DICLOFENAC SODIUM- diclofenac sodium gel
REMEDYREPACK INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DICLOFENAC SODIUM GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM GEL.

DICLOFENAC SODIUM topical gel
Initial U.S. Approval: 2000

WARNING: RISK OF SERIOUS CARDIOVASCULAR EVENTS AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (5.4)
- Diclofenac sodium gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.4)
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.5)

RECENT MAJOR CHANGES

Warnings and Precautions (5.3)11/2024

INDICATIONS AND USAGE

Diclofenac sodium gel is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the topical treatment of actinic keratoses (AK). (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with the individual patient treatment goals. (2)
- Apply to lesion areas twice daily to adequately cover each lesion. (2)
- Use 0.5 g of gel (pea size) on each 5 cm x 5 cm lesion site. (2)
- The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be re-evaluated and management reconsidered. (2)
- Avoid contact in eyes, nose, or mouth. (2)

DOSAGE FORMS AND STRENGTHS

Topical gel, 3% (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac or any components of the drug product. (4, 11)
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. (4)
- Use on damaged skin. (4)
- In the setting of coronary artery bypass graft (CABG) surgery. (4)

WARNINGS AND PRECAUTIONS

- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.1)
- Exacerbation of Asthma Related to Aspirin Sensitivity: Diclofenac sodium gel is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with pre-existing asthma (without aspirin sensitivity). (5.2)
- Serious Skin Reactions: Discontinue diclofenac sodium gel at first appearance of skin rash or other signs of hypersensitivity. (5.3, 5.15)
- Hepatoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.6)

- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.7, 7)
- Heart Failure and Edema: Avoid use of diclofenac sodium gel in patients with severe heart failure. (5.8)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of diclofenac sodium gel in patients with advanced renal disease. (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue diclofenac sodium gel and evaluate clinically. (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including diclofenac sodium gel, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7).
- Photosensitivity: Avoid exposure of treated area(s) to natural or artificial sunlight. (5.15)
- Exposure to Eyes and Mucosal Membranes: Avoid contact of diclofenac sodium gel with eyes and mucosal membranes. (5.16)
- Oral Nonsteroidal Anti-inflammatory Drugs: Avoid concurrent use with oral NSAIDs. (5.17)

ADVERSE REACTIONS

Most common adverse reactions with diclofenac sodium gel are application site reactions, including dermatitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are using diclofenac sodium gel concomitantly with drugs that interfere with hemostasis. (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta- Blockers: Concomitant use with diclofenac sodium gel may diminish the antihypertensive effect of these drugs. (7)
- ACE Inhibitors and ARBs: Concomitant use with diclofenac sodium gel in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. (7)
- Digoxin: Concomitant use with diclofenac sodium gel may increase serum concentration and prolong half-life of digoxin. (7)

USE IN SPECIFIC POPULATIONS

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of diclofenac sodium gel in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use *[see Warnings and Precautions (5.4)]* .**
- **Diclofenac sodium gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.4)]* .**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at a greater risk for serious GI events *[see Warnings and Precautions (5.5)]* .**

1 INDICATIONS AND USAGE

Diclofenac sodium gel is indicated for the topical treatment of actinic keratoses (AK).

2 DOSAGE AND ADMINISTRATION

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]* .

Apply diclofenac sodium gel gently to lesion areas twice daily. to adequately cover each lesion. Use 0.5 g of gel (pea size) on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be re-evaluated and management reconsidered. Avoid contact of diclofenac sodium gel with eyes and mucous membranes.

3 DOSAGE FORMS AND STRENGTHS

Topical gel, 3%. Each gram of Diclofenac Sodium Topical Gel contains 30 mg of diclofenac sodium, USP in a clear, transparent, colorless to slightly yellow gel base. Diclofenac Sodium Gel, 3% is supplied in 100 g tubes.

4 CONTRAINDICATIONS

Diclofenac sodium gel is contraindicated in the following patients:

- With known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product *[see Warnings and Precautions (5.1, 5.3, 5.10) and Description (11)]*
- With the history of asthma, urticaria, or other allergic type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.1, 5.2)]*
- Application on damaged skin resulting from any etiology, including exudative dermatitis, eczema, infected lesions, burns or wounds *[see Warnings and Precautions (5.3)]*
- In the setting of coronary bypass graft (CABG) surgery *[see Warnings and Precautions (5.4)]*

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic Reactions

Diclofenac has been associated with anaphylactic reactions in patients with and without known hypersensitivity to diclofenac and in patients with aspirin-sensitive asthma *[see Contraindications (4) and Warnings and Precautions (5.2)]* .

Seek emergency help if an anaphylactic reaction occurs.

5.2 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, diclofenac sodium gel is contraindicated in patients with this form of aspirin sensitivity. When diclofenac sodium gel is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.3 Serious Skin Reactions

NSAIDs, including diclofenac, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of diclofenac sodium gel at the first appearance of skin rash or any other sign of hypersensitivity. Diclofenac sodium gel is contraindicated in patients with previous serious skin reactions to NSAIDs. Do not apply diclofenac sodium gel to open skin wounds, infections, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug *[see Contraindications (4)]* .

