

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022122Orig1s011

Trade Name: Voltaren Gel, 1%

Generic or Proper Name: diclofenac sodium topical gel

Sponsor: GlaxoSmithKline Consumer Healthcare

Approval Date: February 21, 2018

Indication: for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as knees and those of the hands.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 022122/S-011

SUPPLEMENT APPROVAL

GlaxoSmithKline Consumer Healthcare
184 Liberty Corner Rd, Suite 200
Warren, NJ 07059

Attention: Dan Keravich
Director, Regulatory Affairs

Dear Mr. Keravich:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VOLTAREN GEL (diclofenac sodium topical gel).

This Prior Approval supplemental new drug application proposes the following: changes to the Instructions for Use to clarify the instructions for opening a tube of VOLTAREN GEL, and numerous minor additional changes to the package insert and carton and container labeling related to the removal of Sandoz and Novartis as business partners.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending

“Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on February 1, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022122/S-011.**” Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Mavis Darkwah, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3111
10903 New Hampshire Avenue
Silver Spring, MD
Use zip code **20903** if shipping via United States Postal Service (USPS).
Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mavis Y. Darkwah, PharmD, Regulatory Project Manager, at (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022122Orig1s011

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VOLTAREN GEL safely and effectively. See full prescribing information for VOLTAREN GEL.

VOLTAREN GEL (diclofenac sodium topical gel), 1%,
for topical use only
Initial U.S. Approval: 1988

WARNING: RISK OF SERIOUS CARDIOVASCULAR 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 (5.1)**
- **VOLTAREN GEL is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **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. (5.2)**

INDICATIONS AND USAGE

VOLTAREN GEL is a non-steroidal anti-inflammatory drug indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. (1)

- VOLTAREN GEL was not evaluated for use on joints of the spine, hip, or shoulder. (14.1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- Lower extremities: Apply the gel (4 g) to the affected area 4 times daily. Do not apply more than 16 g daily to any one affected joint of the lower extremities. (2.2)
- Upper extremities: Apply the gel (2 g) to the affected area 4 times daily. Do not apply more than 8 g daily to any one affected joint of the upper extremities. (2.3)
- Total dose should not exceed 32 g per day, over all affected joints. (2.3) VOLTAREN GEL should be measured onto the enclosed dosing card to the appropriate 2 g or 4 g designation. (2)

DOSAGE FORM AND STRENGTH

- VOLTAREN GEL (diclofenac sodium topical gel), 1%, (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac or any components of the drug product. (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
- In the setting of CABG surgery. (4)

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** 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 (5.3)
- **Hypertension:** Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- **Heart Failure and Edema:** Avoid use of VOLTAREN GEL in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- **Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of VOLTAREN GEL in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- **Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs (5.7)
- **Exacerbation of Asthma Related to Aspirin Sensitivity:** VOLTAREN GEL is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- **Serious Skin Reactions:** Discontinue VOLTAREN GEL at first appearance of rash or other signs of hypersensitivity (5.9)
- **Premature Closure of Fetal Ductus Arteriosus:** Avoid use in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2% of patients treated with VOLTAREN GEL and greater than placebo) are application site reactions, including dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline Consumer Healthcare at 1-855-297-3031 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 concomitantly using VOLTAREN GEL with drugs that interfere with hemostasis. Concomitant use of VOLTAREN GEL and analgesic doses of aspirin is not generally recommended (7)
- **ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers:** Concomitant use with VOLTAREN GEL may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- **ACE Inhibitors and ARBs:** Concomitant use with VOLTAREN GEL in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- **Diuretics:** NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- **Digoxin:** Concomitant use with VOLTAREN GEL can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of VOLTAREN GEL in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: Feb 2018

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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 (5.1)].**
- **VOLTAREN GEL is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4) and Warnings and Precautions (5.1)].**

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 greater risk for serious GI events [see Warnings and Precautions (5.2)].**

1 INDICATIONS AND USAGE

VOLTAREN GEL is indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.

- VOLTAREN GEL has not been evaluated for use on the spine, hip, or shoulder.

2 DOSAGE AND ADMINISTRATION

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

2.1 Dosing Card [See the patient Instructions for Use]

The dosing card can be found attached to the inside of the carton.

The proper amount of VOLTAREN GEL should be measured using the dosing card supplied in the drug product carton. The dosing card is made of clear polypropylene. The dosing card should be used for each application of drug product. The gel should be applied within the rectangular area of the dosing card up to the 2 gram or 4 gram line (2 g for each elbow, wrist, or hand, and 4 g for each knee, ankle, or foot). The 2 g line is 2.25 inches long. The 4 g line is 4.5 inches long. The dosing card containing VOLTAREN GEL can be used to apply the gel. The hands should then be used to gently rub the gel into the skin. After using the dosing card, hold with fingertips, rinse, and dry. If treatment site is the hands, patients should wait at least one (1) hour to wash their hands.

2.2 Lower extremities, including the feet, ankles, or knees

Apply the gel (4 g) to the affected foot, ankle, or knee 4 times daily. VOLTAREN GEL should be gently massaged into the skin ensuring application to the entire affected foot, or knee or ankle. The entire foot includes the sole, top of the foot and the toes. Do not apply more than 16 g daily to any single joint of the lower extremities.

2.3 Upper extremities including the hands, wrists, or elbows

Apply the gel (2 g) to the affected hand, wrist, or elbow 4 times daily. VOLTAREN GEL should be gently massaged into the skin ensuring application to the entire affected hand, wrist, or elbow.

The entire hand includes the palm, back of the hands, and the fingers. Do not apply more than 8 g daily to any single joint of the upper extremities.

Total dose should not exceed 32 g per day, over all affected joints.

2.4 Special Precautions

- Avoid showering/bathing for at least 1 hour after the application. Inform patient to wash his/her hands after use, unless the hands are the treated joint. If VOLTAREN GEL is applied to the hand(s) for treatment; inform patient not to wash the treated hand(s) for at least 1 hour after the application.
- Do not apply VOLTAREN GEL to open wounds.
- Avoid contact of VOLTAREN GEL with eyes and mucous membranes.
- Do not apply external heat and/or occlusive dressings to treated joints.
- Avoid exposure of the treated joint(s) to natural or artificial sunlight.
- Avoid concomitant use of VOLTAREN GEL on the treated skin site with other topical products, including sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medications
- Concomitant use of VOLTAREN GEL with oral non-steroidal anti-inflammatory drugs (NSAIDs) has not been evaluated, and may increase adverse NSAIDs effects. Do not use combination therapy with VOLTAREN GEL and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.
- Avoid wearing of clothing or gloves for at least 10 minutes after applying VOLTAREN GEL.

3 DOSAGE FORM AND STRENGTH

VOLTAREN GEL (diclofenac sodium topical gel), 1%

4 CONTRAINDICATIONS

VOLTAREN GEL is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- 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 (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 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 [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, 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 [*see Contraindications (4)*].

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

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including diclofenac, cause serious gastrointestinal (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 3-6 months, and in about 2%-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 VOLTAREN 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)*].

5.3 Hepatotoxicity

In clinical trials, of oral diclofenac-containing products, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) were observed in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In a large, open-label, controlled trial of 3,700 patients treated with oral diclofenac sodium for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of 3,700 patients and included marked elevations (greater than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (greater than 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

In a European retrospective population-based, case-controlled study, 10 cases of diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female gender, doses of 150 mg or more, and duration of use for more than 90 days.

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.), VOLTAREN 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 VOLTAREN GEL immediately, and perform a clinical evaluation of the patient.

To minimize the potential risk for an adverse liver related event in patients treated with VOLTAREN GEL, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing VOLTAREN GEL with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, antibiotics, anti-epileptics).

5.4 Hypertension

NSAIDs, including VOLTAREN GEL, can lead to new onset of hypertension or worsening of preexisting 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.

5.5 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]) [*see Drug interactions (7)*].

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

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

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

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. 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 studies regarding the use of VOLTAREN GEL in patients with advanced renal disease. The renal effects of VOLTAREN GEL may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating VOLTAREN GEL. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or

hypovolemia during use of VOLTAREN GEL [*see Drug Interactions (7)*]. Avoid the use of VOLTAREN GEL in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If VOLTAREN 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.

5.7 Anaphylactoid 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 (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 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, VOLTAREN GEL is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When VOLTAREN GEL is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 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. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of VOLTAREN GEL at the first appearance of skin rash or any other sign of hypersensitivity. VOLTAREN GEL is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Premature Closure of Fetal Ductus Arteriosus

Diclofenac may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VOLTAREN GEL, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

5.11 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 VOLTAREN GEL has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including VOLTAREN 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)*].

5.12 Masking of Inflammation and Fever

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

5.13 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 (5.2, 5.3, 5.6)*].

5.14 Sun Exposure

Patients should minimize or avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in an earlier onset of ultraviolet light induced skin tumors. The potential effects of VOLTAREN GEL on skin response to ultraviolet damage in humans are not known.

