PRODUCT MONOGRAPH

PrNTP-DICLOFENAC SODIUM
PrNTP-DICLOFENAC SODIUM SR

(Diclofenac Sodium)

50 mg Enteric Coated Tablets
75 mg Slow Release Tablets

Non steroidal Anti-Inflammatory Drug (NSAID)

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(diclofenac sodium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Enteric Coated Tablets, 50 mg Slow Release Tablets, 75 mg	lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NTP-DICLOFENAC SODIUM (diclofenac sodium) and NTP-DICLOFENAC SODIUM SR (diclofenac sodium) are indicated for the following:

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

Throughout this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR, as NSAIDs, do NOT treat clinical disease or prevent its progression.

NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR, as NSAIDs, only relieves symptoms and decreases inflammation for as long as the patients continue to take it.

Patient Subsets

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

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

CONTRAINDICATIONS

NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR are contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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 risk 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
- known hypersensitivity to NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR or to any of the components/excipients
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS** – ***Hypersensitivity Reactions - Anaphylactoid Reactions***)
- active gastric / duodenal / peptic ulcer, active GI bleeding or perforation, regional ulcer, gastritis or ulcerative colitis
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease
- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS** -***Renal***)
- known hyperkalemia (see **WARNINGS AND PRECAUTIONS** -***Renal*** -***Fluid and Electrolyte Balance***)
- children and adolescents less than 16 years of age

- suppositories are contraindicated in patients with inflammatory lesions of the rectum or anus and in patients with a recent history of rectal or anal bleeding.

WARNINGS AND PRECAUTIONS

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

NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR are non-steroidal anti-inflammatory drugs (NSAIDs). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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 also WARNINGS AND PRECAUTIONS -*Renal - Fluid and Electrolyte Balance*).

Randomized clinical trials with diclofenac sodium have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR.

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

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

***General*:**

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an**

adverse event, the lowest effective dose should be used for the shortest possible duration. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

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

Diclofenac sodium should not be used concomitantly with diclofenac potassium (e.g. NTP-DICLOFENAC SODIUM-K) since both exist in plasma as the same active organic ion.

***Carcinogenesis and Mutagenesis*:**
(See **TOXICOLOGY**)

***Cardiovascular*:**
NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR are non-steroidal anti-inflammatory drugs (NSAIDs). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. Large population-based observational studies, meta-analyses and systematic reviews suggest an increased risk of myocardial infarction and stroke also in association with the use of diclofenac. 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.

Caution should be exercised in prescribing NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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 I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

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

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

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs 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.**

***Endocrine and Metabolism*:**
Corticosteroids: NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR (diclofenac sodium) 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 **DRUG INTERACTIONS – Drug-Drug Interactions *Glucocorticoids***).

Gastrointestinal (GI)
Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 **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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even a short-term therapy has its risks.

Caution should be taken if prescribing NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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, fluotexine, paroxetine, sertraline)

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent or reduce the occurrence of gastrointestinal adverse events associated with the use of NTP-DICLOFENAC SODIUM SR or the enteric-coated or suppository formulation of NTP-DICLOFENAC SODIUM. Concurrent administration of histamine H2-receptor antagonists and/or antacids with the enteric-coated version of NTP-DICLOFENAC SODIUM might results 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs

and anticoagulants increases the risk of bleeding. Concurrent therapy of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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.

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

Concomitant administration of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction, while on therapy with NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them

with fatal outcomes, have been reported with diclofenac.

Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Caution is advised when using NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR in patients with hepatic porphyria, since diclofenac sodium may trigger an attack.

Hypersensitivity Reactions
Anaphylactoid reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to diclofenac sodium. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving diclofenac sodium. NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 **CONTRAINDICATIONS**).

***ASA-intolerance*:** NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 **CONTRAINDICATIONS**).

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

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

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

Infection
NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM 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.

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

Sun exposure in patients using NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 **CONTRAINDICATIONS -**Coronary Artery Bypass Graft Surgery)

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

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

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

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR).

In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR< 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 **WARNING AND PRECAUTIONS-Monitoring and Laboratory Tests -*Renal***)

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

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

Use of NSAIDs, such as NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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, cyclosporin, or some diuretics. Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

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.

Sexual Function / Reproduction

The use of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR should be considered.

Skin

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

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

Special Populations

Pregnant Women: **NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see TOXICOLOGY)**.