5.4 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic

events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as diclofenac, increases the risk of serious gastrointestinal (GI) events.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first-year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of diclofenac sodium gel in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If diclofenac sodium gel is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.5 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including diclofenac, cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID

therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-Treated Patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue diclofenac sodium gel until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]* .

5.6 Hepatotoxicity

In clinical trials with diclofenac sodium gel, 2 to 3% of subjects had elevations of liver function tests (LFTs) *[see Clinical Trials Experience (6.1)].* To minimize the potential risk for an adverse liver-related event in patients treated with diclofenac sodium gel, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing diclofenac sodium gel with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, antibiotics, anti-epileptics).

Physicians should measure transaminases at baseline and periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac sodium gel should be discontinued immediately.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue diclofenac

sodium gel immediately, and perform a clinical evaluation of the patient.

5.7 Hypertension

NSAIDs, including diclofenac sodium gel, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]* .

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.8 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of diclofenac may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)].

Avoid the use of diclofenac sodium gel in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If diclofenac sodium gel is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.9 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical trials regarding the use of diclofenac sodium gel in patients with advanced renal disease. The renal effects of diclofenac sodium gel may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating diclofenac sodium gel. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of diclofenac sodium gel *[see Drug Interactions (7)]* .Avoid the use of diclofenac sodium gel in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If diclofenac sodium gel is used in patients with advanced renal disease,

monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as diclofenac sodium gel. Some of these events have been fatal or life-threatening. 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. 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. If such signs or symptoms are present, discontinue diclofenac sodium gel and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including diclofenac sodium gel, in pregnant women at about 30 weeks gestation and later. NSAIDs, including diclofenac sodium gel, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including diclofenac, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. 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. Oligohydramnios is often, but not always, reversible with treatment discontinuation. 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 alternative treatment options for actinic keratoses, NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit diclofenac sodium gel use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if diclofenac treatment extends beyond 48 hours. Discontinue diclofenac sodium gel if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]* .

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a

patient treated with diclofenac sodium gel has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including diclofenac sodium gel, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]* .

5.13 Masking of Inflammation and Fever

The pharmacological activity of diclofenac sodium gel in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically *[see Warnings and Precautions (5.5,* 5.6, 5.9*)]*.

5.15 Photosensitivity

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using diclofenac sodium gel. If patients need to be outdoors while using diclofenac sodium gel, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with diclofenac sodium gel at the first evidence of sunburn.

5.16 Exposure to Eyes and Mucosal Membranes

Avoid contact of diclofenac sodium gel with eyes and mucosa. Advise patients that if contact in the eye, or mucosal membranes occurs, immediately wash out the eye or mucosal membranes with water or saline and consult a physician if irritation persists for more than an hour.

5.17 Oral Nonsteroidal Anti-inflammatory Drugs

Concomitant use of oral and topical NSAIDs may result in a higher rate of hemorrhage, more frequent abnormal creatinine, urea and hemoglobin. Do not use diclofenac sodium gel in combination with an oral NSAID unless the benefit outweighs the risk and periodic laboratory evaluations are conducted.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Anaphylactic Reactions *[see Warnings and Precautions (*5.1*)]*
- Exacerbation of Asthma Related to Aspirin Sensitivity *[see Warnings and Precautions (5.2)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.3)]*
- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.4)]*

- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.5)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*
- Hypertension *[see Warnings and Precautions (5.7)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.8)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.9)]*
- DRESS *[see Warnings and Precautions (5.10)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.12)]*
- Photosensitivity *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Of the 423 subjects evaluable for safety in adequate and well-controlled trials, 211 were treated with diclofenac sodium gel drug product and 212 were treated with a vehicle gel. Eighty-seven percent (87%) of the diclofenac sodium gel-treated subjects (183 subjects) and 84% of the vehicle-treated subjects (178 subjects) experienced one or more adverse events (AEs) during the trials. The majority of these reactions were mild to moderate in severity and resolved upon discontinuation of therapy.

Of the 211 subjects treated with diclofenac sodium gel, 172 (82%) experienced AEs involving skin and the application site compared to 160 (75%) vehicle-treated subjects. Application site reactions (ASRs) were the most frequent AEs in both diclofenac sodium gel-and vehicle-treated groups. Of note, four reactions, contact dermatitis, rash, dry skin and exfoliation(scaling) were significantly more prevalent in the diclofenac sodium gel group than in the vehicle-treated subjects.

Eighteen percent of diclofenac sodium gel-treated subjects and 4% of vehicle-treated subjects discontinued from the clinical trials due to adverse events (whether considered related to treatment or not). These discontinuations were mainly due to skin irritation or related cutaneous adverse reactions.

Table 1 below presents the AEs reported at an incidence of >1% for subjects treated with either diclofenac sodium gel or vehicle (60- and 90-day treatment groups) during the phase 3 trials.

