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Submitted via Regulations.gov

March 30, 2020

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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CITIZEN PETITION REGARDING
OVER-THE-COUNTER LABELING OF DICLOFENAC GEL 1%

Wiley Rein LLP submits this petition pursuant to 21 C.F.R. § 10.30 pertaining to the recently approved over-the-counter (OTC) labeling for Voltaren Arthritis Pain (diclofenac sodium) topical gel 1%, corresponding to new drug application (NDA) 22122, held by GlaxoSmithKline Consumer Healthcare Holdings (US) LLC ("GSK"). Prior to February 14, 2020, this product was dispensed by prescription only. On that date, however, FDA approved supplemental NDA (NDA22122/S-14) for the full switch of the product to OTC status.

Petitioner's concern is that important safety information contained in the previously-approved prescription labeling of diclofenac topical gel 1%, is not adequately reflected in the OTC labeling approved on February 14, 2020.

I. ACTIONS REQUESTED

Petitioner requests that the Food and Drug Administration ("FDA" or "Agency") withdraw or rescind its approval of NDA22122/S-14, because the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1% corresponding to NDA 22122 fails to contain, in a manner appropriate for consumer understanding, important safety information contained in the following sections of the most recently revised version of the prescription labeling for Voltaren Gel:[1]

1. Sec. 2.4 - Special Precautions, in particular, concomitant use of Voltaren Gel with oral non-steroidal anti-inflammatory drugs (NSAIDs)
2. Sec. 5.7 - Anaphylactic Reactions
3. Sec. 5.11 - Hematologic Toxicity
4. Sec. 5.12 - Masking of Inflammation and Fever
5. Sec. 5.14 - Sun Exposure
6. Sec. 7 - Drug Interactions, in particular, concomitant use of diclofenac and digoxin
7. Sec. 8.3 - Females of Reproductive Potential, Infertility

[1] The prescription labeling (Revised Feb. 2018) is attached as Exhibit A and the OTC labeling approved on February 14, 2020, is attached as Exhibit B.

In each case, the Petitioner requests specific revisions be made to any approved OTC labeling, should the Agency, upon reexamination, conclude that diclofenac gel 1% is still an appropriate product to be sold over the counter. The Petitioner, however, defers to the Agency regarding the precise language of any revision and the most appropriate label placement of the revision.

II. STATEMENT OF GROUNDS

A. Background

1. Diclofenac

Diclofenac sodium is a benzeneacetic acid derivative, and is a nonsteroidal anti-inflammatory drug (NSAID) that has analgesic, anti-inflammatory, and anti-pyretic properties. Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. The mode of action of diclofenac may be due to a decrease of prostaglandins in peripheral tissues.[2]

Diclofenac was first approved in the United States in 1988. The first approved diclofenac product was Voltaren enteric-coated tablets,[3] labeled for pain relief, including the relief of the signs and symptoms of osteoarthritis.[4]

The subject of this citizen petition, Voltaren Gel (NDA 22122), was approved in October 2007, and was the first topically applied diclofenac product in the United States labeled for use in osteoarthritis ("relief of the pain of osteoarthritis of joints amendable to topical treatment, such as the knees and those of the hands"). No diclofenac product was approved for OTC use prior to February 14, 2020, when FDA approved a supplement to NDA 22122 providing for OTC labeling of diclofenac topical gel 1%.

2. Prescription to Over-the Counter Switch

The change of a product from prescription-only to over-the-counter (commonly referred to as an "Rx-to-OTC switch") represents a significant milestone in the life-cycle of a product. Over the last 20 years, several products have been switched,[5] but it remains the case that most prescription drugs remain prescription-only throughout their life-cycle.

According to FDA, OTC drugs generally have the following characteristics: their benefits outweigh their risks, the potential for misuse and abuse is low, a consumer can use them for

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[2] See Voltaren Gel prescription labeling (Exhibit A) at sections 11 and 12.1.

[3] See FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* (Orange Book), https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019201#2660 - last visited March 28, 2020.

[4] Labeling available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019201 - last visited March 28, 2020.

[5] FDA maintains a year-by-year list of switched products, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/prescription-over-counter-otc-switch-list - last visited March 26, 2020.

self-diagnosed conditions, they can be adequately labeled, and health practitioners are not needed for the safe and effective use of the product.[6]

While many NSAIDs, a class of drugs including diclofenac, have been marketed OTC for pain reduction in osteoarthritis for several years, diclofenac topical gel 1%, has been a prescription product for over 13 years. In this case, therefore, the Rx-to-OTC switch review should consist primarily of a close consideration of the adequacy of the proposed labeling.

As the Agency readily recognizes, the consideration of the adequacy of labeling includes whether or not a consumer can comprehend the contents of the label.[7] The central issue presented in this citizen petition concerns the inadequacy of the OTC labeling where important safety information has been omitted from this labeling.