Caution should be exercised in prescribing NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR during the first and second trimesters of pregnancy (see TOXICOLOGY).

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

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

Diclofenac sodium readily crosses the placental barrier.

Nursing Women:
(See **CONTRAINDICATIONS**)

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

Geriatrics: Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are 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.

Monitoring and Laboratory Tests

Cardiovascular *(Hypertension)****:*** Blood pressure should be monitored regularly during therapy with NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR.

Hematologic: Patients on long-term treatment with NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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.

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

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

Renal: Patients with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors,

angiotensin-II receptor blockers, cyclosporin, diuretics, and the elderly should have their renal function monitored (e.g. urine output, serum creatinine, creatinine clearance and serum urea) during therapy with NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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, cyclosporin, or some diuretics.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Although not all adverse drug reactions have been reported with diclofenac sodium, 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 1: Most Common Adverse Drug Reactions (≥ 1%)

Gastrointestinal disorders	Very common	nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia
Nervous System	Common	dizziness, headache, vertigo
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

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

Gastrointestinal disorders	Uncommon	gastritis, gastrointestinal hemorrhage, hemorrhagic diarrhea, melena, hematemesis, gastric and intestinal ulcerations (with or without bleeding or perforation).
	Very rare	lower gut disorders (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), diaphragm-like intestinal strictures, hyperacidity, stomatitis, glossitis, coated tongue, esophageal lesions, constipation, pancreatitis
Nervous System	Uncommon	drowsiness, malaise, impaired concentration, tiredness.
	Very rare	sensory disturbances including paresthesia, memory disturbance, convulsions, anxiety, tremor, aseptic meningitis, cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage)
Special senses	Very rare	vision disturbances (blurred vision, diplopia), impaired hearing, tinnitus, taste alteration disorders.
Cardiac disorders	Uncommon	palpitation, angina, arrhythmias
	Very Rare	exacerbation of cardiac failure, hypertension, myocardial infarction
Skin and subcutaneous disorders	Uncommon	urticaria
	Very rare	bullous eruption, erythema, eczema, erythema multiforme, Stevens-Johnson Syndrome, Lyell Syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura, allergic purpura
Renal and urinary disorders	Uncommon	edema (facial, general, peripheral)
	Very rare	acute renal failure, nephrotic syndrome, urinary abnormalities (eg. hematuria and proteinuria), interstitial 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, jaundice
	Very rare	fulminant hepatitis
Immune system disorders	Uncommon	hypersensitivity, anaphylactic / anaphylactoid systemic reactions (including hypotension and shock)
	Very rare	angioneurotic edema, (including face edema)
Psychiatric disorders	Very rare	disorientation, depression, insomnia, nightmare, irritability, psychotic disorder
Respiratory disorders	Uncommon	asthma
	Very rare	pneumonitis
Other		administration of the suppositories may occasionally give rise to local irritation, proctitis, rarely local bleeding and exacerbation of hemorrhoids.

Post-Market Adverse Drug Reactions

Hepatic: hepatic necrosis, hepatic failure

DRUG INTERACTIONS

Drug-Drug Interactions

Table 3: Established Potential Drug-Drug Interactions

NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR	Clinical comment
Acetaminophen	There may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs.
Acetylsalicylic acid (ASA) or other NSAIDs	The use of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR 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, possible by competing with ASA for access to the active site of cyclooxygenase-1. **Diclofenac sodium should not be used concomitantly with diclofenac potassium (e.g. NTP-DICLOFENAC SODIUM-K) since both exist in plasma as the same active organic ion.** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.
Alcohol	There may be an increased risk of gastrointestinal side effects, including ulceration or hemorrhage, when administered concomitantly with NSAIDs.
Antacids	Concomitant administration of antacids with NSAIDs may affect the rate, but generally not the extent of the absorption of the NSAID
Anticoagulants	(See **WARNINGS AND PRECAUTIONS – *Hematologic - Anticoagulants***)
Anti-hypertensives	NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. Combinations of ACE inhibitors, angiotensin-II antagonists or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure (see **WARNINGS AND PRECAUTIONS – Renal**). Therefore the combination should be administered with caution and patients, especially the elderly (see **WARNINGS AND PRECAUTIONS Monitoring and Laboratory Tests**).
Anti-platelet agents (including ASA)	There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR (see **WARNINGS AND PRECAUTIONS – *Hematologic - Anti-platelet Effects***).
Cyclosporin or Tacrolimus	Nephrotoxicity of cyclosporin and 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 cyclosporin or tacrolimus.
Digoxin	Diclofenac may increase the plasma concentration of digoxin. Dosage adjustment may be required. Monitoring of serum digoxin level is recommended.
Diuretics	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics (see **WARNINGS AND PRECAUTIONS – *Renal)***.

