recommended daily dose is 100 mg.

APO-DICLO should be taken with food and the tablets should be swallowed whole.

APO-DICLO SR 75 mg and 100 mg (slow-release tablets)

- Patients with rheumatoid arthritis or osteoarthritis on a maintenance dose of 75 mg diclofenac sodium per day may be changed to a once daily dose of APO-DICLO SR 75 mg administered morning or evening.
- Patients on a maintenance dose of 100 mg diclofenac sodium per day may be changed to a once daily dose of APO-DICLO SR 100 mg, administered morning or evening.
- The maximum recommended daily dose is 100 mg.

APO-DICLO SR tablets should be swallowed whole with liquid, preferably at mealtime.

Pediatrics (< 16 years of age): Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

Geriatrics (> 65 years of age): For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision Caution is indicated especially for frail elderly patients or those with a low body weight (see 7.1.4 Geriatrics).

Renal Impairment: APO-DICLO or APO-DICLO SR is contraindicated in patients with severe renal impairment or deteriorating renal disease (see 2 CONTRAINDICATIONS). Lower doses of APO-DICLO or APO-DICLO SR should be considered in patients with impaired renal function (see 7 WARNINGS AND PRECAUTIONS — Renal).

Hepatic Impairment: APO-DICLO or APO-DICLO SR is contraindicated in patients with severe hepatic impairment or active liver disease (see 2 CONTRAINDICATIONS). Lower doses of APO-DICLO or APO-DICLO SR should be considered in patients with impaired hepatic function (see 7 WARNINGS AND PRECAUTIONS — Hepatic/Biliary/Pancreatic).

4.4 Administration

APO-DICLO and APO-DICLO SR should be taken with food and the tablets should be swallowed whole.

4.5 Missed Dose

Patients who miss one or more doses of APO-DICLO (diclofenac sodium) 25 and 50 mg tablets or APO-DICLO SR 75 and 100 mg tablets should not increase the dose of APO-DICLO (diclofenac sodium) or APO-DICLO SR to compensate for the missed dose or doses, but should continue with their therapy as soon as possible.

5 OVERDOSAGE

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 APO-DICLO or APO-DICLO SR, 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 APO-DICLO or APO-DICLO SR, 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Oral	Delayed-Release Tablets, 25 mg, 50 mg	Colloidal silicon dioxide, dextrates, D&C yellow #10 aluminum lake 14-18% (25 mg tablet), FD & C yellow #6 aluminum lake, ferric oxide yellow, hydroxypropyl methylcellulose, methanol, magnesium stearate, methylcellulose, polyethylene glycol, polyvinylacetate phthalate, stearic acid, titanium dioxide and triethyl citrate.
	Slow Release Tablets, 75 mg, 100 mg	Carnauba wax, dextrates, ferric oxide red, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

Description

APO-DICLO (diclofenac sodium) Delayed-Release Tablets 25 mg: mustard yellow, round, biconvex, coated tablet, engraved '25' on one side, other side plain.

APO-DICLO (diclofenac sodium) Delayed-Release Tablets 50 mg: mocha-brown, round, biconvex, coated tablet, engraved '50' on one side, other side plain.

APO-DICLO SR (diclofenac sodium) Slow-Release Tablets 75 mg: light pink, triangular biconvex bevelled edge, film-coated tablets, engraved 'APO' over '75' on one side, other side plain.

APO-DICLO SR (diclofenac sodium) Slow-Release Tablets 100 mg: pink, round, biconvex bevelled edge, film-coated tablets, engraved 'APO' over '100' on one side, plain on other side.

APO-DICLO is available in bottles of 100 and 500 (50 mg) tablets.

APO-DICLO SR is available in bottles of 100, 250 (100 mg), 500 and 1000 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 sodium 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 9 DRUG INTERACTIONS – Drug/Drug Interactions - *Acetylsalicylic acid (ASA) or other NSAIDs*)**.**

Diclofenac sodium should not be used concomitantly with diclofenac potassium since both exist in plasma as the same active organic ion.

Carcinogenesis and Mutagenesis

(See 16 NON-CLINICAL TOXICOLOGY**)**

Cardiovascular

APO-DICLO and APO-DICLO SR are NSAIDs.
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 APO-DICLO and APO-DICLO SR, 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 APO-DICLO and APO-DICLO SR should hypertension either develop or worsen with its use.

Use of NSAIDs, such as APO-DICLO and APO-DICLO SR, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism (see 7 WARNINGS AND PRECAUTIONS - Renal - *Fluid and Electrolyte Balance*)**.**

Caution should be exercised in prescribing APO-DICLO and APO-DICLO SR 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 3 SERIOUS WARNINGS AND PRECAUTIONS box).