5.15 Eye Exposure

Contact of VOLTAREN GEL with eyes and mucosa, although not studied, should be avoided. Patients should be advised that if eye contact occurs, they should immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

5.16 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 combination therapy with VOLTAREN GEL and an oral NSAID unless the benefit outweighs the risk.

6 ADVERSE REACTIONS

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

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical development, 913 patients were exposed to VOLTAREN GEL in randomized, double-blind, multicenter, vehicle-controlled, parallel-group studies in osteoarthritis of the superficial joints of the extremities. Of these, 513 patients received VOLTAREN GEL for osteoarthritis of the knee and 400 were treated for osteoarthritis of the hand. Additionally, 583 patients were exposed to VOLTAREN GEL in an uncontrolled, open-label, long-term safety trial in osteoarthritis of the knee. Of these, 355 patients were treated for osteoarthritis of 1 knee and 228 were treated for osteoarthritis of both knees. Duration of exposure ranged from 8 to 12 weeks for the placebo-controlled studies, and up to 12 months for the open-label safety trial.

Short-Term Placebo-Controlled Trials:

Adverse reactions observed in at least 1% of patients treated with VOLTAREN GEL: Non-serious adverse reactions that were reported during the short-term placebo-controlled studies comparing VOLTAREN GEL and placebo (vehicle gel) over study periods of 8 to 12 weeks (16 g per day), were application site reactions. These were the only adverse reactions that occurred in >1% of treated patients with a greater frequency in the VOLTAREN GEL group (7%) than the placebo group (2%).

Table 1 lists the types of application site reactions reported. Application site dermatitis was the most frequent type of application site reaction and was reported by 4% of patients treated with VOLTAREN GEL, compared to 1% of placebo patients.

Table 1. Non-serious Application Site Adverse Reactions (≥1% VOLTAREN GEL Patients) – Short-term Controlled Trials

	VOLTAREN GEL N=913	Placebo (vehicle) N=876
Adverse Reaction[†]	N (%)	N (%)
<i>Any application site reaction</i>	62 (7)	19 (2)
Application site dermatitis	32 (4)	6 (<1)
Application site pruritus	7 (<1)	1 (<1)
Application site erythema	6 (<1)	3 (<1)
Application site paresthesia	5 (<1)	3 (<1)
Application site dryness	4 (<1)	3 (<1)
Application site vesicles	3 (<1)	0
Application site irritation	2 (<1)	0
Application site papules	1 (<1)	0

[†]Preferred Term according to MedDRA 9.1.

In the placebo-controlled trials, the discontinuation rate due to adverse reactions was 5% for patients treated with VOLTAREN GEL, and 3% for patients in the placebo group. Application site reactions, including application site dermatitis, were the most frequent reason for treatment discontinuation.

Long-Term Open-Label Safety Trial:

In the open-label, long-term safety study, distribution of adverse reactions was similar to that in the placebo-controlled studies. In this study, where patients were treated for up to 1 year with VOLTAREN GEL up to 32 g per day, application site dermatitis was observed in 11% of patients. Adverse reactions that led to the discontinuation of the study drug were experienced in 12% of patients. The most common adverse reaction that led to discontinuation of the study was application site dermatitis, which was experienced by 6% of patients.

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	
<i>Clinical Impact:</i>	<ul style="list-style-type: none"> • 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.
<i>Intervention:</i>	Monitor patients with concomitant use of VOLTAREN 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 [<i>see Warnings and Precautions (5.11)</i>].
Aspirin	
<i>Clinical Impact:</i>	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. 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 [<i>see Warnings and Precautions (5.2)</i>].
<i>Intervention:</i>	Concomitant use of VOLTAREN GEL and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [<i>see Warnings and Precautions (5.11)</i>]. VOLTAREN GEL is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
<i>Clinical Impact:</i>	<ul style="list-style-type: none"> • 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.

<i>Intervention:</i>	<ul style="list-style-type: none"> • During concomitant use of VOLTAREN GEL and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of VOLTAREN 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 <i>Warnings and Precautions (5.6)</i>]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	During concomitant use of VOLTAREN GEL with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see <i>Warnings and Precautions (5.6)</i>].
Digoxin	
<i>Clinical Impact:</i>	The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
<i>Intervention:</i>	During concomitant use of VOLTAREN GEL and digoxin, monitor serum digoxin levels.
Lithium	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	During concomitant use of VOLTAREN GEL and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
<i>Clinical Impact:</i>	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
<i>Intervention:</i>	During concomitant use of VOLTAREN GEL and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
<i>Clinical Impact:</i>	Concomitant use of VOLTAREN GEL and cyclosporine may increase cyclosporine's nephrotoxicity.

<i>Intervention:</i>	During concomitant use of VOLTAREN GEL and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
<i>Clinical Impact:</i>	Concomitant use of diclofenac with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [<i>see Warnings and Precautions (5.2)</i>].
<i>Intervention:</i>	The concomitant use of diclofenac with other NSAIDs or salicylates is not recommended.
Pemetrexed	
<i>Clinical Impact:</i>	Concomitant use of VOLTAREN GEL and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
<i>Intervention:</i>	<p>During concomitant use of VOLTAREN 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.</p> <p>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.</p> <p>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.</p>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation

Risk Summary

Use of NSAIDs, including VOLTAREN GEL, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VOLTAREN GEL, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of VOLTAREN GEL in pregnant women. Human and animal studies indicate that diclofenac crosses the placenta. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, or rabbits given diclofenac during the period of organogenesis at doses up to approximately 5, 5, and 10 times, respectively, the maximum recommended topical dose of VOLTAREN GEL, despite the presence of maternal and fetal toxicity at these doses [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

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

Data

Animal data

Reproductive and developmental studies in animals demonstrated that diclofenac sodium administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose (MRHD) of VOLTAREN GEL based on bioavailability and body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 5 and 10 times the MRHD based on bioavailability and BSA comparison).

In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (approximately 1 and 2 times the MRHD based on bioavailability and BSA comparison) from Gestation Day 15 through Lactation Day 21, significant maternal toxicity (peritonitis, mortality) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.

8.2 Lactation

Risk Summary

Based on available data, diclofenac may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CATAFLAM and any potential adverse effects on the breastfed infant from the CATAFLAM 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).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including VOLTAREN GEL, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. 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 VOLTAREN GEL, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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 (5.1, 5.2, 5.3, 5.6, 5.13)*].

Of the total number of subjects treated with VOLTAREN GEL in clinical studies, 498 were 65 years of age and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, but greater sensitivity to the effect of NSAIDs in some older individuals cannot be ruled out.

Diclofenac, as with any NSAID, is known to be substantially excreted by the kidney, and the risk of toxic reactions to VOLTAREN GEL may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using VOLTAREN GEL in the elderly, and it may be useful to monitor renal function.

10 OVERDOSAGE

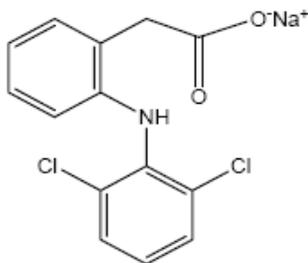
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

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.

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

11 DESCRIPTION

VOLTAREN GEL (diclofenac sodium topical gel) is a nonsteroidal anti-inflammatory drug (NSAID) for topical use only. The chemical name is 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$, and it has the following chemical structure:



It contains the active ingredient, diclofenac sodium, in an opaque, white gel base. Diclofenac sodium is a white to slightly yellow crystalline powder. Diclofenac sodium is a benzeneacetic acid derivative.

The inactive ingredients in VOLTAREN GEL include: carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diclofenac has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of VOLTAREN GEL, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin synthesis *in vitro*. Diclofenac concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

The pharmacokinetics of VOLTAREN GEL were assessed in healthy volunteers following repeated applications during 7 days of VOLTAREN GEL to 1 knee (4 x 4 g per day) or to 2 knees and 2 hands (4 x 12 g per day) versus the recommended oral dose of diclofenac sodium for the treatment of osteoarthritis (3 x 50 mg per day). A summary of the pharmacokinetic parameters is presented in Table 2.

Table 3. Pharmacokinetic Parameters and Comparison of VOLTAREN GEL to Oral Diclofenac Sodium Tablets After Repeated Administration

Treatment	C_{max} (ng/mL) Mean \pm SD % of Oral (CI)	T_{max} (hr) Median Range	AUC_{0-24} (ng·h/mL) Mean \pm SD % of Oral (CI)
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VOLTAREN GEL 4 x 4 g per day (=160 mg diclofenac sodium per day)	15 ± 7.3 0.6% (0.5-0.7)	14 (0-24)	233 ± 128 5.8% (5-6.7)
VOLTAREN GEL 4 x 12 g per day (=480 mg diclofenac sodium per day)	53.8 ± 32 2.2% (1.9-2.6)	10 (0-24)	807 ± 478 19.7% (17-22.8)
Diclofenac sodium tablets, orally 3 x 50 mg per day (=150 mg diclofenac sodium per day)	2270 ± 778 100%	6.5 (1-14)	3890 ± 1710 100%

C_{max} = maximum plasma concentration, t_{max} =time of C_{max} . AUC_{0-24} =area under the concentration time curve. SD=standard deviation. CI=confidence interval.