	Class Statement Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels. (see **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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR, are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing toxicity.
Oral hypoglycemics	Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac; however, there are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac, which necessitated changes in the dosage of hypoglycemic agents. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.
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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR, and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS – *Gastrointestinal (GI***)).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

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

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

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Geriatrics*:** 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 (see **WARNINGS AND PRECAUTIONS – Special Populations - *Geriatrics)

Renal Insufficiency: Lower doses of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR should be considered in patients with impaired renal function (see **WARNINGS AND PRECAUTIONS– Renal**).

Hepatic Impairment: Lower doses of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR should be considered in patients with impaired hepatic function (see **WARNINGS AND PRECAUTIONS – *Hepatic/Biliary/Pancreatic***).

Recommended Dose and Dose Adjustment

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

NTP-DICLOFENAC SODIUM Tablets 50 mg (enteric-coated)

In the symptomatic treatment of rheumatoid arthritis, the recommended starting dose of NTP-DICLOFENA SODIUM (diclofenac sodium) is 25 to 50 mg three times daily depending on the severity of the condition. For maintenance, the dose should be reduced to the minimum amount that will provide continuous control of symptoms, usually 25 mg taken three or four times daily. In osteoarthritis, the recommended starting dose and maintenance dose is usually 25 mg three times daily, however, this dose should be adjusted individually to the minimum dose which will provide control of symptoms.

NTP-DICLOFENAC SODIUM 50 mg enteric-coated tablets are to be used for maintenance therapy only.

Rheumatoid arthritis and osteoarthritis patients may use **NTP-DICLOFENAC SODIUM** (diclofenac sodium) 50 mg enteric-coated tablets if:

- They were previously initiated at the lowest dose of 75 mg (enteric-coated) 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.
- For patients experiencing an inflammatory flare, who do not achieve control of symptoms with 100 mg of diclofenac, the dosage may be increased to a maximum of 150 mg per day in divided doses (50 mg TID), for the shortest possible duration and under close monitoring (See WARNINGS and PRECAUTIONS – Cardiovascular).

  In elderly patients, and patients with renal insufficiency, hepatic impairment or with a cardiovascular risk, the maximum daily dose should not exceed 100 mg of diclofenac (see Dosing Considerations).

NTP-DICLOFENAC SODIUM should be taken with food and the tablets should be swallowed whole.

NTP-DICLOFENAC SODIUM SR 75 mg (slow-release tablets)
NTP-DICLOFENAC SODIUM SR 75 mg tablets are to be used for maintenance therapy only.

- 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 **NTP-DICLOFENAC SODIUM SR** 75 mg slow release tablet administered morning or evening.

- The maximum recommended daily dose is 100 mg.

- For patients experiencing an inflammatory flare, who do not achieve control of symptoms with 100 mg of diclofenac, the dosage may be increased to a maximum of 150 mg per day in divided doses (75 mg administered morning and evening), for the shortest possible duration and under close monitoring (See WARNINGS and PRECAUTIONS – Cardiovascular). In elderly patients, and patients with renal insufficiency, hepatic impairment or with a cardiovascular risk, the maximum daily dose should not exceed 100 mg of diclofenac (see Dosing Considerations).

NTP-DICLOFENAC SODIUM SR tablets should be swallowed whole with liquid, preferably at mealtime.

Missed Dose

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

OVERDOSAGE

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

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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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 NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM 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.

ACTION AND CLINICAL PHARMACOLOGY

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.

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

Pharmacokinetics

Absorption: In humans, 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 µg/mL (5 µmol/L) is attained, on average, 2 hours after ingestion of one 50 mg enteric-coated 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 enteric-coated tablet administration. Mean plasma concentrations of 13 ng/mL (40 nmol/L) were produced 24 hours after diclofenac sodium 100 mg slow release tablets, or 16 hours after diclofenac sodium 75 mg slow release tablets (single dose). Trough levels are approximately 22-25 ng/mL (70-80 nmol/L) during treatment with diclofenac sodium 100 mg slow release tablets once daily or diclofenac sodium 75 mg slow release tablets twice daily. In pharmacokinetic studies no accumulation of diclofenac sodium was found following repeated once daily administration of diclofenac sodium 100 mg slow release tablets or repeated twice daily administration of diclofenac sodium 75 mg slow release tablets.