Driving and Operating Machinery

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

Endocrine and Metabolism

Corticosteroids: APO-DICLO and APO-DICLO SR are NOT a substitute for corticosteroids. They do 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 9 DRUG INTERACTIONS - Drug-Drug Interactions -*Glucocorticoids*).

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic/duodenal ulceration, inflammation, perforation, peritonitis, obstruction, gastrointestinal bleeding, gastrointestinal stenosis and ischemic colitis can occur at any time, with or without warning symptoms, in patients treated with APO-DICLO or APO-DICLO SR. 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 APO-DICLO or APO-DICLO SR, 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 7.1.4 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 APO-DICLO or APO-DICLO SR 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 to 6 months, and in about 2 to 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.

Diclofenac may be associated with increased risk of gastrointestinal anastomotic leak, serious outcomes of which have included multiple surgeries and death. Close medical surveillance and caution are recommended when using APO-DICLO or APO-DICLO SR after gastrointestinal surgery.

Caution should be taken if prescribing APO-DICLO or APO-DICLO SR 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, fluoxetine, 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 sodium slow release tablet or the delayed-release formulation of diclofenac sodium. Concurrent administration of histamine H_2-receptor antagonists and/or antacids with the delayed-release version of diclofenac sodium might result in altered absorption.

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 APO-DICLO or APO-DICLO SR 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 APO-DICLO or APO-DICLO SR 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 APO-DICLO or APO-DICLO SR 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 sodium (delayed-release tablets and slow release tablets) 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 9 DRUG INTERACTIONS - Drug-Drug Interactions - *Acetylsalicylic Acid (ASA) or other NSAIDs*).

Concomitant administration of APO-DICLO or APO-DICLO SR 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 APO-DICLO and APO-DICLO SR. 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 APO-DICLO and APO-DICLO SR, 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 APO-DICLO or APO-DICLO SR, 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 regularly monitor hepatic function in patients receiving APO-DICLO or APO-DICLO SR. If abnormal liver function 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.

APO-DICLO and APO-DICLO SR are 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 APO-DICLO or APO-DICLO SR in patients with hepatic porphyria, since APO-DICLO or APO-DICLO SR may trigger an attack.

Immune

APO-DICLO and APO-DICLO SR, 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.

Monitoring and Laboratory Tests

Cardiovascular (Hypertension): Blood pressure should be monitored regularly during therapy with APO-DICLO or APO-DICLO SR.

Hematologic: Patients on long-term treatment with APO-DICLO or APO-DICLO SR 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 APO-DICLO or APO-DICLO SR with warfarin requires close monitoring of the international normalized ratio (INR).

Hepatic: Hepatic function (e.g. serum transaminases, bilirubin) should be monitored regularly during therapy with APO-DICLO or APO-DICLO SR.

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

Pregnancy: If APO-DICLO or APO-DICLO SR are administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on APO-DICLO or APO-DICLO SR be closely monitored for amniotic fluid volume since APO-DICLO or APO-DICLO SR may result in reduction of amniotic fluid volume and even oligohydramnios (see 7.1 Special Populations). APO-DICLO or APO-DICLO SR are contraindicated for use in the third trimester of pregnancy.

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 APO-DICLO or APO-DICLO SR.

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.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, insomnia, depression, tinnitus or hearing loss with the use of NSAIDs, such as APO-DICLO and APO-DICLO SR. 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, APO-DICLO or APO-DICLO SR should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving APO-DICLO or APO-DICLO SR for an extended period of time.

Sun exposure in patients using APO-DICLO or APO-DICLO SR 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 **2 CONTRAINDICATIONS**)

Psychiatric

(See 7 **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 10 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 APO-DICLO or APO-DICLO SR, 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 7 WARNING AND PRECAUTIONS - Monitoring and Laboratory Tests - *Renal*).

Advanced Renal Disease: (see **2 CONTRAINDICATIONS**)

Fluid and Electrolyte Balance: Use of NSAIDs, such as APO-DICLO or APO-DICLO SR, can promote sodium retention in a dose-dependent 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 APO-DICLO or APO-DICLO SR in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular**).**

Use of NSAIDs, such as APO-DICLO or APO-DICLO SR, 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 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS – Drug-Drug Interactions).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAIDs 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.

Reproductive Health: Female and Male Potential

- Fertility

  The use of APO-DICLO or APO-DICLO SR, 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 APO-DICLO or APO-DICLO SR should be considered.