Systemic exposure (area under the concentration-time curve) and maximum plasma concentrations of diclofenac are significantly lower with VOLTAREN GEL than with comparable oral treatment of diclofenac sodium.

Systemic exposure with recommended use of VOLTAREN GEL (4 x 4 g per day applied to 1 knee) is on average 17 times lower than with oral treatment. (Basis: treatment with VOLTAREN GEL of 1 knee, 4 times a day versus 50 mg, 3 times a day of oral diclofenac tablets.) The amount of diclofenac sodium that is systemically absorbed from VOLTAREN GEL is on average 6% of the systemic exposure from an oral form of diclofenac sodium.

The average peak plasma concentration with recommended use of VOLTAREN GEL (4 x 4 g per day applied to 1 knee) is 158 times lower than with the oral treatment.

The pharmacokinetics of VOLTAREN GEL has been tested under conditions of moderate heat (application of a heat patch for 15 minutes prior to gel application) and of moderate exercise (first gel application followed by a 20-minute treadmill exercise). No clinically relevant differences of systemic absorption and of tolerability were found between applications of VOLTAREN GEL (4 x 4 g per day on 1 knee) with and under the conditions tested. However, the pharmacokinetics of VOLTAREN GEL were not tested under the condition of heat application following gel application. Therefore, concurrent use of VOLTAREN GEL and heat is not recommended.

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [see *Drug Interactions* (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day (approximately 0.5 and 1 times, respectively, the maximum recommended human topical dose of VOLTAREN GEL based on bioavailability and body surface area (BSA) comparison) resulted in no significant increases in tumor incidence.

In a dermal carcinogenicity study conducted in albino mice, daily topical applications of a diclofenac sodium gel product for two years at concentrations up to 0.035% diclofenac sodium (a

29-fold lower diclofenac sodium concentration than present in VOLTAREN GEL) did not increase neoplasm incidence.

In a photocarcinogenicity study conducted in hairless mice, topical application of a diclofenac sodium gel product at doses up to 0.035% diclofenac sodium (a 29-fold lower diclofenac sodium concentration than present in VOLTAREN GEL) resulted in an earlier median time of onset of tumors.

Mutagenesis

Diclofenac was not mutagenic or clastogenic in a battery of genotoxicity tests that included the bacterial reverse mutation assay, *in vitro* mouse lymphoma point mutation assay, chromosomal aberration studies in Chinese hamster ovarian cells *in vitro*, and *in vivo* rat chromosomal aberration assay of bone marrow cells.

Impairment of Fertility

Diclofenac did not affect male or female fertility in rats at doses up to 4 mg/kg/day (approximately 2 times than the maximum human topical dose of VOLTAREN GEL based on bioavailability and BSA comparison).

14 CLINICAL STUDIES

14.1 Pivotal Studies in Osteoarthritis of the Superficial Joints of the Extremities

Study 1 evaluated the efficacy of VOLTAREN GEL for the treatment of osteoarthritis of the knee in a 12-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial. VOLTAREN GEL was administered at a dose of 4 g, 4 times daily, on 1 knee (16 g per day). Pain as assessed by the patients at Week 12 using the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) Pain Subindex was lower in the VOLTAREN GEL group than the placebo group.

Study 2 evaluated the efficacy of VOLTAREN GEL for the treatment of osteoarthritis in subjects with osteoarthritis of the hand in an 8-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group study. VOLTAREN GEL was administered at a dose of 2 g per hand, 4 times daily, on both hands (16 g per day). Pain in the target hand as assessed by the patients at Weeks 4 and 6 on a visual analog scale from 0 to 100 was lower in the VOLTAREN GEL group than the placebo group.

Table 4. Efficacy outcomes of VOLTAREN GEL in Studies 1 and 2

		VOLTAREN GEL	Placebo (Vehicle)	Adjusted Difference (Placebo – VOLTAREN GEL)
Study 1 (Knee) WOMAC Pain^{**} at Week 12	Sample Size	127	119	
	Mean Outcome	28	37	$\Delta=7\ddagger$
	95% Confidence Interval			(1, 12)
Study 2 (Hand) Pain Intensity[#] at Week 4	Sample Size	198	187	
	Mean Outcome	43	50	$\Delta=7\ddagger$

	95% Confidence Interval			(2, 12)
Study 2 (Hand Pain Intensity# at Week 6)	Sample Size	198	187	
	Mean Outcome	40	47	$\Delta=7\ddagger$
	95% Confidence Interval			(1, 13)

* WOMAC = Western Ontario McMaster Osteoarthritis Index.

Scale from 0 (best) to 100 (worst).

† Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment and center and baseline covariate.

‡ Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment, center, indicator of pain in the CMC-1 joint, and baseline as a covariate, and the treatment-by-CMC-1 strata.

16 HOW SUPPLIED/STORAGE AND HANDLING

VOLTAREN GEL (diclofenac sodium topical gel, 1%) is available in tubes containing 100 grams of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%).

100 grams tube.....NDC 63481-684-47

Storage

Store at room temperature 68°F to 77°F (20°C to 25°C) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your VOLTAREN GEL.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) that accompanies each prescription dispensed. Patients, families, or their caregivers should be informed of the following information before initiating therapy with VOLTAREN GEL and periodically during the course of ongoing therapy.

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 (5.1)*].

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 (5.2)*].

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). If these occur, instruct patients to stop VOLTAREN GEL and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

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 (5.5)*].

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 (5.7)*].

Serious Skin Reactions

Advise patients to stop VOLTAREN GEL immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see *Warnings and Precautions (5.9)*].

Female Fertility

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

Fetal Toxicity

Inform pregnant women to avoid use of VOLTAREN GEL and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see *Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of VOLTAREN GEL with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see *Warnings and Precautions (5.2) 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 VOLTAREN GEL until they talk to their healthcare provider [see *Drug Interactions (7)*].

Eye Exposure

Instruct patients to avoid contact of VOLTAREN GEL with the eyes and mucosa, although not studied, should be avoided. Advise patients that if eye contact occurs, immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour [see *Warnings and Precautions (5.15)*].

Special Application Instructions

Instruct patients how to use the dosing card to measure the proper dose of VOLTAREN GEL to apply.

If the patient loses their dosing card, instruct them that they can call 1-1-855-297-3031 to request a replacement dosing card or ask their pharmacist for a new dosing card.

Instruct patients how to correctly measure the 2.25 inches (2 g) dose or 4.5 inches (4 g) dose while waiting for a replacement dosing card [see *Dosage and Administration (2.2)*].

Instruct patients not to apply VOLTAREN GEL to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug.

Instruct patients to avoid concomitant use of VOLTAREN GEL with other topical products, including sunscreens, cosmetics, lotions, moisturizers, and insect repellants. Concomitant use may result in skin reactions or change the absorption of VOLTAREN GEL.

Instruct patients to minimize or avoid exposure of treated areas to natural or artificial sunlight [*see Warnings and Precautions (5.14) and Dosage and Administration (2.4)*].

Comments or Questions?

Call toll-free 1-855-297-3031

Manufactured by:
GSK Consumer Healthcare
Warren, NJ 07059

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about 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 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 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 are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, 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. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

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.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”

- new or worse high blood pressure

- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life threatening allergic reactions
- **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 taking your NSAID 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

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

These are not all 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 for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured by: GSK Consumer Healthcare Warren, NJ 07059

Distributed by: Endo Pharmaceuticals Inc., Malvern, PA 19355

For more information call 1-800-XXX-XXXX

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: Feb 2018

Instructions for Use

VOLTAREN GEL (diclofenac sodium)
topical gel, 1%

Important: Use the dosing card that is inside the VOLTAREN GEL carton to correctly measure each dose. The dosing card is re-usable. Do not throw the dosing card away. Before you use VOLTAREN GEL for the first time, your healthcare provider or pharmacist should show you how to correctly measure your dose using the dosing card.

Read this **Instructions for Use** before you start using VOLTARENGEL and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider has prescribed VOLTAREN GEL to help relieve arthritis pain in some of your joints. VOLTAREN GEL may be used to treat arthritis pain in the arms (hands, wrists, and elbows) and in the legs (feet, ankles, and knees). It is not known if VOLTAREN GEL is safe and effective if used on your spine, hips, or shoulders.

- Use VOLTAREN GEL exactly how your healthcare provider prescribes it for you. Do not apply VOLTAREN GEL anywhere other than where your healthcare provider tells you to.
- **Do not use more than a total of 32 grams of VOLTAREN GEL each day. If you add up the amount of VOLTAREN GEL as directed by your healthcare provider, it should not be more than 32 grams in one day.**

The dose for your hands, wrists, or elbows is 2 grams of VOLTAREN GEL each time you apply it.

- Apply VOLTAREN GEL 4 times a day (a total of 8 grams each day). Do not apply more than 8 grams each day to any one of your affected hands, wrists, or elbows.

The dose for your feet, ankles, or knees is 4 grams of VOLTAREN GEL each time you apply it.