Suppositories have a more rapid onset, but slower rate of absorption than oral enteric-coated tablets. C_{max} is approximately 2/3 of that produced by an equivalent 50 mg enteric-coated tablet oral dose. T_{max} occurs within 1 hour. The unchanged diclofenac plasma AUC values for rectal administration are within the range of values produced by equivalent oral enteric-coated tablet doses. Since about half the active substance is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half as large as it is following a parenteral dose of equal size.

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.

***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.

Excretion: 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 diclofenac sodium to patients with impaired kidney function (ie GFR < 60 mL/min or 1 mL/sec) (see WARNINGS AND PRECAUTIONS - *Renal*). NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR are contraindicated in patients with severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min (0.5 mL/s) (see **CONTRAINDICATIONS**).

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

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

Geriatrics: The ability of elderly subjects to absorb, metabolize and excrete diclofenac sodium does not appear to differ significantly from those of younger subjects.

STORAGE AND STABILITY

Store between 15°-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NTP-DICLOFENAC SODIUM (diclofenac sodium) is available as 50 mg (light brown) round enteric-coated tablets. Supplied in bottles of 100.

NTP-DICLOFENAC SODIUM SR is available as 75 mg white round biconvex bevel-edge, film-coated slow release tablets printed with black ink SR 75 'novo' on one side and on the reverse containing 75 mg of diclofenac sodium. Supplied in bottles of 100.

NTP-DICLOFENAC SODIUM (diclofenac sodium) 50 mg enteric coated tablets:
Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, silicon dioxide, sodium lauryl sulfate and sodium starch glycolate.
The film coating contains: D&C Yellow # 10, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, maltodextrin, methacrylic acid, polyethylene glycol, talc, titanium dioxide, triethyl citrate

NTP-DICLOFENAC SODIUM SR (diclofenac sodium) 75 mg slow release tablets:
Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate and povidone.
The film coating contains: aquacoat ECD-30, cetyl alcohol, dibutyl sebacate, FD&C Blue #2, FD&C Red #6, FD&C Yellow #40, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

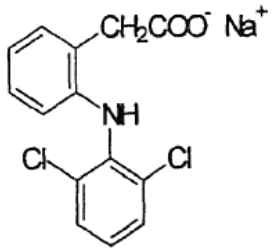
Common name: Diclofenac sodium

Chemical name: Sodium-[o-[2,6-dichloroanilino)phenyl]acetate.

Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$

Molecular mass: 318.13

Structural formula:



Physicochemical properties: Diclofenac sodium is a white to off-white powder with salty bitter taste. At 25°C, diclofenac sodium is 2% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions.

CLINICAL TRIALS

A comparative bioavailability study was performed on three diclofenac sodium enteric coated tablet products, NTP-DICLOFENAC 25 mg tablets, NTP-DICLOFENAC 50 mg tablets and Voltaren® 50 mg tablets. Eighteen volunteers completed the randomized, three-way crossover study. The pharmacokinetic plasma data (mean ± standard deviation) calculated for the NTP-DICLOFENAC and Voltaren® Tablet formulations is tabulated below:

Pharmacokinetic Indices for Diclofenac Sodium

	NTP-DICLOFENAC SODIUM 2 x 25 mg	NTP-DICLOFENAC SODIUM 1 x 50 mg	Voltaren® 1 x 50 mg
Area Under the Curve: (ng•hours/mL); 0-24 hours	1277.45 ± 316.70	1251.16 ± 287.46	1348.41 ± 327.13
Peak Concentration: C_{max} (ng/mL)	1151.88 ± 362.55	1185.77 ± 328.32	1308.69 ± 394.63
Time of Peak Level: T_{max} (hours)	2.03 ± 0.83	1.78 ± 0.75	2.64 ± 1.29
Elimination Half-Life: $t_{1/2}$ (hours)	0.70 ± 0.20	0.66 ± 0.16	0.69 ± 0.21
Elimination Rate Constant: Kel ($hour^{-1}$)	1.06 ± 0.28	1.11 ± 0.25	1.08 ± 0.28

Statistical evaluation by analysis of variance (ANOVA) of 0-24 hour AUC, C_{max}, t-1/2 and Kel showed no significant differences among the three formulations. The T_{max} values for both NTP-DICLOFENAC SODIUM formulations were significantly shorter than the T_{max} for Voltaren®. Therefore, the maximum plasma diclofenac concentration occurred sooner for both NTP-DICLOFENAC SODIUM formulations relative to Voltaren®.