Sensitivity/Resistance

Anaphylactoid reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to APO-DICLO or APO-DICLO SR. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving APO-DICLO or APO-DICLO SR. APO-DICLO or APO-DICLO SR 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 2 CONTRAINDICATIONS).

ASA-intolerance: APO-DICLO or APO-DICLO SR 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 2 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 7 WARNINGS AND PRECAUTIONS - Skin)

Skin

Serious skin reactions: Use of some NSAIDs, such as APO-DICLO and APO-DICLO SR, have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS)
- toxic epidermal necrolysis (TEN)
- exfoliative dermatitis

- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

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

7.1 Special Populations

7.1.1 Pregnant Women

APO-DICLO or APO-DICLO SR are CONTRAINDICATED for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY). Caution is recommended in prescribing APO-DICLO or APO-DICLO SR during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

APO-DICLO or APO-DICLO SR should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

Published studies and postmarketing reports describe maternal NSAID (including diclofenac) use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if APO-DICLO or APO-DICLO SR treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-fetal 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 sodium readily crosses the placental barrier.

7.1.2 Breast-feeding

APO-DICLO or APO-DICLO SR is contraindicated in breast-feeding women. See 2 CONTRAINDICATIONS

7.1.3 Pediatrics

Pediatrics (< 16 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more 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, consideration 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Although not all adverse drug reactions have been reported with APO-DICLO or APO-DICLO SR, the types of adverse drug reactions are expected to be similar to those of diclofenac potassium 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 2 Most Common Adverse Drug Reactions (≥1%)

Gastrointestinal disorders	Very common	nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased 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 3 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), 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 (blurred vision, diplopia)
Ear and labyrinth disorders	Very rare	hearing impaired, tinnitus
Cardiac disorders	Uncommon	myocardial infarction, cardiac failure, palpitations, angina, arrhythmias, chest pain
Vascular disorders	Very rare	hypertension, vasculitis
Skin and subcutaneous disorders	Uncommon	urticaria
	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 (e.g., 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 disorders	Very rare	disorientation, depression, insomnia, nightmare,

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

8.2 Clinical Trial Adverse Reactions

The clinical trial data which the indications were originally approved is not available.

8.5 Post-Market Adverse 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 7 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 3 SERIOUS WARNINGS AND PRECAUTIONS box).

Gastrointestinal Disorders: Gastrointestinal stenosis, perforation which may lead to peritonitis, and ischemic colitis (which are sometimes fatal), anastomotic leak (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal (GI)).

***Immune/Hypersensitivity*:** Kounis syndrome, a serious allergic reaction that can cause myocardial infarction.

9 DRUG INTERACTIONS

9.2 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 sodium (delayed-release tablets or slow release tablets) 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 7 WARNINGS AND PRECAUTIONS - Renal – Fluid and Electrolyte Balance).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 Established Potential Drug-Drug Interactions

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
Acetaminophen	Controlled clinical studies	There may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs.	
Acetylsalicylic acid (ASA) or other NSAIDs	Controlled clinical studies	The use of diclofenac sodium (delayed-release tablets or slow release tablets) 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.	APO-DICLO and APO-DICLO SR should not be used concomitantly with diclofenac potassium since both exist in plasma as the same active organic ion. Concomitant administration of APO-DICLO and APO-DICLO SR 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,	

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
		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.	
Anticoagulants		Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding.	Concurrent therapy of APO-DICLO and APO-DICLO SR, with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. (See 7 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	Therefore the combination should be administered with caution, especially in the elderly (see 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests).

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
		be a substantial increase in blood pressure (see 7 WARNINGS AND PRECAUTIONS - Renal).	
Anti-platelet agents (including ASA)		There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as diclofenac sodium (delayed-release tablets and slow release tablets) (see 7 WARNINGS AND PRECAUTIONS — Hematologic – Anti-platelet Effects).	Concomitant administration of APO-DICLO and APO-DICLO SR with low dose ASA increases the risk of GI ulceration and associated complication.
Cyclosporine		Nephrotoxicity of cyclosporine may be increased because of the effect of NSAIDs on renal prostaglandins.	It should be given at doses lower than those that would be used in patients not receiving cyclosporine.
CYP2C9 inducers		Caution is recommended when co-prescribing APO-DICLO and APO-DICLO SR 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 APO-DICLO and APO-DICLO SR 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		APO-DICLO and APO-DICLO SR 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-	NSAIDs can reduce the effect of diuretics (see 7 WARNINGS AND	Concomitant treatment with