Table 1. Adverse Events Reported (>1% in Any Treatment Group) During Diclofenac Sodium Gel Phase 3 Clinical Trials Incidences for 60-Day and 90-Day Treatments

	60-day Treatment		**90-day Treatment**	
	Diclofenac Sodium Gel (%)	**Gel Vehicle (%)**	**Diclofenac Sodium Gel (%)**	**Gel Vehicle (%)**
	N=48	**N=49**	**N=114**	**N=114**
• **BODY AS A WHOLE**	**21**	**20**	**20**	**18**
• Abdominal Pain	2	0	1	0
• Accidental Injury	0	0	4	2

• Allergic Reaction	0	0	1	3
• Asthenia	0	0	2	0
• Back Pain	4	0	2	2
• Chest Pain	2	0	1	0
• Chills	0	2	0	0
• Flu Syndrome	10	6	1	4
• Headache	0	6	7	6
• Infection	4	6	4	5
• Neck Pain	0	0	2	0
• Pain	2	0	2	2
• **CARDIOVASCULAR SYSTEM**	**2**	**4**	**3**	**1**
• Hypertension	2	0	1	0
• Migraine	0	2	1	0
• Phlebitis	0	2	0	0
• **DIGESTIVE SYSTEM**	**4**	**0**	**6**	**8**
• Constipation	0	0	0	2
• Diarrhea	2	0	2	3
• Dyspepsia	2	0	3	4
• **METABOLIC AND NUTRITIONAL DISORDERS**	**2**	**8**	**7**	**2**
• Creatine Phosphokinase Increased	0	0	4	1
• Creatinine Increased	2	2	0	1
• Edema	0	2	0	0
• Hypercholesteremia	0	2	1	0
• Hyperglycemia	0	2	1	0
• SGOT Increased	0	0	3	0

• SGPT Increased	0	0	2	0
• **MUSCULOSKELETAL SYSTEM**	**4**	**0**	**3**	**4**
• Arthralgia	2	0	0	2
• Arthrosis	2	0	0	0
• Myalgia	2	0	3	1
• **NERVOUS SYSTEM**	**2**	**2**	**2**	**5**
• Anxiety	0	2	0	1
• Dizziness	0	0	0	4
• Hypokinesia	2	0	0	0
• **RESPIRATORY SYSTEM**	**8**	**8**	**7**	**6**
• Asthma	2	0	0	0
• Dyspnea	2	0	2	0
• Pharyngitis	2	8	2	4
• Pneumonia	2	0	0	1
• Rhinitis	2	2	2	2
• Sinusitis	0	0	2	0
• **SKIN AND APPENDAGES**	**75**	**86**	**86**	**71**
• Acne	0	2	0	1
• Application Site Reaction	75	71	84	70
• Acne	0	4	1	0
• Alopecia	2	0	1	1
• Contact Dermatitis	19	4	33	4
• Dry Skin	27	12	25	17
• Edema	4	0	3	0
• Exfoliation	6	4	24	13
• Hyperesthesia	0	0	3	1

• Pain	15	22	26	30
• Paresthesia	8	4	20	20
• Photosensitivity Reaction	0	2	3	0
• Pruritus	31	59	52	45
• Rash	35	20	46	17
• Vesiculobullous Rash	0	0	4	1
• Contact Dermatitis	2	0	0	0
• Dry Skin	0	4	3	0
• Herpes Simplex	0	2	0	0
• Maculopapular Rash	0	2	0	0
• Pain	2	2	1	0
• Pruritus	4	6	4	1
• Rash	2	10	4	0
• Skin Carcinoma	0	6	2	2
• Skin Nodule	0	2	0	0
• Skin Ulcer	2	0	1	0
• **SPECIAL SENSES**	**2**	**0**	**4**	**2**
• Conjunctivitis	2	0	4	1
• Eye Pain	0	2	2	0
• **UROGENITAL SYSTEM**	**0**	**0**	**4**	**5**
• Hematuria	0	0	2	1
• **OTHER**	**0**	**0**	**0**	**3**
• Procedure	0	0	0	3

Skin and Appendages Adverse Events Reported for Diclofenac Sodium Gel at Less Than 1% Incidence in the Phase 3 Studies:skin hypertrophy, paresthesia, seborrhea, urticaria, application site reactions (skin carcinoma, hypertonia, skin hypertrophy lacrimation disorder, maculopapular rash, purpuric rash, vasodilation).

Adverse Reactions Reported for *Oral*Diclofenac Dosage Form (not topical

diclofenac sodium gel): *Incidence Greater than 1% marked with asterisk.

Body as a Whole:abdominal pain or cramps*, headache*, fluid retention*, abdominal distention*, malaise, swelling of lips and tongue, photosensitivity, anaphylaxis, anaphylactoid reactions, chest pain.

Cardiovascular:hypertension, congestive heart failure, palpitations, flushing, tachycardia, premature ventricular contractions, myocardial infarction, hypotension.

Digestive:diarrhea*, indigestion*, nausea*, constipation*, flatulence*, liver test abnormalities*, PUB*, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer, vomiting, jaundice, melena, esophageal lesions, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, hepatic necrosis, cirrhosis, hepatorenal syndrome, appetite change, pancreatitis with or without concomitant hepatitis, colitis, intestinal perforation.