- Apply VOLTAREN GEL 4 times a day (a total of 16 grams each day). Do not apply more than 16 grams each day to any one of your affected feet, ankles, or knees.

Some examples of VOLTAREN GEL application include:

- If you use 2 grams of VOLTAREN GEL on one hand, 4 times a day, your total dose for one day is 8 grams.
- If you use 4 grams of VOLTAREN GEL on one knee, 4 times a day, your total dose for one day is 16 grams.
- Your total dose for one day, treating one hand and one knee, is 8 grams plus 16 grams, which equals 24 grams of VOLTAREN GEL.
- Before you use a new tube of VOLTAREN GEL for the first time: Unscrew cap and press the indent on the top of the cap (see Figure A) onto the star-shaped seal on the tube. Firmly turn the cap to remove the safety seal (see Figure B).

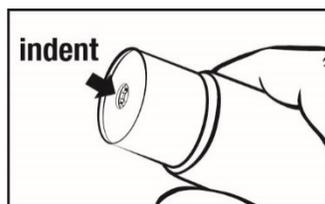
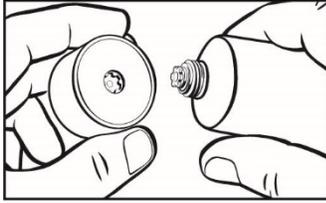
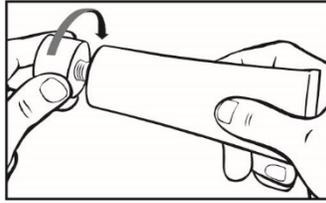


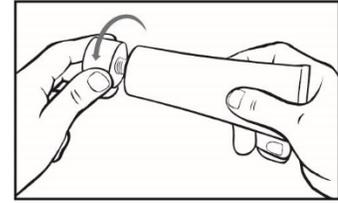
Figure A



1. Take the cap off the tube. Open the safety seal by firmly pressing the indent on the top of the cap onto the star-shaped seal on the tube.



2. Firmly turn the cap to remove the safety seal.
3. Do not open the safety seal with scissors or other sharp objects.



4. After use, put the cap back on the end of the tube and store in an upright position.

Figure B

- Remember to remove the dosing card from the carton to measure your dose (see Figure C).

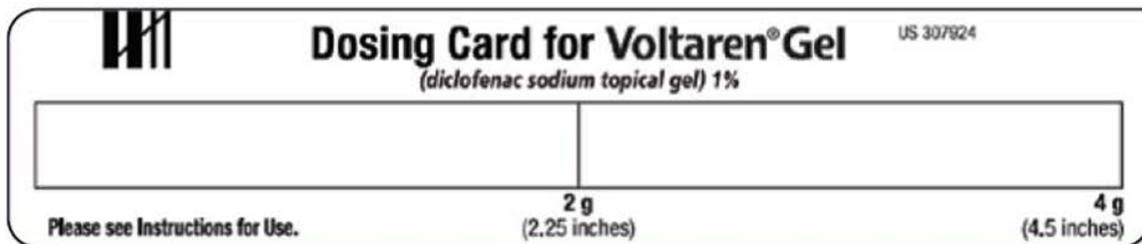


Figure C

- Apply VOLTAREN GEL to clean, dry skin that does not have any cuts, open wounds, infections, or rashes.
- Do not use heating pads or apply bandages to where you have applied VOLTAREN GEL.
- Avoid exposing skin where you apply VOLTAREN GEL to sunlight and artificial light, such as tanning booths.
- Do not use sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medicines on the same skin areas where you have applied VOLTAREN GEL.
- Do not get VOLTAREN GEL in your eyes, nose, or mouth. VOLTAREN GEL is only to be used on your skin (topical use). If you get VOLTAREN GEL in your eyes, rinse your eyes right away with water or saline. Talk with your healthcare provider if eye irritation lasts for more than one hour.

What if I miss a dose?

- If you miss a dose of VOLTAREN GEL, continue with your next scheduled dose using the prescribed amount of VOLTAREN GEL. **Do not double the dose.**

Applying 2 grams (2 g) of VOLTAREN GEL to hands, wrists, or elbows:

Step 1. Remove the dosing card that is attached inside the VOLTAREN GEL carton. Use the dosing card to correctly measure each dose of VOLTAREN GEL. To measure the correct amount of VOLTAREN GEL, place the dosing card on a flat surface so that you can read the print. If the print is backwards, flip dosing card over (see Figure A). If you lose or misplace your dosing card, you can ask your pharmacist for a new one or call. 1-855-297-3031. Ask your healthcare provider or pharmacist to show you how to correctly measure your dose of VOLTAREN GEL while you are waiting to receive your new dosing card.

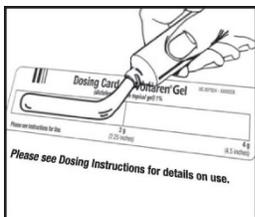


Figure D

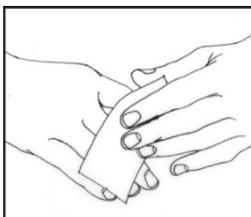


Figure E

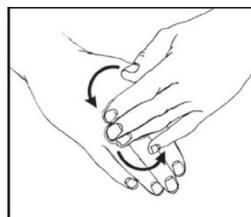


Figure F

Step 2. Squeeze VOLTAREN GEL onto the dosing card evenly, up to the 2 g line (a 2.25 inch length of gel). Make sure that the gel covers the 2 g area of the dosing card (see Figure D). Put the cap back on the tube of VOLTAREN GEL. Ask your healthcare provider or pharmacist if you are not sure how to correctly measure your dose of VOLTAREN GEL.

Step 3. Apply the gel to your hand, wrist, or elbow. You can use the dosing card to apply the gel (see Figure E). Then, use your hands to gently rub the gel into the skin (see Figure F). Do not share your dosing card with another person. Make sure to cover the entire affected hand, wrist, or elbow with the gel. Remember that the hand includes the palm of your hand, the top of your hand, and your fingers.

Step 4. After using the dosing card, hold end with fingertips, rinse and dry. **Store the dosing card until next use.** Do not shower or bathe for at least 1 hour after applying VOLTAREN GEL. Do not wash your treated hands for at least 1 hour after applying the VOLTAREN GEL.

Step 5. After applying VOLTAREN GEL, wait 10 minutes before covering the treated skin with gloves or clothing.

Applying 4 grams (4 g) of VOLTAREN GEL to feet, ankles, or knees:

Step 1. Refer to **Step 1** above.

Step 2. Squeeze VOLTAREN GEL onto the dosing card evenly up to the 4 g line (a 4.5 inch length of gel), making sure the gel covers the 4 g area of the dosing card (see Figure G). Put the cap back on the tube of VOLTAREN GEL. Ask your healthcare provider or pharmacist if you are not sure how to correctly measure your dose of VOLTAREN GEL.

Step 3. Apply VOLTAREN GEL to your foot, ankle, or knee. You can use the dosing card to apply the gel (see Figure H). Then, use your hands to gently rub the gel into the skin (see Figure I). Do not share your dosing card with another person. Make sure to cover your entire foot, ankle, or knee area with the gel. For example, cover the skin above, below, inside and outside the knee cap. Remember that the foot includes the sole of your foot, the top of your foot, and your toes.

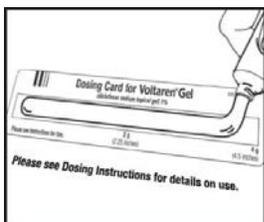


Figure G



Figure H



Figure I

Refer to Steps 4 and 5 above. Wash your hands after applying VOLTAREN GEL to your foot, ankle, or knee.

What are the ingredients in VOLTARENGEL?

Active ingredient: diclofenac sodium

Inactive ingredients: carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.

How should I store VOLTARENGEL?

- Store at 68°F to 77°F (20°C to 25°C).
- **Do not** freeze VOLTAREN GEL.
- Store the dosing card with your VOLTAREN GEL.

Keep VOLTAREN GEL, the dosing card, and all medicines out of the reach of children.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured by:
GSK Consumer Healthcare
Warren, NJ 07059

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Revised: Feb 2018

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/s/

SHARON H HERTZ
02/21/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022122Orig1s011

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022122/S-011

Name of Drug: VOLTAREN GEL (diclofenac sodium topical gel)

Applicant: GlaxoSmithKline Consumer Healthcare

Labeling Reviewed

Submission Date: August 21, 2017

Receipt Date: August 21, 2017

Background and Summary Description: On August 21, 2017, the applicant submitted a Prior Approval supplement. This supplemental application proposes the following: changes to the Instructions for Use to clarify the instructions for opening a tube of VOLTAREN GEL, and numerous minor additional changes to the package insert and carton and container labeling related to the removal of Sandoz and Novartis as business partners.