A comparative bioavailability study was performed on two 100 mg diclofenac sodium slow release products under fed conditions. The pharmacokinetic plasma data calculated for the NTP-DICLOFENAC SODIUM SR and VOLTAREN® SR tablet formulations is tabulated below:

Pharmacokinetic Indices for Diclofenac Sodium

Geometric mean Arithmetic mean (C.V.)			
	NTP-DICLOFENAC SODIUM SR (1 x 100 mg)	VOLTAREN®SR (1 x 100 mg)	Percentage of VOLTAREN®SR
AUC_T (ng•h/mL)	2416 2531 (35)	2566 2924 (75)	94
AUC_I (ng•h/mL)	2322 2362 (19)	2465 2523 (24)	94
C_{max} (ng/mL)	692 763 (42)	614 761 (64)	113

T_{max}* (h)	7.56 (4.93)	8.37 (6.18)	—
T1/2* (h)	2.08 (1.54)	2.25 (1.32)	—

*For the T_{max} and T1/2 parameters these are the arithmetic means (standard deviation).

A comparative bioavailability study was performed on two 100 mg diclofenac sodium slow release products under fasting state in normal, healthy, male volunteers. The pharmacokinetic plasma data calculated for the NTP-DICLOFENAC SODIUM SR and VOLTAREN® SR tablet formulations is tabulated below:

Pharmacokinetic Indices for Diclofenac Sodium

Geometric mean Arithmetic mean (C.V.)			
	NTP-DICLOFENAC SODIUM SR (1 x 100 mg)	VOLTAREN®SR (1 x 100 mg)	Percentage of VOLTAREN®SR
AUC_T (ng•h/mL)	1998 2066 (23)	2122 2155 (19)	94
AUC_I (ng•h/mL)	2143 2179 (19)	2276 2322 (18)	94
C_{max} (ng/mL)	513 606 (63)	464 535 (52)	110
T_{max}* (h)	5.17 (2.3)	4.83 (2.24)	—
T1/2* (h)	4.23 (7.45)	5.40 (4.71)	—

*For the T_{max} and T1/2 parameters these are the arithmetic means (standard deviation).

A comparative bioavailability study was performed on two 100 mg diclofenac sodium suppository products, NTP-DICLOFENAC SODIUM 100 mg suppositories and VOLTAREN® 100 mg suppositories. The pharmacokinetic plasma data calculated for the NTP-DICLOFENAC SODIUM suppository and VOLTAREN® suppository formulations is tabulated below:

Pharmacokinetic Indices for Diclofenac Sodium

Geometric mean Arithmetic mean (C.V.)			
	NTP-DICLOFENAC SODIUM (100 mg Suppository)	VOLTAREN® (100 mg Suppository)	Percentage of VOLTAREN®
AUC_T (ng•h/mL)	2864 2996 (31)	2807 2887 (26)	102
AUC_I (ng•h/mL)	2922 3033 (31)	2836 2928 (26)	103
C_{max} (ng/mL)	1652 1751 (36)	1863 1928 (30)	89
T_{max}* (h)	0.98 (0.45)	0.69 (0.19)	—
T1/2*	1.39 (0.64)	1.72 (1.61)	—

(h)			

*For the T_{max} and T1/2 parameters these are the arithmetic means (standard deviation).

Randomized clinical trials with diclofenac sodium 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.

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.

Enteric coated tablets

The therapeutic safety and efficacy of diclofenac sodium 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 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 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 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 tablets is similar as that reported from the diclofenac sodium enteric coated tablets with the Cmax being attained approximately four hours

after the administration of a single 100 mg diclofenac sodium slow release tablet. Repeated administration of the diclofenac sodium slow release 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 slow release tablet.