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
	marketing observations	PRECAUTIONS - Renal).	potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels (see 7 WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests – Renal).
Glucocorticoids		Some studies have shown that 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 APO-DICLO and APO-DICLO SR, are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing toxicity.	
Oral Contraceptives		No drug interaction data are available for diclofenac sodium (delayed-release tablets and slow release tablets) co-administered with oral contraceptives.	
Oral Hypoglycemics	Pharmacodyna-mic studies	Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac; however, there	Monitoring of the blood glucose level is recommended as a precautionary

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
		are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac, which necessitated changes in the dosage of hypoglycemic agents. There have also been reports of metabolic acidosis when diclofenac was co-administered with metformin, particularly in the context of renal impairment.	measure during concomitant therapy. Caution is recommended when co-prescribing APO-DICLO and APO-DICLO SR with metformin.
Phenytoin		An expected increase in exposure to phenytoin.	When using phenytoin concomitantly with APO-DICLO and APO-DICLO SR, monitoring of phenytoin plasma concentrations is recommended
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 probenecid 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 APO-DICLO and APO-DICLO SR, and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal (GI)).	

Diclofenac sodium (delayed-release tablets or slow release tablets)	Source of Evidence	Effect	Clinical comment
Sulfinpyrazone		Caution is recommended when co-prescribing APO-DICLO and APO-DICLO SR 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, it should be given at doses lower than those that would be used in patients not receiving tacrolimus.
Voriconazole		Caution is recommended when co-prescribing APO-DICLO and APO-DICLO SR 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID). The mode of action is not fully known but it does not act through the pituitary-adrenal axis. Diclofenac sodium inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. This inhibitory effect may partially explain its actions.

10.2 Pharmacodynamics

The effects of diclofenac sodium (delayed-release tablets or slow release tablets) 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.

10.3 Pharmacokinetics

Absorption

In humans, orally-administered diclofenac sodium is rapidly and almost completely absorbed and distributed to blood, liver, and kidneys. The plasma concentrations show a linear relationship to the amount of drug administered. No accumulation occurs provided the recommended dosage intervals are observed.

Enteric coating may delay the onset of absorption from 50 mg tablets. Absorption occurs more rapidly when the drug is administered on an empty stomach (T_{max} 2.5 hours), than with meals (T_{max} 6 hours). The bioavailability remains the same under both conditions. The mean peak plasma concentration of 1.5 mcg/mL (5 mcmol/L) is attained, on average, 2 hours after ingestion of one 50 mg delayed-release tablet.

Following administration of slow-release (SR) diclofenac sodium, C_{max} is reached at approximately 4 hours or later. Significant drug plasma concentrations persist when levels would have dropped almost to baseline values following delayed-release tablet administration. Mean plasma concentrations of 13 ng/mL (40 nmol/L) were produced 24 hours after diclofenac sodium slow-release (SR) 100 mg tablets, or 16 hours after diclofenac sodium slow-release (SR) 75 mg tablets (single dose). Trough levels are approximately 22 to 25 ng/mL (70 to 80 nmol/L) during treatment with diclofenac sodium slow-release (SR) 100 mg tablets once daily or diclofenac sodium slow-release (SR) 75 mg tablets twice daily. In pharmacokinetic studies no accumulation of diclofenac sodium was found following repeated once daily administration of diclofenac sodium slow-release (SR) 100 mg tablets or repeated twice daily administration of

diclofenac sodium slow-release (SR) 75 mg tablets.

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 2 CONTRAINDICATIONS).

Metabolism

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.

Elimination

Plasma clearance of diclofenac is 263 ± 56 mL/min. The mean terminal drug half-life in plasma is 1.8 hours after oral doses. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces. More than 90% of an oral dose is accounted for in elimination products within 72 hours. 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 APO-DICLO or APO-DICLO SR to patients with impaired kidney function (i.e. GFR < 60 mL/min or 1 mL/sec) (see 7 WARNINGS AND PRECAUTIONS - Renal). APO-DICLO or APO-DICLO SR are contraindicated in patients with severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min (0.5 mL/s) (see 2 CONTRAINDICATIONS**).**

Hepatic impairment: In a study of ten patients with impaired hepatic function (chronic hepatitis and non-decompensated cirrhosis) receiving a single oral dose of 100 mg diclofenac sodium,

the kinetics and metabolism of diclofenac, were the same as in patients without liver disease.

Pediatrics: APO-DICLO or APO-DICLO SR are contraindicated in children and adolescents less than 16 years of age (see 2 CONTRAINDICATIONS).