Hemic and Lymphatic:hemoglobin decrease, leukopenia, thrombocytopenia, eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura, allergic purpura, bruising.

Metabolic and Nutritional Disorders:azotemia, hypoglycemia, weight loss.

Nervous System:dizziness*, insomnia, drowsiness, depression, diplopia, anxiety, irritability, aseptic meningitis, convulsions, paresthesia, memory disturbance, nightmares, tremor, tic, abnormal coordination, disorientation, psychotic reaction.

Respiratory:epistaxis, asthma, laryngeal edema, dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages:rash*, pruritus*, alopecia, urticaria, eczema, dermatitis, bullous eruption, erythema multiforme major, angioedema, Stevens-Johnson syndrome, excess perspiration, exfoliative dermatitis.

Special Senses:tinnitus*, blurred vision, taste disorder, reversible and irreversible hearing loss, scotoma, vitreous floaters, night blindness, amblyopia.

Urogenital:nephrotic syndrome, proteinuria, oliguria, interstitial nephritis, papillary necrosis, acute renal failure, urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of diclofenac sodium gel and other topical diclofenac products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions from diclofenac sodium gel: burning sensation, hypersensitivity.

Adverse reactions from other topical diclofenac products: hypoesthesia, gait disturbance, musculoskeletal stiffness.

Skin and Appendages: exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with diclofenac.

Table 2: Clinically Significant Drug Interactions with Diclofenac

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Diclofenac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of diclofenac and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	• Monitor patients with concomitant use of diclofenac sodium gel with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding *[see Warnings and Precautions (5.5)]* .
Aspirin	
Clinical Impact:	• In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.5)]* .
Intervention:	• Concomitant use of diclofenac sodium gel and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.12)]* . Diclofenac sodium gel is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of diclofenac sodium gel and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of diclofenac sodium gel and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.9)]* .

Diuretics	
Clinical Impact:	• Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	• During concomitant use of diclofenac sodium gel with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions (5.9)]* .
Digoxin	
Clinical Impact:	• The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	• During concomitant use of diclofenac sodium gel and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	• NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	• During concomitant use of diclofenac sodium gel and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	• Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	• During concomitant use of diclofenac sodium gel and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	• Concomitant use of diclofenac sodium gel and cyclosporine may increase cyclosporine’s nephrotoxicity.
Intervention:	• During concomitant use of diclofenac sodium gel and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	• Concomitant use of diclofenac sodium gel with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity *[see Warnings and Precautions (5.5)]* .
Intervention:	• The concomitant use of diclofenac sodium gel with other NSAIDs or

	salicylates is not recommended.
Pemetrexed	
Clinical Impact:	• Concomitant use of diclofenac sodium gel and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	• During concomitant use of diclofenac sodium gel and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including diclofenac sodium gel, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of diclofenac sodium gel use between about 20 and 30 weeks of gestation and avoid diclofenac sodium gel use at about 30 weeks of gestation and later in pregnancy.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including diclofenac sodium gel, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, no evidence of malformations was observed in mice, rats, or rabbits given diclofenac during the period of organogenesis at doses at least 15 times, the maximum recommended human dose (MRHD) of diclofenac sodium gel *(see Data)*. Based on published animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization, and administration of prostaglandin synthesis inhibitors such as diclofenac sodium, resulted in increased pre- and post-implantation loss. Prostaglandins

also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including diclofenac sodium gel, can cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

If after careful consideration of alternative treatment options for actinic keratoses, an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If diclofenac sodium gel treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue diclofenac sodium gel and follow up according to clinical practice.

Labor or Delivery

There are no studies on the effects of diclofenac sodium gel during labor or delivery. In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a

control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use.

Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

The multiples provided in this labeling are based on an MRHD that assumes 10% bioavailability following topical application of 2 g diclofenac sodium gel per day (1 mg/kg diclofenac sodium).

Reproductive studies performed with diclofenac sodium alone at oral doses up to 20 mg/kg/day (15 times the MRHD based on body surface area (BSA) comparisons) in mice, 10 mg/kg/day (15 times the MRHD based on BSA comparisons) in rats, and 10 mg/kg/day (30 times the MRHD based on BSA comparisons) in rabbits have revealed no evidence of malformations despite the induction of maternal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

8.2 Lactation

Risk Summary

Data from published literature cases with oral preparations of diclofenac indicate the presence of small amounts of diclofenac in human milk. There are no data on the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for diclofenac sodium gel and any potential adverse effects on the breastfed infant from the diclofenac sodium gel or from the underlying maternal condition.

Data

One woman treated orally with a diclofenac salt, 150 mg/day, had a milk diclofenac level of 100 mcg/L, equivalent to an infant dose of about 0.03 mg/kg/day. Diclofenac was not detectable in breast milk in 12 women using diclofenac (after either 100 mg/day orally for 7 days or a single 50 mg intramuscular dose administered in the immediate postpartum period). The systemic bioavailability after topical application of diclofenac sodium gel is lower than after oral dosing *[see Clinical Pharmacology (12.3)]* .