Review

The applicant proposed the following changes to the label:

HIGHLIGHTS

~~RECENT MAJOR CHANGES~~

~~Boxed Warning (b) (4)~~

~~Warnings and Precautions, Cardiovascular Thrombotic Events (5.1) (b) (4)~~

~~Warnings and Precautions, Heart Failure and Edema (5.5) (b) (4)~~

ADVERSE REACTIONS

**To report SUSPECTED ADVERSE REACTIONS, contact ~~Sandoz~~
~~the GlaxoSmithKline Consumer Healthcare at . at 1-800-525-87471-~~
~~855- 297-3031~~ or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.**

FULL PRESCRIBING INFORMATION

17 PATIENT COUNSELING INFORMATION

Special Application Instructions

If the patient loses their dosing card, instruct them that they can call 1-800-398-5876-1-855-297-3031 to request a replacement dosing card or ask their pharmacist for a new dosing card.

Comments or Questions?

Call toll-free 1-855-297-3031

~~1-800-398-5876~~

Marketed

Distributed by: Endo

Pharmaceuticals Inc.

Malvern, PA 19355

Manufactured by:

GSK Consumer

Healthcare Warren,

NJ 07059

~~Novartis Pharma Produktions~~

~~GmbH, Wehr, Germany for~~

~~Sandoz Inc., Princeton, NJ 08540~~

Revised:  (b) (4)

The Applicant proposed the following changes to the MEDICATION GUIDE

Marketed

Distributed by: Endo

Pharmaceuticals Inc

Malvern, PA 19355

Manufactured by:

GSK Consumer

Healthcare Warren,

NJ 07059

~~Novartis Pharma Produktions~~

~~GmbH, Wehr, Germany for~~

~~Sandoz Inc., Princeton, NJ 08540~~

GlaxoSmithKline Consumer Healthcare

Revised:  (b) (4)

The Applicant proposed the following changes to the Instructions for Use

Before you use a new tube of VOLTAREN® GEL for the first time Unscrew cap, press the indent on the (b) (4) of the cap onto the star-shaped seal on the tube. Firmly turn the cap to remove the safety seal..

Applying 2 grams (2 g) of VOLTAREN® GEL to hands, wrists, or elbows:

Step 1. Remove the dosing card that is attached inside the VOLTAREN® GEL carton. Use the dosing card to correctly measure each dose of VOLTAREN® GEL. To measure the correct amount of VOLTAREN® GEL, place the dosing card on a flat surface so that you can read the print. If the print is backwards, flip dosing card over (see Figure A). If you lose or misplace your dosing card, you can ask your pharmacist for a new one or call ~~1-800-452-0051~~, 1-855-297-3031. Ask your healthcare provider or pharmacist to show you how to correctly measure your dose of VOLTAREN® GEL while you are waiting to receive your new dosing card.

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Manufactured by:

GSK Consumer Healthcare

Warren, NJ 07059

(b) (4)

After Review, the Division sent the following recommendation to the Applicant on January 26, 2018:

Instructions For Use:

1. We recommend adding a labeled figure (Figure B) showing the tube with the cap in place, and labeling the indent so that patients can locate it prior to removing the cap. Reference the figure in the adjacent text. We discussed this recommendation with DMEPA and they concur.
2. We recommend adding a labeled figure (Figure C) showing how to correctly place and turn the cap to remove the safety seal from the tube. Reference the figure in the adjacent text. We discussed this recommendation with DMEPA and they concur.
3. Revise the sequential lettering of the additional existing figures in the IFU.
4. We revised the temperature range to state the °F first, and then the °C in parentheses since in the U.S. patients are more familiar with °F.

Professional Sample Carton Labeling for Voltaren Gel

1. Add the statement, "Use the Dosing Card Attached Inside Carton," to the principal display panel (PDP) for consistency with the PDP of the prescription carton.

2. Add the statement, "Store the dosing card with your Voltaren Gel," to the storage statement on the back panel for consistency with the back panel of the prescription carton.

On February 1, 2018, the Sponsor responded and agreed to all the Division's proposed changes. (b) (4)

The Following was sent to the Sponsor on February 7, 2018:

1. (b) (4)

Full Prescribing Information for Voltaren Gel

2. In response to our information request dated September 5, 2017, you stated that you plan to discontinue the 3-pack (3 tubes containing 100 g each) and 5-pack (5 tubes containing 100 g each) packaging configurations. Thus, we recommend removing these packaging configurations from the *How Supplied* section for accuracy.

The sponsor responded and agreed to the changes on February 8, 2018.

Recommendations

Supplement 11 should be approved

Mavis Darkwah	February 20, 2018
Regulatory Project Manager	Date
Matt Sullivan	Feb 20, 2018
Chief, Project Management Staff	Date

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/s/

MAVIS Y DARKWAH
02/21/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 6, 2018

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 022122/S-011

Product Name and Strength: Voltaren Gel (diclofenac sodium topical gel), 1%

Applicant/Sponsor Name: GlaxoSmithKline Consumer Healthcare (GSKCH)

FDA Received Date: February 1, 2018

OSE RCM #: 2017-1755-1

DMEPA Safety Evaluator: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised carton labeling and prescribing information for Voltaren Gel (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton labeling for Voltaren Gel is acceptable from a medication error perspective. However, the revised prescribing information is unacceptable from a medication error perspective. The Applicant did not revise the *How Supplied* section to remove the 3-pack (3 tubes containing 100 g each) and 5-pack (5 tubes containing 100 g each) packaging configurations, which the Applicant indicated they plan to discontinue in response to our information request dated September 5, 2017.

^a Shah M. Label and Labeling Review for Voltaren Gel (NDA 022122/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 02. RCM No.: 2017-1755.

3 RECOMMENDATIONS FOR GLAXOSMITHKLINE CONSUMER HEALTHCARE (GSKCH)

We recommend the following be implemented prior to approval of this supplement:

A. Full Prescribing Information for Voltaren Gel

1. In response to our information request dated September 5, 2017, the Applicant stated that they plan to discontinue the 3-pack (3 tubes containing 100 g each) and 5-pack (5 tubes containing 100 g each) packaging configurations. Thus, we recommend removing these packaging configurations from the *How Supplied* section for accuracy.

4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MILLIE C BRAHMBHATT
02/06/2018

OTTO L TOWNSEND
02/06/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 29, 2017

To: Sharon Hertz, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Koung Lee, RPh, MSHS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): VOLTAREN Gel (diclofenac sodium topical gel)
DICLOFENAC SODIUM

Dosage Form and Route: topical gel, 1% for topical use only

Application Type/Number: NDA 022122

Supplement Number: S-011

Applicant: GlaxoSmithKline Consumer Healthcare

1 INTRODUCTION

On August 21, 2017, GlaxoSmithKline Consumer Healthcare (GSKCH) submitted for the Agency's review a Prior Approval Supplement (PAS)- Labeling to their approved New Drug Application (NDA) 022122/S-011 for VOLTAREN Gel (diclofenac sodium topical gel), 1% and the authorized generic product DICLOFENAC SODIUM topical gel, 1%. In this supplement, the Applicant proposes the following:

- Minor labeling changes to support this change in control from Sandoz to GSKCH
- Removal of the summary of major changes in the label
- Removal of trademarks from the current packaging
- The addition of a serialization code location to the exterior 100g cartons
- A minor change to the instructions on how to break the seal on the tube with a cap
- Removal of Novartis as a manufacturing site.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on August 28, 2017, and November 15, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for VOLTAREN gel (diclofenac sodium topical gel), 1% and for the authorized generic product DICLOFENAC SODIUM topical gel, 1%.

A separate DMEPA review of the IFU was completed on November 2, 2017.

2 MATERIAL REVIEWED

- Draft VOLTAREN Gel (diclofenac sodium topical gel), 1% MG and IFU received on August 21, 2017, and received by DMPP on November 15, 2017.
- Draft DICLOFENAC SODIUM topical gel), 1% MG and IFU received on August 21, 2017, and received by DMPP on November 15, 2017.
- Draft VOLTAREN Gel (diclofenac sodium topical gel), 1% PI received on August 21, 2017, revised throughout the review cycle and, received by DMPP on November 15, 2017.
- Draft DICLOFENAC SODIUM topical gel), 1% PI received on August 21, 2017, revised throughout the review cycle, and received by DMPP on November 15, 2017.
- Draft VOLTAREN GEL (diclofenac sodium topical gel), 1% Prescribing Information (PI), MG, and IFU received on August 21, 2017, and received by OPDP on November 15, 2017.
- Draft DICLOFENAC SODIUM topical gel, 1% PI, MG, and IFU received on August 21, 2017, and received by OPDP on November 15, 2017.

- Approved VOLTAREN GEL (diclofenac sodium topical gel), 1% labeling dated May 9, 2016

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/29/2017

KOUNG U LEE
11/29/2017

LASHAWN M GRIFFITHS
11/29/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 28, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction (DAAAP)

Mavis Darkwah, PharmD, Regulatory Project Manager, DAAAP

Lisa Basham, MS, Associate Director for Labeling, DAAAP

From: Koung Lee, RPh, MSHS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for Voltaren Gel (diclofenac sodium topical gel), 1% and Authorized Generic

NDA: 22122/Supplement 011

In response to DAAAP's consult request dated November 15, 2017, OPDP has reviewed the proposed prescribing information (PI), Medication Guide and Instructions for Use (IFU) labeling for Voltaren Gel (diclofenac sodium topical gel) 1% and its authorized generic. This supplement (S-011) provides for revised labeling to reflect revisions to the IFU and carton and container labeling change in company names.