Geriatrics: The ability of elderly subjects to absorb, metabolize and excrete diclofenac sodium (delayed-release tablets or slow release tablets) does not appear to differ significantly from those of younger subjects.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C) and protect from high humidity.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable

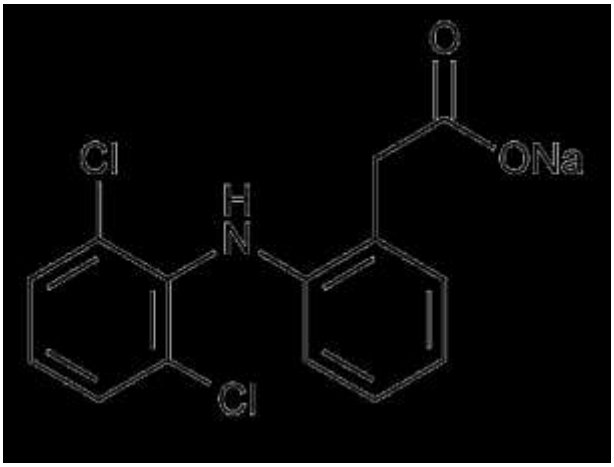
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Diclofenac sodium
Chemical name:	Sodium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate
Molecular formula and molecular mass:	$C_{14}H_{10}Cl_2NNaO_2$; 318.1 g/mol

Structural formula:



Physicochemical properties:	White or slightly yellowish, slightly hygroscopic crystalline powder.
Solubility:	Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96%), slightly soluble in acetone.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The clinical trial data on which the original indication was authorized is not available.

14.2 Study Results

Randomized clinical trials with diclofenac sodium (delayed-release tablets or slow release tablets) 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.

14.3 Comparative Bioavailability Studies

A bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single 50 mg oral dose of APO-DICLO (diclofenac sodium) 25 mg and VOLTAREN 25 mg enteric coated tablets was measured and compared. The results are summarized as follows:

Table 5: Comparative Bioavailability Data for Enteric Coated Tablets

	VOLTAREN 25 mg	**APO-DICLO 25 mg**	**% diffr.**
AUC_{0-12} (ng.hr/mL)	1357.87	1338.55	-1.4
C_{max} (ng/mL)	1220.29	1236.58	+1.3
T_{max} (hr)	1.16	1.34	+15.5
$t_{1/2}$ (hr)	1.1	1.0	-9.1

A randomized, double blinded, two-treatment, two-period, two-sequence, single oral dose (1 x 100 mg), crossover comparative bioavailability study of APO-DICLO SR slow release tablets 100 mg (Apotex Inc.) and VOLTAREN SR slow release tablets 100 mg (Ciba-Geigy), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 14 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diclofenac (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	2500 2584 (25)	2361 2435 (25)	105.9	96.1 – 116.6
AUC_I (ng.h/mL)	2561 2643 (24)	2417 2489 (25)	105.9	96.8 – 116.0
C_{max} (ng/mL)	529 558 (27)	537 585 (42)	98.4	80.6 – 120.2
T_{max}[3] (h)	3.50 (1.00-10.00)	4.00 (1.00-8.00)		
$T_{½}$[4] (h)	3.42 (46)	3.43 (41)		

[1] APO-DICLO SR (diclofenac sodium) slow-release tablets, 100 mg (Apotex Inc.)
[2] VOLTAREN SR (diclofenac sodium) slow-release tablets, 100 mg (Ciba-Geigy, Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

A randomized, double blinded, two-treatment, two-period, two-sequence, single oral dose (1 x 100 mg), crossover comparative bioavailability study of APO-DICLO SR slow release tablets 100 mg (Apotex Inc.) and VOLTAREN SR slow release tablets 100 mg (Ciba-Geigy), was conducted in healthy, adult male subjects under fed conditions. Comparative bioavailability data from 19 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Diclofenac (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	2704 2847 (36)	2561 2724 (36)	105.7	95.4 – 117.1
AUC_I (ng.h/mL)	2944 3094 (34)	3024 3142 (31)	100.8	92.9 – 109.4

Diclofenac (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
C_{max} (ng/mL)	351 379 (44)	381 457 (59)	92.6	72.1 – 118.9
T_{max}[3] (h)	6.00 (3.00-11.00)	7.00 (4.00-24.00)		
$T_{½}$[4] (h)	4.81 (66)	4.84 (55)		

[1] APO-DICLO SR (diclofenac sodium) slow-release tablets, 100 mg (Apotex Inc.)
[2] VOLTAREN SR (diclofenac sodium) slow-release tablets, 100 mg (Ciba-Geigy, Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

Enteric coated tablets

The therapeutic safety and efficacy of diclofenac sodium delayed-release tablets in arthritic conditions has been investigated in both short and long-term (three months) controlled clinical studies, followed by extended controlled and non-controlled studies. The majority of the comparative studies were double blind, within patient or between patient design, using placebo and indomethacin as controls. Acetylsalicylic acid (ASA), ibuprofen, phenylbutazone and acetaminophen were also used as comparative standards.