8.3 Females and Males of Reproductive Potential

Female Infertility

Based on the mechanism of action, the use of prostaglandin mediated NSAIDs, including diclofenac sodium gel, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women *[see Clinical Pharmacology (12.1)]* .

Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible

delay in ovulation. Consider withdrawal of NSAIDs, including diclofenac sodium gel, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Actinic keratoses is not a condition seen within the pediatric population. diclofenac sodium gel should not be used by children.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.9, 5.14)].*

Of the 211 subjects treated with diclofenac sodium gel in controlled clinical trials, 143 subjects were 65 years of age and over. Of those 143 subjects, 55 subjects were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding, hypertension, acute renal failure, respiratory depression, and coma have been reported. *[see Warnings and Precautions (5.4, 5.5, 5.7, 5.9)]* .

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

In the event of oral ingestion, resulting in significant systemic side effects, it is recommended that the stomach be emptied by vomiting or lavage. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac.

For additional information about overdosage treatment, call a poison control center (1-800-222-1222).

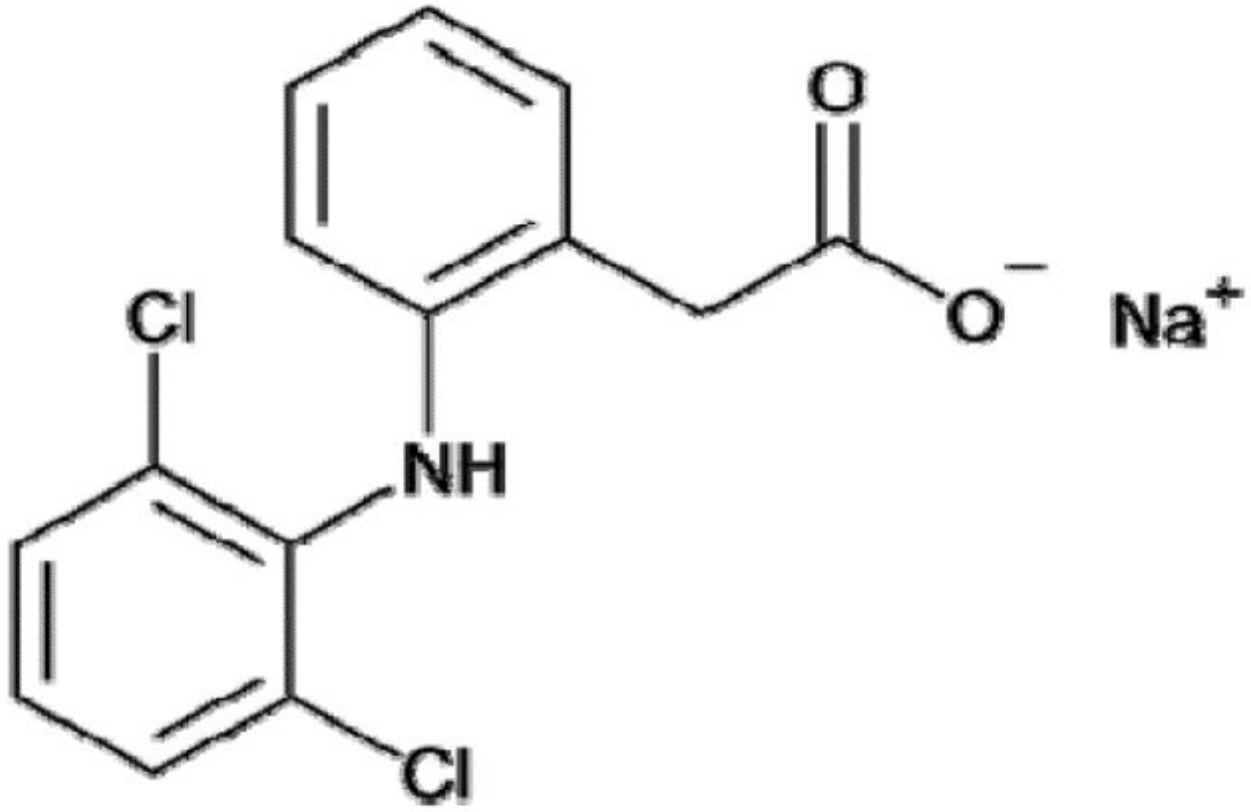
11 DESCRIPTION

Diclofenac Sodium Topical Gel, 3%, intended for dermatologic use, contains the active ingredient, diclofenac sodium, USP in a clear, transparent, colorless to slightly yellow gel base. Diclofenac sodium, USP is a white to slightly yellowish, hygroscopic crystalline powder, and melts at about 284°C. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in water, slightly soluble in acetone, and partially insoluble in chloroform and ether. The chemical name for diclofenac sodium is:

Sodium [*o*-(2,6-dichloranilino) phenyl] acetate

Diclofenac sodium has a molecular weight of 318.13.