PI: OPDP has reviewed the attached proposed PI's and we do not have any comments. The PI's were received by electronic mail from DAAAP on November 15, 2017.

Medication Guide and IFU:

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the sponsor to the electronic document room on August 21, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (301) 240-8686 or by email at Koung.lee@fda.hhs.gov.

61 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KOUNG U LEE
11/28/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 2, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 022122/S-011
Product Name and Strength:	Voltaren Gel (diclofenac sodium topical gel), 1%
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	GlaxoSmithKline Consumer Healthcare (GSKCH)
Submission Date:	August 21, 2017
OSE RCM #:	2017-1755
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review provides a response to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for our evaluation of the proposed container label and carton labeling for Voltaren Gel (diclofenac sodium topical gel) and the authorized generic from a medication error perspective. The Applicant submitted a prior approval labeling supplement (S-011) with the following:

- Minor labeling changes to support this change in control from Sandoz to GSKCH
- Removal of the summary of major changes in the label
- Removal of trademarks from the current packaging
- The addition of a serialization code location to the exterior 100 g cartons
- A minor change to the instructions on how to break the seal on the tube with a cap.
- Removal of Novartis as a manufacturing site.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other-DMEPA Information Request and Response	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas that can be improved.

Container Label and Carton Labeling

Our review of the professional sample carton labeling identified that the statement, “Use the Dosing Card Attached Inside Carton,” is missing from the principal display panel (PDP), which is present on the PDP of the prescription carton. Additionally, we identified that the statement, “Store the dosing card with your Voltaren Gel,” is missing from the storage statement on the back panel, which is present on the prescription carton. Thus, we recommend adding these

statements to the professional sample carton labeling to ensure consistency with the prescription carton and to minimize the risk for administration errors.

Prescribing Information (PI) and Instructions for Use (IFU)

In response to our information request, the Applicant stated that they plan to discontinue the 3-pack (3 tubes containing 100 g each) and 5-pack (5 tubes containing 100 g each) packaging configurations (see Appendix F). Thus, we recommend removing these packaging configurations from the *How Supplied* section of the Voltaren Gel PI for accuracy.

Our review of the IFU determined that the revised instructions to open the tube are acceptable from a medication error perspective.

Postmarketing Surveillance

We previously completed a review in 2012 in response to the CBE-30 supplement proposing the addition of the statement, [REDACTED] ^{(b) (4)} to the Principal Display Panel of the carton labeling. During our previous review, we identified wrong technique medication errors and made recommendations to address these wrong technique errors that involved patients not using the dosing card to measure the correct dose of Voltaren Gel. In response, the Applicant added the statement, “Use the Dosing Card Attached Inside Carton” to the principal display panel of the carton labeling.^a In our previous review, we also recommended the Applicant remove the dosing card from the inside wall of the carton labeling and allow it to be loose within the carton. At that time, the Applicant stated that it was not technically possible to remove the dosing card from the inside of the carton labeling from a production standpoint.^b Since our previous review, our FAERS search determined that we continue to receive hundreds of medication errors related to patients not using the dosing card to measure the correct dose (See Appendix F). Failure to use the dosing card to measure the correct dose may result in an overdose or underdose; however, the reports do not indicate a severe adverse event or outcome associated with the medication error. Thus, we do not have compelling evidence to recommend revisions to labeling or the user interface at this time.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS FOR THE DIVISION

We revised the *How Supplied* section of the Full Prescribing Information (PI) and provided a detailed summary below for review and consideration by DAAAP.

^a Baugh, D. Label and Labeling Review for Voltaren Gel NDA 22122/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012-AUG-30. RCM No 2012-1411.

^b Baugh, D. Label and Labeling Review for Voltaren Gel NDA 22122/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013-MAR-28. RCM No 2012-1411.

A. Full Prescribing Information

1. In response to our information request, the Applicant stated that they plan to discontinue the 3-pack (3 tubes containing 100 g each) and 5-pack (5 tubes containing 100 g each) packaging configurations (see Appendix F). Thus, we recommend removing these packaging configurations from the *How Supplied* section for accuracy.

4.2 RECOMMENDATIONS FOR GLAXOSMITHKLINE CONSUMER HEALTHCARE (GSKCH)

We recommend the Applicant implement the following prior to approval of this supplement:

A. Professional Sample Carton Labeling for Voltaren Gel

1. Add the statement, "Use the Dosing Card Attached Inside Carton," to the principal display panel (PDP) for consistency with the PDP of the prescription carton.
2. Add the statement, "Store the dosing card with your Voltaren Gel," to the storage statement on the back panel for consistency with the back panel of the prescription carton.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Voltaren Gel (diclofenac sodium topical gel) that GlaxoSmithKline Consumer Healthcare (GSKCH) submitted on August 21, 2017.

Table 2. Relevant Product Information for Voltaren Gel (diclofenac sodium topical gel)	
Initial Approval Date	October 17, 2007
Active Ingredient	Diclofenac sodium
Indication	relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.
Route of Administration	topical
Dosage Form	Gel
Strength	1%
Dose and Frequency	4 g to the affected foot, ankle, or knee 4 times daily 2 g to the affected hand, wrist, or elbow 4 times daily.
How Supplied	100 g tube 3 Pack (3 Tubes containing 100 g each) 5 Pack (5 Tubes containing 100 g each)
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your VOLTAREN® GEL
Container Closure	Collapsible lacquer-lined aluminum tube with a membrane (blind-end), the tubes are closed with (b) (4) screw cap with a built-in-point to pierce the aluminum seal and a crimp sealant ring. A rigid, plastic reusable dosing stick with demarcated 2 and 4 gram lines printed for dose measurement is also included.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 8, 2017, we searched DMEPA’s previous reviews using the term, Voltaren. Our search identified five previous reviews^{c,d,e,f,g,h,i} and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 8, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria in Table 3 below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

Table 3. ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care and Community/Ambulatory Care
Search Strategy and Terms	Match Exact Word or Phrase: Voltaren

D.2 Results

Our search did not result in any newsletter articles that described medication errors or actions possibly associated with the label and labeling.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

^c Fava, W. Label and Labeling Review for Voltaren Gel NDA 22122. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2007-APR 25. RCM No 2007-790.

^d Miller, C. Label and Labeling Review for Voltaren Gel NDA 22122. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009-JUN 25. RCM No 2009-418.

^e Maslov, Y. Label and Labeling Review for Voltaren Gel NDA 22122. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010-DEC 2. RCM No 2010-1936.

^f Baugh, D. Label and Labeling Review for Voltaren Gel NDA 22122/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012-AUG-30. RCM No 2012-1411.

^g Baugh, D. Label and Labeling Review for Voltaren Gel NDA 22122/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013-MAR-28. RCM No 2012-1411.

^h Borders-Hemphill, V. Label and Labeling Review for Voltaren Gel NDA 22122. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014-JUN-26. RCM No 2012-1411.

ⁱ Schlick, J. Label and Labeling Review for Voltaren Gel NDA 22122/S-009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015-APR-30. RCM No 2015-918.

On September 21, 2017, we searched FAERS using the criteria in Table 4 below and identified 2,330 cases. We downloaded the cases to Excel, and limited them to 580 cases that reported the dosage form as 'gel' (e.g., diclofenac gel or Voltaren gel).

Table 4. Criteria used to search FAERS	
Search Field	Search Terms
Initial FDA Receive Dates:	01/01/2014 to 09/01/2017
Product Active Ingredient:	Diclofenac or Diclofenac Sodium
Drug Role:	Primary Suspect
Preferred Terms (PTs):	Wrong technique in product usage process, Incorrect dose administered, Incorrect dosage administered*
Country (Derived):	USA

*We limited our search to these PTs because our weekly review of medication errors associated with Voltaren gel found these were the PTs usually associated with not using the dosing card.