At time of approval, the safety and efficacy of diclofenac sodium delayed-release tablets for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis was demonstrated in short-term prospective comparative clinical trials conducted in 105 patients with osteoarthritis and 654 patients with rheumatoid arthritis. The controls used in these trials included: indomethacin, acetylsalicylic acid, acetaminophen and ibuprofen.

Several of the long-term double-blind, between patient studies comparing a three times daily dosing of diclofenac sodium delayed-release tablets to that of indomethacin were of three months duration. Patients received either drug at dosages ranging from 50 to 125 mg. In the treatment of patients with rheumatoid arthritis there was no clear difference between the treatment groups for therapeutic effect.

The safety and efficacy of diclofenac sodium delayed-release tablets compared to indomethacin for relief of the signs and symptoms of rheumatoid arthritis was also studied in longer-term studies of 6 to 30 months.

Slow release tablets

Bioavailability studies have demonstrated that the absorption of active drug from the diclofenac sodium slow release (SR) tablets is similar as that reported from the diclofenac sodium delayed-release tablets with the C_{max} being attained approximately four hours after the administration of a single 100 mg diclofenac sodium SR tablet. Repeated administration of the diclofenac sodium SR tablets for seven days or longer did not result in any accumulation of active drug and food intake did not alter absorption from the diclofenac sodium SR tablet.

A regimen of multiple doses of the 75 mg diclofenac sodium SR tablet (every 12 hours) provided an equivalent AUC_{0-24} to that of the 50 mg diclofenac sodium delayed-release tablet dosed every eight hours; an indication that the 75 mg diclofenac sodium SR tablet is an effective and desirable alternate to the 50 mg diclofenac sodium delayed-release tablet for the treatment of rheumatoid arthritis or osteoarthritis.

Safety and efficacy of diclofenac sodium SR 100 mg tablets were demonstrated in a randomized, double-blind, parallel, short-term (two weeks) clinical study when compared to diclofenac sodium delayed-release tablets and placebo in patients suffering from adult onset rheumatoid arthritis. A second comparative clinical trial was conducted in patients with established osteoarthritis of the hip and knee. No statistically significant differences were seen between the 2 diclofenac sodium regimens.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Diclofenac sodium is a phenyl-acetic acid derivative possessing anti-inflammatory activities as shown in various pharmacological models.

In vitro diclofenac sodium does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Anti-Inflammatory Activity in Rats

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

Preparation	Inhibition of edema induced by	
	Carrageenin (ED_{50} mg/kg) P.O.*	Kaolin (ED_{50} mg/kg) P.O.*
Diclofenac sodium	2.1	1.2

*determined by graphic interpolation from 3 or more doses.

Inhibition of Prostaglandin

A close correlation exists between certain febrile reactions and increased prostaglandin levels in the brain. Diclofenac (0.5 mcg/mL) reduces prostaglandin E_2 formation which parallels antipyresis but does not induce hypothermia in the afebrile animal. The inhibition of prostaglandin synthesis *in vitro* (IC_{50} mcM/L) is 1.6.

Platelet Adhesiveness

At 15 mcg/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, oral doses of 17 mg/kg diclofenac sodium caused a blood loss of 150 mcL in 72 hours, as measured by the administration of ^{51}Cr-labelled erythrocytes.

General Toxicology:

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/day 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 feed 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 ESR 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.

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.

Genotoxicity

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.

Reproductive and Developmental Toxicology

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 oral doses of *5* or 10 mg/animal/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 2 CONTRAINDICATIONS and 7.1 WARNINGS AND PRECAUTIONS – Special Populations).