The CAS number is CAS-15307-79-6. The structural formula is represented below:



Diclofenac Sodium Gel, 3% also contains benzyl alcohol, sodium hyaluronate, polyethylene glycol monomethyl ether, and purified water.

1 g of Diclofenac Sodium Topical Gel, 3% contains 30 mg of the active substance, diclofenac sodium, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of diclofenac sodium in the treatment of actinic keratoses (AK) is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of diclofenac sodium gel in the treatment of actinic keratosis has not been assessed.

12.3 Pharmacokinetics

Absorption

Diclofenac levels were measured at the end of treatment from 60 patients with AK lesions treated with diclofenac sodium gel in three adequate and well-controlled clinical trials. Each patient was administered 0.5 g of diclofenac sodium gel twice a day for up to 105 days. There were up to three 5 cm x 5 cm treatment sites per patient on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were, on average, at or below 20 ng/mL.

Distribution

Diclofenac binds tightly to serum albumin.

Metabolism

Biotransformation of diclofenac following oral administration involves conjugation at the carboxyl group of the side chain or single or multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much smaller extent than diclofenac. Metabolism of diclofenac following topical administration is thought to be similar to that after oral administration. The small amounts of diclofenac and its metabolites appearing in the plasma following topical administration makes the quantification of specific metabolites imprecise.

Elimination

Diclofenac and its metabolites are excreted mainly in the urine after oral dosing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There did not appear to be any increase in drug-related neoplasms following daily topical applications of diclofenac sodium gel for 2 years at concentrations up to 0.035% diclofenac sodium and 2.5% hyaluronate sodium in albino mice.

When administered orally for 2 years, diclofenac showed no evidence of carcinogenic potential in rats given diclofenac sodium at up to 2 mg/kg/day (3 times the MRHD based on BSA comparison), or in mice given diclofenac sodium at up to 0.3 mg/kg/day in males and 1 mg/kg/day in females (25% and 83%, respectively, of the MRHD based on BSA comparison).

Diclofenac was not genotoxic in *in vitro* point mutation assays in mammalian mouse lymphoma cells and Ames microbial test systems, or when tested in mammalian *in vivo* assays including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. It was also negative in the transformation assay utilizing BALB/3T3 mouse embryo cells.

Fertility studies have not been conducted with diclofenac sodium gel. Diclofenac sodium showed no evidence of impairment of fertility after oral treatment with 4 mg/kg/day (7 times the MRHD based on BSA comparison) in male or female rats.

14 CLINICAL STUDIES

Clinical trials were conducted involving a total of 427 patients (213 treated with diclofenac sodium gel and 214 with a gel vehicle). Each patient had no fewer than five AK lesions in a major body area, which was defined as one of five 5 cm x 5 cm regions: scalp, forehead, face, forearm and hand. Up to three major body areas were studied in any patient. All patients were 18 years of age or older (male and female) with no clinically significant medical problems outside of the AK lesions and had undergone a 60-day washout period from disallowed medications (masoprocol, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronan-containing cosmetics. Patients were excluded from participation for reasons of known or suspected hypersensitivity to any diclofenac sodium gel ingredient, pregnancy, allergies to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), or other dermatological conditions which might affect the absorption of the study medication. Application of dermatologic products such as sunscreens, cosmetics, and other drug products was not permitted. Patients were instructed to apply a small amount of diclofenac sodium gel (approximately 0.5 g) onto the affected skin, using their fingers, and gently smoothing the gel over the lesion. In addition, all patients were instructed to avoid sun exposure. Complete clearing of the AK lesions 30 days after completion of treatment was the primary efficacy variable. No long-term patient follow-ups, after the 30-day assessments, were performed for the detection of recurrence.

• **Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment (all locations)**			
	• **Diclofenac Sodium Gel**	• **Vehicle**	• **p-value**
• Study 1 90 days treatment	• 27/58 (47%)	• 11/59 (19%)	• <0.001
• Study 2 90 days treatment	• 18/53 (34%)	• 10/55 (18%)	• 0.061
• Study 3 60 days treatment	• 15/48 (31%)	• 5/49 (10%)	• 0.021
• 30 days treatment	• 7/49 (14%)	• 2/49 (4%)	• 0.221

Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment (by location)					
	Scalp	**Forehead**	**Face**	**Arm/Forearm**	**Back of Hand**
Study 1 90 days treatment					
• Diclofenac Sodium Gel	• 1/4 (25%)	• 17/30 (57%)	• 9/17 (53%)	• 4/12 (33%)	• 6/16 (38%)
• Vehicle	• 3/9 (33%)	• 8/24 (33%)	• 5/17 (29%)	• 4/12 (33%)	• 0/14 (0)