A regimen of multiple doses of the 75 mg diclofenac sodium slow release tablet (every 12 hours) provided an equivalent AUC0-24 to that of the 50 mg diclofenac sodium enteric coated tablet dosed every eight hours; an indication that the 75 mg diclofenac sodium slow release tablet is an effective and desirable alternate to the 50 mg diclofenac sodium enteric coated tablet for the treatment of rheumatoid arthritis or osteoarthritis.

Safety and efficacy of diclofenac sodium 100 mg slow release tablets were demonstrated in a randomized, double-blind, parallel, short-term (two weeks) clinical study when compared to diclofenac sodium enteric coated 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.

Suppositories

The compilation of data to compare the bioavailabilty of diclofenac sodium from various dosage forms (enteric coated tablets and suppositories) has shown that the time to Cmax following the administration of the suppository was slightly shorter (0.5 to 2 hours) than that observed for the diclofenac sodium enteric coated tablet (1 to 3 hours) and that the AUC(corr) values of unchanged diclofenac sodium were directly proportional to the doses administered, irrespective of the dosage form used.

Seventy-five percent or more of patients suffering from osteoarthritis who received a once daily dose regimen of 100 mg diclofenac sodium or indomethacin as suppositories reported improved symptoms or became symptom free after one week of treatment. There were no significant differences in the treatment efficacy between treatment regimens.

Table 4: Summary of 3 clinical trials with diclofenac sodium suppository in osteoarthritis (OA)

Study design	Patients	Treatment duration	Medication dose/day	Efficacy variables
Double-blind, parallel,	98	7 days	Diclofenac sodium 100 mg suppositories -Indomethacin 100 mg suppositories	- Severity of pain at rest and on movement

DETAILED PHARMACOLOGY

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).

	Inhibition of edema induced by	
Preparation	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 μg/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} μM/L) is 1.6.

Platelet Adhesiveness
At 15 μg/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 μL in 72 hours, as measured by the administration of ^{51}Cr-labelled erythrocytes.

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.

Reproduction Studies

Rats: Doses of 2 and 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods.

At the higher dose, prolonged gestation and dystocia were observed. Embryotoxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated animals were comparable to those of controls except for slightly retarded growth at the higher dose.

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

Rabbits: Pregnant females treated with 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.

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

Carcinogenicity Studies
Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day have revealed no significant increases in tumour incidence. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats.

In a 2-year mouse study, only controls and animals at the two lower daily doses of 0.1 and 0.3 mg/kg showed survival sufficient for assessment of carcinogenic potential. The two higher daily doses of 1 and 2 mg/kg resulted in a shortening of lifespan, particularly in males, as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to non-steroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. Diclofenac sodium was not carcinogenic to mice under the conditions of this study.

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PART III: CONSUMER INFORMATION

PrNTP-DICLOFENAC SODIUM
PrNTP-DICLOFENAC SODIUM SR
(diclofenac sodium)

Read this information each time you refill your prescription in case new information has been added. This leaflet is Part III of a three-part "Product Monograph" published when NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will NOT tell you everything about NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the Medication is used for:
Your health care provider has prescribed NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR for you to relieve pain and swelling in rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR are used for maintenance therapy only.

What it does: NTP-DICLOFENAC SODIUM and NTP-DICLOFENAC SODIUM SR (diclofenac sodium), as nonsteroidal anti-inflammatory drugs (NSAIDs), can reduce the chemicals prostaglandins produced by your body which cause pain and swelling.

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

When it should not be used:
***DO NOT TAKE NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR* if you have any of the following conditions:**

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

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

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

What the medicinal ingredient is:
Diclofenac sodium

What the nonmedicinal ingredients are:

NTP-DICLOFENAC SODIUM (diclofenac sodium) 50 mg enteric coated tablets:
Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, silicon dioxide, sodium lauryl sulfate and sodium starch glycolate.
The film coating contains: D&C Yellow # 10, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, maltodextrin, methacrylic acid, polyethylene glycol, talc, titanium dioxide, triethyl citrate,

NTP-DICLOFENAC SODIUM SR (diclofenac sodium) 75 slow release tablets:
Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate and povidone.
The film coating contains: aquacoat ECD-30, cetyl alcohol, dibutyl sebacate, FD&C Blue #2, FD&C Red #6, FD&C Yellow #40, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate and titanium dioxide.

What dosage forms it comes in:
50 mg enteric coated tablets
75 mg SR (slow release) tablets:

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

WARNINGS AND PRECAUTIONS

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

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

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

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives

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

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR should be considered.