17 SUPPORTING PRODUCT MONOGRAPHS

1. VOLTAREN® and VOLTAREN® SR (diclofenac sodium) Suppositories 50 mg and Slow-Release Tablets 100 mg, submission control number 260554, Product Monograph, Novartis Pharmaceuticals Canada Inc. JUN 08, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-DICLO
Diclofenac Sodium Delayed-Release Tablets

[Pr]APO-DICLO SR
Diclofenac Sodium Slow-Release Tablets

Read this carefully before you start taking **APO-DICLO** and **APO-DICLO SR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-DICLO** and **APO-DICLO SR**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- APO-DICLO and APO-DICLO SR can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take APO-DICLO or APO-DICLO SR for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or had heart problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- APO-DICLO and APO-DICLO SR, can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage pain.

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

Pregnancy:

- **DO NOT** take APO-DICLO or APO-DICLO SR if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) only take APO-DICLO or APO-DICLO SR if you are told to do so by your doctor.
- Medicines like APO-DICLO or APO-DICLO SR may cause harm to you and your baby. Your doctor will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe APO-DICLO or APO-DICLO SR during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment APO-DICLO or APO-DICLO SR.

What is APO-DICLO and APO-DICLO SR used for?

- to treat patients 16 years and older with symptoms of arthritis disorders such as:
  - Osteoarthritis, including osteoarthritis of the hip
  - Rheumatoid arthritis

How does APO-DICLO and APO-DICLO SR work?

- APO-DICLO and APO-DICLO SR (diclofenac sodium) belong to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). They can reduce the chemicals produced by your body which cause pain and swelling.

- APO-DICLO or APO-DICLO SR only treats the symptoms and relieves pain as long as you take it. APO-DICLO and APO-DICLO SR do NOT cure your illness or stop it from getting worse.

What are the ingredients in APO-DICLO and APO-DICLO SR?

Medicinal ingredient: Diclofenac sodium
Non-medicinal ingredients:

- APO-DICLO: Colloidal silicon dioxide, dextrates, D&C yellow #10 aluminum lake 14-18% (25 mg tablet) FD & C yellow #6 aluminum lake, ferric oxide yellow, hydroxypropyl methylcellulose, methanol, magnesium stearate, methylcellulose, polyethylene glycol, polyvinylacetate phthalate, stearic acid, titanium dioxide and triethyl citrate.
- APO-DICLO SR: Carnauba wax, dextrates, ferric oxide red, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

APO-DICLO and APO-DICLO SR comes in the following dosage forms:

APO-DICLO: Delayed-release tablets, 25 mg and 50 mg.

APO-DICLO SR: Slow release tablets, 75 mg and 100 mg.

Do not use APO-DICLO and APO-DICLO SR if you:

- Are planning to have or have recently had heart bypass surgery.
- Have severe, uncontrolled heart failure.
- Have bleeding in the brain or other bleeding disorders.
- Are pregnant and in a later stage of pregnancy (from 28 weeks or later).
- Are breastfeeding (or planning to breastfeed).
- Are allergic to diclofenac sodium or any of the ingredients in this medicine or the container.
- Have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.

- Have active stomach or intestine ulcers.
- Have active bleeding from the stomach or gut.
- Have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- Have liver disease (active or severe).
- Have kidney disease (severe or worsening).
- Have high potassium in the blood.
- Are under 16 years of age.

To help avoid side effects and ensure proper use, talk to your health professional before you take APO-DICLO and APO-DICLO SR. Talk about any health conditions or problems you may have, including if you:

- Have high blood pressure, high cholesterol or diabetes
- Have or had heart attacks, chest pain, heart disease, stroke or heart failure
- Have poor blood flow to your extremities (like your hands and feet)
- Smoke or used to smoke
- Drink a lot of alcohol
- Have a stomach infection
- Have recently had stomach or intestine tract surgery
- Have liver or kidney disease, urine problems or are dehydrated
- Have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- Previous bleeding in the brain
- Have other bleeding or blood problems
- Have asthma or other lung problems
- Have immune system problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA) or other NSAIDs
- Are on a low-salt diet
- Are pregnant, planning on becoming or become pregnant while taking APO-DICLO or APO-DICLO SR

Other Warnings:
Serious Side Effects: APO-DICLO and APO-DICLO SR can cause serious side effects, including:

- **Blood and bleeding problems:**
  - APO-DICLO and APO-DICLO SR can cause blood problems, bleeding and prolonged bleeding.
  - Taking APO-DICLO and APO-DICLO SR with the following drugs can increase the risk of bleeding:
    - anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory) or antidepressants like selective serotonin reuptake inhibitors (SSRIs).
- **Serious skin reactions:** In rare cases, serious, life-threatening allergic and skin reactions

have been reported with some NSAIDs, such as APO-DICLO and APO-DICLO SR. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

APO-DICLO and APO-DICLO SR might cause you to become more sensitive to sunlight or UV light. 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 or UV light, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with APO-DICLO and APO-DICLO SR to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. APO-DICLO and APO-DICLO SR can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and Using Machines: APO-DICLO and APO-DICLO SR may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking APO-DICLO and APO-DICLO SR, do NOT drive or operate machinery.