E.2 Results

Our search identified that we continue to receive medication error reports associated with the following Preferred Terms:

Table 5. U.S. FAERS Case Counts for Diclofenac or Diclofenac Sodium Gel for Select Medication Error Preferred Terms (PT), 01Jan2014 to 01Sep2017, n=580 cases					
Preferred Term	FAERS Case Counts by Initial FDA Receive Date*				
	2014	2015	2016	2017 (to 01Sep2017)	Total
Wrong technique in product usage process	42	146	163	71	422
Incorrect dose administered	11	22	58	27	118
Incorrect dosage administered	1	0	43	43	87

*Numbers may not sum because a case may be coded with more than one PT

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded

using the FAERS Product Dictionary. More information about FAERS can be found at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX F. OTHER-DMEPA INFORMATION REQUESTS AND RESPONSES

On September 5, 2017, to help us evaluate the packing configurations that the Applicant intends to market, we issued an Information Request to GlaxoSmithKline Consumer Healthcare. Relevant findings from the firm's response are listed below. The entire response is available from:

<\\cdsesub1\evsprod\nda022122\0252\m1\us\cover-letter.pdf>

- The Applicant indicated they will discontinue and delist both the 3 and 5 pack counts

On October 18, 2017, to help us evaluate the wrong technique medication errors of patients not using the dosing card, we issued an Information Request to GlaxoSmithKline Consumer Healthcare. The firm responded via electronic mail and the text of their response is below:

Packaging Characteristics

- *The manufacturer (Novartis) currently has the dosing card glued into the carton by the carton supplier (b) (4). There has been no changes to this process in years.*
- *It is important to note the following packaging labeling also addresses this attachment issue.*
- *The carton's primary display panel and the back panel both has a prominent statement on the bottom that states the following: **Use the Dosing Card attached Inside Carton.***
- *There is a thumb like perforation in the PDP panel of the carton that allows the consumer to have easy access to the inside of the carton.*
- *Please refer to the attached scanned document of the current Rx product. The document shows both back and front panels of the current carton. You can see the statements and the perforation for access.*

Request for Sample Supply

- *I have arranged for a shipment directly to your address previously provided. Endo will ship 3 x 100gm cartons we currently sell in the US. I am not sure of the timings but will notify you once I know more.*

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^j along with postmarket medication error data, we reviewed the following Voltaren Gel (diclofenac sodium topical gel) and authorized generic labels and labeling submitted by GlaxoSmithKline Consumer Healthcare (GSKCH) on August 21, 2017.

- Container Label
- Carton Labeling
- Professional Sample Container Label
- Professional Sample Carton Labeling
- Dosing Card
- Prescribing Information

G.2 Label and Labeling Images

Voltaren Gel Container Label

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^j Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MILLIE C BRAHMBHATT
11/02/2017

OTTO L TOWNSEND
11/02/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022122Orig1s011

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: [Darkwah, Mavis](#)
To: dan.p.keravich@gsk.com
Subject: NDA 022122 S-011 Labeling
Date: Friday, January 26, 2018 3:05:00 PM
Attachments: [draft-labeling-branded FDA 26Jan18.doc](#)
[draft-labeling-generic FDA 26Jan18.doc](#)
[diclofenac sodium \(Voltaren gel \) branded IFU NDA 022122 S-011 FDA 26Jan18.docx](#)
[diclofenac sodium \(Voltaren Gel\) MG branded NDA 022122 S-011 FDA 26Jan18.docx](#)
[Diclofenac Sodium IFU generic NDA 022122 S-011 FDA 26Jan18 \(2\).docx](#)
[Diclofenac sodium MG generic NDA 022122 S-011 FDA 26Jan18.docx](#)
Importance: High

Dear Dan,

Refer to your Supplement 11, submitted on August 21, 2017, for Voltaren. Attached please find the word version of the PI, MG, and IFU with our proposed changes. We have accepted your proposed changes we agree with, and rejected the proposed changes we do not agree with. Please return a version of the PI, MG, and IFU with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word versions. Additionally, we have the following comments and recommendations:

Professional Sample Carton Labeling for Voltaren Gel

1. Add the statement, "Use the Dosing Card Attached Inside Carton," to the principal display panel (PDP) for consistency with the PDP of the prescription carton.
2. Add the statement, "Store the dosing card with your Voltaren Gel," to the storage statement on the back panel for consistency with the back panel of the prescription carton.

We request a response as soon as possible, preferably by close of business February 1, 2018.

Let me know if there are any questions.

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
02/14/2018

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Mavis Darkwah, PharmD, for Sharon Hertz, M.D., Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), HFD-170
---------------------------------	---

REQUEST DATE: 11/15/17	IND NO.	NDA/BLA NO. NDA 022122/S-011	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) sNDA Labeling supplement
----------------------------------	---------	---------------------------------	---

NAME OF DRUG: Voltaren Gel (diclofenac sodium) topical gel, 1%	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 11/29/2017
--	-------------------------------------	------------------------	---

NAME OF FIRM: GlaxoSmithKline Consumer Healthcare	PDUFA Date: February 21, 2018.
---	--------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
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EDR link to submission:

EDR Location: <\\CDSESUB1\evsprod\NDA022122\022122.enx>

EDR Location: <\\CDSESUB1\evsprod\NDA022122\0251>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, “substantially complete” labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: The sponsor submitted labeling supplement, Supp-011, which proposes a change to the Instructions for Use on how to break the seal on the tube with a cap, and revision to Carton & Container labeling. DAAAP requests review of these propose changes.

SIGNATURE OF REQUESTER
Mavis Y. Darkwah, PharmD
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 240-402-3158
Email: Mavis.darkwah@fda.hhs.gov

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
 eMAIL

HAND

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/s/

MAVIS Y DARKWAH
11/15/2017

From: [Dan Keravich](#)
To: [Darkwah, Mavis](#)
Subject: RE: NDA 22122 S-011 Information Request
Date: Friday, October 20, 2017 4:36:22 PM
Attachments: [image004.png](#)
[image001.png](#)
[PDP and Back Carton image.pdf](#)

Mavis

I wanted to update you on the status of the information request from the DMEPA reviewer regarding the attachment of dosing card. I am confident this information is what was requested.

Packaging Characteristics

- The manufacturer (Novartis) currently has the dosing card glued into the carton by the carton supplier (b)(4). There has been no changes to this process in years.
- It is important to note the following packaging labeling also addresses this attachment issue.
 - The carton's primary display panel and the back panel both has a prominent statement on the bottom that states the following: **Use the Dosing Card attached Inside Carton**
 -
 - There is a thumb like perforation in the PDP panel of the carton that allows the consumer to have easy access to the inside of the carton.

Please refer to the attached scanned document of the current Rx product. The document shows both back and front panels of the current carton. You can see the statements and the perforation for access.

Request for Sample Supply

- I have arranged for a shipment directly to your address previously provided. Endo will ship 3 x 100gm cartons we currently sell in the US. I am not sure of the timings but will notify you once I know more.

Please advise of next steps and if a teleconference is warranted or needed.

Best regards
Dan

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, October 18, 2017 12:04 PM
To: Dan Keravich <Dan.P.Keravich@gsk.com>
Subject: RE: NDA 22122 S-011 Information Request
Importance: High

EXTERNAL

Dan,

We have received postmarketing reports of patients not using the dosing card to measure the correct dose of Voltaren Gel, which results in overdose or underdose medication errors. Some patients indicate that the root cause of not using the dosing card is because they did not see the dosing card in the carton. Therefore, we request you submit the carton and dosing card in your proposed configuration for our review. If this is not possible, clarify the configuration of the dosing card within the carton. Is the dosing card glued to the inside wall of the carton or is it located freely in the carton? Given our review timelines, we request your response no later than October 23, 2017.

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

From: Dan Keravich [<mailto:Dan.P.Keravich@gsk.com>]
Sent: Tuesday, October 17, 2017 1:38 PM
To: Darkwah, Mavis <Mavis.Darkwah@fda.hhs.gov>
Subject: RE: NDA 22122 S-011 Information Request

Mavis

As discussed in our informal teleconference yesterday, we are requesting additional clarity on how to proceed with this second request for information. GSKCH is somewhat confused with this new request. We need some additional clarity on the needs of the reviewer and the reviewer's intent of verifying the adequacy of the opening instructions. Please note that GSKCH submitted exactly what was requested initially. The sample blank tubes allow the reviewer to physically see the proposed tube and cap in order to address the adequacy of the new directions for opening the product.

Could you please pass these following comments to the reviewer in order to help us understand the issues and requirements to finish the review.

1. Request to submit 3 sample tubes (container) and cartons: GSKCH has submitted 3 empty tubes directly from the manufacturing line for Voltaren Gel that GSKCH markets in other

countries. GSKCH sells Voltaren Gel in a different salt formulation to over 46 countries, and this tube and cap is currently approved in many of those countries. These empty tubes we believe were sufficient for the reviewer to verify that the instructions in the PIL and the proposed label did make sense, were valid and complete. Translations of the language is not helpful here since I am not sure which country this comes from and in some countries, the directions on how to open the tube may not be provided in either the carton or tube label.

2. Request to submit the Dosing Cards- The dosing card was not initially requested in the first IR request. It is important to note the dosing card was not submitted in the PAS since it will not change and we will use the same dosing card that is currently in the approved NDA. It is unclear why the dosing card is needed to be re-reviewed. Can the reviewer please provide comments as to why the dosing cards are needed?
3. Please resubmit the sample container, carton, and dosing card in English. This request is confusing since the Agency has received the proposed artwork for the tube (container) and carton in English within this submission. The Agency has the currently approved carton and tube labels in the ECTD. There is not a supply of sample finished products yet available with the new proposed label components. GSKCH will not have finished product available until the PAS is approved. We are not able to send you Voltaren Gel finished product from other countries since the product is technically unapproved. In all but 2 countries, diclofenac gel is marketed as a different salt and not the sodium salt which is the only salt approved in the US. We could provide you with the current labeling with opening instructions in English from the product we market in Canada which also uses this same tube and cap if requested. One option we have is to have this request contracted out and provide some makeshift versions- again this takes time and we would respectfully ask why this is needed.
 - To note: This is the first time GSK has seen this type of formal request for preprinted sample products with the proposed labeling as part of a PAS review on an established product. Is this something that industry should expect moving forward? As a post FDACDER reviewer/project manager, this type of request is also news to me.