• p-value	• 0.7646	• 0.0908	• 0.1682	• 1.000	• 0.0650
Study 2 90 days treatment					
• Diclofenac Sodium Gel	• 2/6 (33%)	• 9/19 (47%)	• 4/5 (80%)	• 5/8 (63%)	• 1/17 (6%)
• Vehicle	• 0/4 (0)	• 6/22 (27%)	• 2/8 (25%)	• 0/5 (0)	• 3/16 (19%)
• p-value	• 0.4235	• 0.1870	• 0.0727	• 0.0888	• 0.2818
Study 3 60 days treatment					
• Diclofenac Sodium Gel	• 3/7 (43%)	• 13/31 (42%)	10/19 (53%)	• 0/1 (0)	• 2/8 (25%)
• Vehicle	• 0/6 (0)	• 5/36 (14%)	• 2/13 (15%)	• 0/2 (0)	• 1/9 (11%)
• p-value	• 0.2271	• 0.0153	• 0.0433	• -	• 0.4637
Study 3 30 days treatment					
• Diclofenac Sodium Gel	• 2/5 (40%)	• 4/29 (14%)	• 3/14 (21%)	• 0/0 (0)	• 0/9 (0)
• Vehicle	• 0/5 (0)	• 2/29 (7%)	• 2/18 (11%)	• 0/1 (0)	• 1/9 (11%)
• p-value	• 0.2299	• 0.3748	• 0.4322	• -	• 0.6521
All data combined					
• Diclofenac Sodium Gel	• 8/22 (36%)	• 43/109 (39%)	26/55 (47%)	• 9/21 (43%)	• 9/50 (18%)
• Vehicle	• 3/24 (13%)	• 21/111 (19%)	11/56 (20%)	• 4/20 (20%)	• 5/48 (10%)
• p-value	• 0.0903	• 0.0013	• 0.0016	• 0.2043	• 0.3662

16 HOW SUPPLIED/STORAGE AND HANDLING

Each gram of Diclofenac Sodium Topical Gel, 3% contains 30 mg of diclofenac sodium, USP. Diclofenac Sodium Gel, 3% is available as follows:

NDC: 70518-3315-00

PACKAGING: 1 in 1 CARTON, 100 g in 1 TUBE, TYPE 0

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing.

Repackaged and Distributed By:

Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed, as well as the Directions for Use on the product packaging. Inform patients, families, or their caregivers of the following information before initiating therapy with diclofenac sodium gel and periodically during the course of ongoing therapy.

Special Application Instructions

- Instruct patients not to apply diclofenac sodium gel to damaged skin resulting from any etiology, e.g., exudative dermatitis, eczema, infected lesion, burns or wounds.
- Instruct patients to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using diclofenac sodium gel. If patients need to be outdoors while using diclofenac sodium gel, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with diclofenac sodium gel at the first evidence of sunburn.

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Contraindications (4) and Warnings and Precautions (* 5.1*)]*.

Exacerbation of Asthma Related to Aspirin Sensitivity

Inform patients with aspirin sensitive asthma not to use diclofenac sodium gel. Advise patients with preexisting asthma to report any changes in the signs and symptoms of asthma to their healthcare provider *[see Contraindications (4) and Warnings and Precautions (5.2)]* .

Serious Skin Reactions including DRESS

Advise patients to stop using diclofenac sodium gel immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.3, 5.10)]* .

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *[see Warnings*

and Precautions (5.4)] .

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *[see Warnings and Precautions (5.5)]* .

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). Inform the patient that diclofenac sodium gel may increase the risk of elevated liver enzymes. Advise the patient that laboratory evaluation is needed prior to and periodically during treatment. Advise the patient that if signs or symptoms of liver injury occur, discontinue diclofenac sodium gel and seek medical advice promptly *[see Warnings and Precautions (5.6)]* .

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.8)]* .

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including diclofenac sodium gel, may be associated with reversible delay in ovulation *[see Use in Specific Populations (8.3)]* .

Fetal Toxicity

Inform pregnant women to avoid use of diclofenac sodium gel and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with diclofenac sodium gel is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.11) and Use in Specific Populations (* 8.1*)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of diclofenac sodium gel with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity *[see Warnings and Precautions (5.5)and Drug Interactions (**7**)]* . Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with diclofenac sodium gel until they talk to their healthcare provider *[see Drug Interactions (7)]*.

Exposure to Eyes and Mucosal Membranes

Instruct patients to avoid contact of diclofenac sodium gel with the eyes and mucosal membranes. Advise patients that if eye or mucosal membrane contact occurs,

immediately wash out with water or saline and consult a physician if irritation persists for more than an hour *[see Warnings and Precautions (5.16)]* .

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Medication Guide available at

www.glenmarkpharma-us.com/medguides

Repackaged By / Distributed By: RemedyRepack Inc.

625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

Medication Guide

Dispense with Medication Guide available at: www.glenmarkpharma-us.com/medguides
• **Diclofenac Sodium (dye-KLOE-fen-ak SOE-dee-um) Gel**

What is the most important information I should know about diclofenac sodium gel and medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take or use NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)". Avoid taking NSAIDs after a recent heart attack unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take or use NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age

- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What is diclofenac sodium gel?
Diclofenac sodium gel is an NSAID that is used on the skin (topical) to treat a skin condition called actinic keratosis. Diclofenac sodium gel is not for use in children.