Fertility in Women: APO-DICLO and APO-DICLO SR may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking APO-DICLO and APO-DICLO SR. Talk to your healthcare professional if you have questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of APO-DICLO and APO-DICLO SR. They will monitor your health during and after treatment.

Tell your health professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-DICLO and APO-DICLO SR:

- Acetaminophen, used to treat fever and pain
- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation, like:
  - e.g. ASA, celecoxib, diclofenac, diclofenac potassium, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Alcohol
- Antacids, used to treat symptoms of excess stomach acid
- Blood pressure medications like enalapril, lisinopril, perindopril, Ramipril, candesartan,

irbesartan, losartan, valsartan, metoprolol
- Corticosteroids (including glucocorticoids, such as prednisone, used as an anti-inflammatory
- Digoxin, used to treat heart disorders
- Phenytoin, used to treat seizures
- Trimethoprim, used to treat urinary tract infections
- Voriconazole, used to treat fungal infections
- Lithium, used as a mood stabilizer
- Medicines used as blood thinners or to prevent blood clots, like warfarin, ASA, clopidogrel
- Medicines used to lower the risk of organ rejection, like tacrolimus and cyclosporine
- Medicines used to treat bacteria infections (antibiotics) like rifampin, quinolone
- Medicines used to treat gout like sulfinpyrazone, probenecid
- Medicines used to lower extra fluid levels (diuretics) like furosemide, hydrochlorothiazide
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline
- Methotrexate, used to treat some kinds of cancer
- Medicines used to treat diabetes, like metformin or other oral hypoglycemics

How to take APO-DICLO or APO-DICLO SR:
APO-DICLO and APO-DICLO SR:
- Take APO-DICLO or APO-DICLO SR as directed by your healthcare professional. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- **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.**
- It is best to take your dose at the same time each day.
- Take APO-DICLO or APO-DICLO SR tablets with food.
- You should remain standing or sitting upright (do not lie down) for about 15 to 30 minutes after taking the APO-DICLO or APO-DICLO SR.
- If you will be using APO-DICLO or APO-DICLO SR for more than 7 days, see your health care provider regularly. They will check if it is working for you and if it is causing you any unwanted effects.

Swallow tablet whole with water at mealtime. Do NOT chew or divide the tablet.

Usual dose:
APO-DICLO and APO-DICLO SR:

Patients 16 years of age and older:
- Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may lower your dose, stop your treatment for a period of

time or recommend that you stop treatment completely. This may happen if you:

- experience serious side effects, or
- your disease gets worse.

Overdose

If you think you, or a person you are caring for, have taken too much APO-DICLO or APO-DICLO SR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of APO-DICLO and APO-DICLO SR, take the dose as soon as possible.
- Do not take a bigger dose to make up for the missed dose.

What are possible side effects from using APO-DICLO and APO-DICLO SR?

These are not all the possible side effects you may have when taking APO-DICLO or APO-DICLO SR. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Headache, dizziness, light-headedness
- Feeling of burning/prickliness/numbing
- Confusion, hard to concentrate or think, short-term memory loss, nervousness
- Bruises
- Skin rash, itchy skin
- Taste disorder, thirst, dry mouth
- Muscle pain
- Mouth sores
- Hair loss
- Increased sweating
- Problems with your period (women)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
inflamed tongue, rectal itching or bleeding			
Vertigo (a sense of severe spinning dizziness, light headedness)		✓	
UNCOMMON			
Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock, chills, fever, muscle aches or pains, or other flu-like symptoms, low blood pressure			✓
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		✓	
Liver problems (including hepatitis, liver failure): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
unusual dark urine, unusual tiredness			
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, feeling faint and possible irregular heartbeat			✓
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			✓
RARE			
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin			✓
VERY RARE			
Abnormal thoughts and behaviour, including depression: irritability, difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide, disorientated		✓	
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): Headaches, stiff neck, nausea and vomiting, fever or clouding of		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
consciousness			
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

APO-DICLO and APO-DICLO SR: Store at room temperature between (15°C to 30°C) and protect from high humidity.

Do NOT keep expired medicine or medicine no longer needed. Return to your healthcare professional.

Keep out of reach and sight of children.

If you want more information about APO-DICLO or APO-DICLO SR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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