GSKCH would like to propose another source of information that may be helpful in the review.

Option 1: Reliance on a Reference Product: Opening instructions are already approved as NDAs

If the goal of the reviewer is to verify the accuracy of the proposed opening instructions for this tube and cap with the star seal, we refer the reviewer to NDA 202736. This same tube and cap with the star seal is currently approved and marketed commercially in the US by Sanofi Pasteur and Arbor Pharmaceuticals under the Trade name Sklice (ivermectin) Lotion, 0.5% for topical use. The product has been marketed since 2012. I have attached the products PIL and opening instructions below for opening the product. Please note that Sanofi's and Arbors Pharmaceuticals NDA does not have any instructions for opening on the tube or container label. The opening instructions are only embedded in the PIL (page 8). The products label and opening instructions can also be reviewed within dailymed.

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4c5557cd-c4cf-11df-851a->

Sklice: Opening Instructions in PIL

Figure A



Use the top of cap to break the tamper seal on the tube (see [Figure A](#))

GSKCH's Opening Instructions

PIL

- Before you use a new tube of (b) (4) for the first time, unscrew cap, press the indent on the (b) (4) of the cap onto the star-shaped seal on the tube. Firmly turn the cap to remove the safety seal.

Container (tube) label

To open tube: Unscrew cap, press the indent on the (b) (4) of the cap onto the star-shaped seal on the tube. Firmly turn the cap to remove the safety seal

GSKCH is confident that the proposed opening instructions is sufficient to accurately inform consumers on how to open the tube using the cap to break the seal. If the proposed new instructions for opening the tube with the cap is found to be incomplete or insufficient, (b) (4)

(b) (4) We would commit to making this change and submitting this change with the FPL.

GSKCH is requesting a teleconference between the DMEPA reviewer and GSKCH to resolve the reviewers needs for additional information is the informal correspondence does not adequately address the reviewers request.

Best regards,
Dan Keravich

Dan Keravich, RPh., MSc., MBA., RAC
Director, US OTC Switch and Regulatory Policy
Global Regulatory Affairs
GSK Consumer Healthcare
Email Dan.P.Keravich@gsk.com
Mobile +443 745 4200



From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Thursday, October 12, 2017 1:53 PM
To: Dan Keravich <Dan.P.Keravich@gsk.com>
Subject: RE: NDA 22122 S-011 Information Request
Importance: High

EXTERNAL

Dear Dan,

The dosing cards were not included. Resubmit the sample container and carton with the dosing card for all of the package configurations you are proposing. Also, the language on the submitted container is not in English. Please resubmit the sample container, carton, and dosing card in English.

Regards,

Mavis

From: Darkwah, Mavis
Sent: Wednesday, October 11, 2017 11:17 AM
To: 'Dan Keravich'
Subject: RE: NDA 22122 S-011 Information Request

Dear Dan,

This is to confirm receipt of the package.

Regards,

Mavis

From: Dan Keravich [<mailto:Dan.P.Keravich@gsk.com>]
Sent: Friday, October 06, 2017 11:26 AM
To: Darkwah, Mavis
Subject: RE: NDA 22122 S-011 Information Request

Mavis

Just a FYI, I was informed by my packaging team that the tubes you requested were being shipped today from Europe. We have used either UPS/Fedex parcel carrier, and not the mail system. I would guess you will get them by Monday or Tuesday next week.

Best regards

Dan

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]

Sent: Tuesday, October 03, 2017 8:42 AM

To: Dan Keravich <Dan.P.Keravich@gsk.com>

Subject: RE: NDA 22122 S-011 Information Request

Importance: High

EXTERNAL

Dear Dan,

Per the reviewer, the actual tube with cartons for all package configurations that you are proposing needs to be submitted. The instructions were changed to open the tube and we need to make sure the instructions are clear. The tubes can be empty or contain placebo.

Regards,

Mavis

From: Dan Keravich [<mailto:Dan.P.Keravich@gsk.com>]

Sent: Monday, October 02, 2017 3:23 PM

To: Darkwah, Mavis

Subject: RE: NDA 22122 S-011 Information Request

Mavis

Apologies, was off on Friday!

Can you please advise and let me know what do you mean by samples?

Do you mean 20gm product (3) or 3 empty cartons of the 20gm and 100gm

Sorry, I want to make sure we get this right!

Thanks

Dan

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Thursday, September 21, 2017 10:44 AM
To: Dan Keravich <Dan.P.Keravich@gsk.com>
Subject: NDA 22122 S-011 Information Request
Importance: High

EXTERNAL

Dear Mr. Keravich,

Please provide 3 samples of Voltaren (NDA 022122/S-011) with the proposed changes for review as soon as possible. Send the samples to:

Mavis Y. Darkwah, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3111
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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/s/

MAVIS Y DARKWAH
10/24/2017

From: Darkwah, Mavis
To: ["dan.p.keravich@gsk.com"](mailto:dan.p.keravich@gsk.com)
Subject: NDA 22122 S-011
Date: Tuesday, September 05, 2017 4:16:00 PM
Importance: High

Dear Mr. Keravich,

We refer to your submission dated August 21, 2017 for Voltaren Gel (NDA 022122/S-011). We request you submit the carton labeling for the 3-pack and 5-pack configurations for our review. Given our review timelines, we request a response no later than September 12, 2017.

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

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/s/

MAVIS Y DARKWAH
09/05/2017



NDA 022122/S-011

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

GlaxoSmithKline Consumer Healthcare
184 Liberty Corner Rd, Suite 200
Warren, NJ 07059

Attention: Dan Keravich
Director, Regulatory Affairs

Dear Mr. Keravich:

We have received your supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022122
SUPPLEMENT NUMBER: S-011
PRODUCT NAME: VOLTAREN GEL (diclofenac sodium topical gel)
DATE OF SUBMISSION: August 21, 2017
DATE OF RECEIPT: August 21, 2017

This supplemental application proposes the following: changes to the Instructions for Use to clarify the instructions for opening a tube of VOLTAREN GEL, and numerous minor additional changes to the package insert and carton and container labeling related to the removal of Sandoz and Novartis as business partners.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 20, 2017, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be February 21, 2018.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Mavis Y. Darkwah, PharmD
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MAVIS Y DARKWAH
08/29/2017

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM: Mavis Darkwah, PharmD, for

Sharon Hertz, M.D., Director

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP),
HFD-170

DATE 08/28/17	IND NO.	NDA NO. 022122/S-011	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT 08/21/17
NAME OF DRUG Voltaren Gel (diclofenac sodium) topical gel, 1%		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 29, 2017

NAME OF FIRM: GlaxoSmithKline Consumer Healthcare

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE--NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> MEDICATION ERRORS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|---|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

DAAAP received this Prior Approval labeling supplement that proposes to add a serialization code location to the exterior 100 gm cartons, and removal of trademarks from the current packaging. We are requesting DMEPA review of revised carton & container labeling. All questions and requests can be sent to Mavis Darkwah, PharmD, Regulatory Health Project Manager. All files can be found at:

EDR Location: <\\CDSESUB1\evsprod\NDA022122\022122.enx>

EDR Location: <\\CDSESUB1\evsprod\NDA022122\0251>

SIGNATURE OF REQUESTER
Mavis Y. Darkwah, PharmD
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 240-402-3158
Email: Mavis.darkwah@fda.hhs.gov

METHOD OF DELIVERY (Check all that apply)
 MAIL DARRTS HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

06/18/2013

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/s/

MAVIS Y DARKWAH
08/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Mavis Darkwah, PharmD, for Sharon Hertz, M.D., Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), HFD-170	
REQUEST DATE: 08/28/17	NDA/BLA NO.: 022122/S-011	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW) sNDA Labeling supplement	
NAME OF DRUG: Voltaren Gel (diclofenac sodium) topical gel, 1%	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) Nov. 29, 2017
SPONSOR: GlaxoSmithKline Consumer Healthcare		PDUFA Date: February 21, 2018.	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA/ANDA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA022122\022122.enx EDR Location: \\CDSESUB1\evsprod\NDA022122\0251			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: The sponsor submitted labeling supplement, Supp-011, which proposes a change to the Instructions for Use on how to break the seal on the tube with a cap, and revision to Carton & Container labeling. DAAAP requests review of these propose changes.			
SIGNATURE OF REQUESTER Mavis Y. Darkwah, PharmD Regulatory Health Project Manager FDA/CDER/ODE II/DAAAP Tel: 240-402-3158 Email: Mavis.darkwah@fda.hhs.gov			
SIGNATURE OF RECEIVER			

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/s/

MAVIS Y DARKWAH
08/28/2017