Long-term use of NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR might increase the risk of heart attacks or strokes.

INTERACTIONS WITH THIS MEDICATION

What About Taking Other Drugs At The Same Time?
See your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

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

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

PROPER USE OF THIS MEDICATION

Usual Dose:

Medical Condition (Age Group)	Maintenance Dose	Maximum Dose (per day) *	
NTP-DICLOFENAC SODIUM 50 mg enteric-coated tablets			
Rheumatoid Arthritis (16 years of age and older)	**Maintenance dose only:** 50 mg 2 times a day.	100 mg	
Osteoarthritis (16 years of age and older)	**Maintenance dose only:** 50 mg 2 times a day.	100 mg	
NTP-DICLOFENAC SODIUM SR 75 slow-release tablets			
Rheumatoid Arthritis (16 years of age and older	75 mg once daily	100 mg	
Osteoarthritis (16 years of age and older)	75 mg once daily	100 mg	

***** If your symptoms are not adequately controlled, you should contact your doctor, who may increase the total daily dose to a maximum of 150 mg in divided doses for a short period and with close monitoring. If you are older than 65 years, have liver problems, kidney problems, or heart problems, the maximum total dose per day should not exceed 100 mg of NTP-DICLOFENAC SODIUM (50 mg twice a day).

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

Make sure that you do not take more than a total of 100 mg per day, unless directed by your doctor.

If you will be using NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

NTP-DICLOFENAC SODIUM (enteric coated tablets): NTP-DICLOFENAC SODIUM tablets are a delayed-release product. Tablets should be taken with food and the tablets should be swallowed whole with water, and must not be divided or chewed.

Taking NTP-DICLOFENAC SODIUM SR Tablets Once A Day: If you are taking NTP-DICLOFENAC SODIUM SR 75 mg tablet **once** a day, it is best to take this tablet at the same time each day unless your doctor has told you differently.

Taking NTP-DICLOFENAC SODIUM SR Tablets Twice A Day: If your doctor has prescribed 150 mg of NTP-DICLOFENAC SODIUM SR for a short period of time, you should take NTP-DICLOFENAC SODIUM SR 75 mg tablet twice a day, in the morning and evening.

To help reduce the possibility of stomach upset you should take NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR tablets immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor

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.

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

Missed dose:
If you forget to take one or more doses of NTP-DICLOFENAC SODIUM (diclofenac sodium), 50 mg tablets or NTP-DICLOFENAC SODIUM SR (diclofenac sodium) 75 mg slow release tablets, you should not increase the dose of NTP-DICLOFENAC SODIUM (diclofenac sodium) or NTP-DICLOFENAC SODIUM SR to make up for the missed dose or doses, but you should continue taking your tablet or suppository at the next prescribed or regular time.

Overdose:
If you have accidentally taken more than the prescribed dose of NTP-DICLOFENAC SODIUM tablets or NTP-DICLOFENAC SODIUM SR tablets **tell your doctor or pharmacist or contact your regional Poison Control Centre or go to the hospital emergency unit at once.** You may require medical attention.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking NTP-DICLOFENAC SODIUM or NTP-

DICLOFENAC SODIUM SR, do NOT drive or operate machinery.

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

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

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM		
Symptom	**STOP taking NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR and get emergency medical attention IMMEDIATELY**	**STOP taking NTP-DICLOFENAC SODIUM or NTP-DICLOFENAC SODIUM SR and talk to your physician or pharmacist**
Bloody or black tarry stools	✓	
Shortness of breath, wheezing, any trouble breathing or chest tightness	✓	
Skin rash, hives, swelling or itching	✓	
Blurred vision, or any visual disturbance	✓	
Any change in the amount or colour of your urine (red or brown)	✓	
Any pain or difficulty experienced while urinating		✓
Swelling of the feet, lower legs; weight gain		✓
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓
Yellow discolouration of the skin or eyes (signs of liver failure), with or without itchy skin		✓
Malaise, fatigue, loss of appetite		✓
Headaches, stiff neck		✓
Mental confusion, depression		✓
Dizziness, lightheadedness		✓
Hearing problems		✓
Rectal itching or bleeding		✓

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

HOW TO STORE IT

Store between 15°-30°C. Unit dose strips should be stored between 15°-25°C and protected from high humidity.

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

Keep this and all medication out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited.
at: 1-800-268-4127 ext. 5005 (English Canada)
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