- **Do not use diclofenac sodium gel:**

- if you have had an allergic reaction to any of the ingredients in diclofenac sodium gel. See the end of this Medication Guide for a complete list of ingredients in diclofenac sodium gel.
- if you have a history of asthma, hives, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe allergic reactions that can sometimes lead to death, have happened in people with a history of these types of allergic reactions to NSAIDs.
- on skin that is inflamed, or has eczema, infected sores (lesions), burns or wounds
- right before or after heart bypass surgery.

Before using diclofenac sodium gel, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will use diclofenac sodium gel or breastfeed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements.NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

How should I use diclofenac sodium gel?
- Use diclofenac sodium gel exactly as your healthcare provider tells you to use it.
- Apply diclofenac sodium gel 2 times a day.
- Apply enough diclofenac sodium gel to cover each skin lesion (usually a pea-sized amount) and gently rub in.
- Diclofenac sodium gel may be used for 60 to 90 days. You may not see improvement of skin lesions for up to 30 days after stopping treatment. See your healthcare provider if lesions do not respond to treatment.

- Avoid getting diclofenac sodium gel in your eyes, nose and mouth. If diclofenac sodium gel gets into your eyes, nose or mouth wash out your eyes, nose or mouth with water or saline right away. Call your healthcare provider if irritation continues for more than 1 hour.
- Wash your hands well after applying diclofenac sodium gel.

What should I avoid while using diclofenac sodium gel?

- Avoid spending time in sunlight or artificial light, such as tanning beds or sunlamps. Diclofenac sodium gel can make your skin sensitive to sunlight and the light from tanning beds and sunlamps. Talk to your healthcare provider about sun protection measures and wear loose-fitting clothes that cover your skin while out in sunlight. Stop using diclofenac sodium gel if you notice that you are beginning to get sunburn.
- Do not apply diclofenac sodium gel to open skin wounds, skin infections, or peeling skin.

What are the possible side effects of diclofenac sodium gel?
Diclofenac sodium gel and other NSAIDs can cause serious side effects, including:
See "What is the most important information I should know about diclofenac sodium gel and medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- life threatening allergic reactions
- worsening of asthma in people who are aspirin-sensitive
- life-threatening skin reactions
- liver problems including liver failure
- new or worse high blood pressure
- heart failure
- kidney problems including kidney failure
- low red blood cells (anemia)

Other side effects of NSAIDs include:stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.
Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop using diclofenac sodium gel and call your healthcare provider right away if you get any of the following symptoms:

• nausea
• more tired or weaker than usual
• diarrhea
• itching
• your skin or eyes look yellow
• indigestion or stomach pain
• flu-like symptoms
• vomit blood
• there is blood in your bowel movement or it is black and sticky like tar

• unusual weight gain
• skin rash or blisters with fever
• swelling of the arms, legs, hands and feet

Application site skin reactions are common with diclofenac sodium gel including:skin redness, itching, rash, dry skin, scaling, and peeling.

If you take too much NSAID, call your healthcare provider or get medical help right away.

- Diclofenac sodium gel may cause fertility problems in females, which may affect your ability to have a child. Talk to your healthcare provider if this a concern for you.
- These are not all of the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs.

How should I store diclofenac sodium gel?

- Store diclofenac sodium gel at room temperature 68°F to 77°F (20°C to 25°C).
- Keep diclofenac sodium gel away from heat. Avoid freezing diclofenac sodium gel.

Keep diclofenac sodium gel and all medicines out of the reach of children.

General information about the safe and effective use of diclofenac sodium gel.

1. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use diclofenac sodium gel for a condition for which it was not prescribed. Do not give diclofenac sodium gel to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about diclofenac sodium gel, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about diclofenac sodium gel that is written for health professionals.

What are the ingredients in diclofenac sodium gel?

Active ingredient:diclofenac sodium

Inactive ingredients:benzyl alcohol, sodium hyaluronate, polyethylene glycol monomethyl ether, and purified water.

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- This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2025

Repackaged By / Distributed By: RemedyRepack Inc.

625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

DRUG: DICLOFENAC SODIUM

GENERIC: diclofenac sodium

DOSAGE: GEL

ADMINSTRATION: TOPICAL

NDC: 70518-3315-0

PACKAGING: 100 g in 1 TUBE

OUTER PACKAGING: 1 in 1 CARTON

ACTIVE INGREDIENT(S):
- DICLOFENAC SODIUM 30mg in 1g

INACTIVE INGREDIENT(S):
- BENZYL ALCOHOL
- HYALURONATE SODIUM
- PEG-6 METHYL ETHER
- WATER

DICLOFENAC SODIUM

diclofenac sodium gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70518-3315(NDC:68462-355)
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

DICLOFENAC SODIUM (UNII: QTG126297Q) (DICLOFENAC - UNII:144O8QL0L1)	DICLOFENAC SODIUM	30 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCOHOL (UNII: LKG8494WBH)	
HYALURONATE SODIUM (UNII: YSE9PPT4TH)	
PEG-6 METHYL ETHER (UNII: WXH089JZ5E)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70518-3315-0	1 in 1 CARTON	12/28/2021	
1		100 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208301	12/28/2021	

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