B. Significant Omissions in the OTC Labeling of Diclofenac Topical Gel 1%

Petitioner requests that information from seven sections of the prescription labeling for diclofenac topical gel 1%, identified above, be incorporated into the OTC labeling for diclofenac topical gel 1% should the Agency, upon reexamination, conclude that diclofenac gel 1% is still an appropriate product to be sold over the counter. The seven sections are listed below in the order in which they appear in the prescription drug labeling, but does not reflect Petitioner's view of the relative significance of each requested change. Indeed, Petitioner recognizes the relevance of some of the requested changes to the labeling of OTC NSAIDs other than diclofenac topical gel 1%. Of particular importance is Petitioner's requested change regarding the diagnosis of infection, which has broader OTC NSAID applicability and directly implicates the current COVID-19 pandemic.

1. Section 2.4 - Special Precautions, in particular concomitant use of diclofenac topical gel, 1%, with oral non-steroidal anti-inflammatory drugs (NSAIDs)

The approved OTC labeling for Voltaren Arthritis Pain (diclofenac sodium) topical gel 1%, contains no precaution regarding the concomitant use of the product with oral NSAIDS. In the OTC labeling, the Drug Facts/Warnings section reads:

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking any other drug

[6] See "Regulatory Approaches for Prescription to OTC Switch," Theresa M. Michele, M.D., Director, Division of Nonprescription Drug Products, CDER, FDA, available at https://www.fda.gov/files/drugs/published/Presentation--Regulatory-Approaches-for-Prescription-to-OTC-Switch.pdf - last visited March 28, 2020.

[7] To address this fundamental question, label comprehension studies are often performed. *Id.*

The omission of a warning concerning the concomitant use of the product with oral NSAIDS is significant where there are known drugs of concern--especially drugs likely to be used by the intended population—such as those for people experiencing pain due to rheumatoid arthritis. It is extremely likely that anyone considering purchasing OTC diclofenac topical gel 1%, might be taking an oral NSAID.

Petitioner therefore requests that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel1% (NDA 22122) be revised so that the second bullet of the above-referenced portion of the Drug Facts/Warning section contains the following warning:

> **Ask a doctor or pharmacist before use if you are**
> - under a doctor's care for any serious condition
> - taking an oral non-steroidal anti-inflammatory drug (NSAID), or any other drug

2. Sec. 5.7 - Anaphylactic Reactions

Section 5.7 states that diclofenac has been associated with anaphylactic reactions in patients with and without known hypersensitivity to diclofenac, in patients with aspirin-sensitive asthma, and advises that emergency help should be sought if an anaphylactic reaction occurs. The Medication Guide[8] distributed to everyone receiving *prescription* diclofenac gel 1% states the following:

> **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

The approved OTC labeling, however, contains nothing regarding seeking emergency help. Important, life-saving recommendations are given to a patient receiving diclofenac topical gel 1% via prescription, but inexplicably *not* given to a patient buying the product OTC.

Petitioner therefore requests that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel, 1% (NDA 22122) be revised so that the Drug Facts/Warning section contains the identical language to that in the Medication Guide, set forth above.

3. Sec. 5.11 - Hematologic Toxicity

Section 5.11 states that anemia has occurred in NSAID-treated patients, and that in occult or gross blood loss, this may be due to fluid retention or an incompletely described effect on

[8] Medication Guide, at page 2. The Medication Guide is regarded as part of, and appears at the end of the prescription labeling, found at Exhibit A.

erythropoiesis. While the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1%, addresses blood loss, the labeling does not caution patients about other causes of anemia:

> **Stop use and ask a doctor if**
>
> […]
>
> - you experience any of the following signs of stomach bleeding:
>   • feel faint • have blood or black stools • vomit blood
>   • have stomach pain that does not get better

Petitioner therefore requests that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1% (NDA 22112) be revised so that the above-referenced portion of the Drug Facts/Warning section contains the following warning:

> **Stop use and ask a doctor if**
>
> […]
>
> - you experience any of the following signs of anemia or stomach bleeding:
>   • feel faint • experience extreme fatigue or weakness
>   • have blood or black stools • vomit blood
>   • have stomach pain that does not get better

4. Sec. 5.12 - Masking of Inflammation and Fever

On March 19, 2020, FDA published an advisory that stated the following:

> FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, could worsen coronavirus disease (COVID-19). These news reports followed a March 11, 2020 letter in The Lancet medical journal [9] which hypothesized that an enzyme (a molecule that aids a biochemical reaction in the body) is increased by NSAIDs and could aggravate COVID-19 symptoms.
>
> At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available. ***However, all prescription NSAID labels warn that "the pharmacological activity of NSAIDs in reducing inflammation, and possible fever,***

[9] https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930116-8 - last visited March 24, 2020.

> ***may diminish the utility of diagnostic signs in detecting infections.***"[10] (Emphasis added.)

Notably, in the context of NSAID use and COVID-19, the Agency points to the serious aspect of prescription NSAID labeling that is quite relevant in the diagnosis of infections such as COVID-19, *i.e.*, reducing-fever NSAIDs may impair the diagnosis of an infectious condition.

With respect to diclofenac gel 1%, the above quoted warning that "the pharmacological activity of NSAIDs in reducing inflammation, and possible fever, may diminish the utility of diagnostic signs in detecting infections," is contained in the approved prescription labeling for diclofenac topical gel 1%, at section 5.12. The warning, however, is *not* in the OTC labeling.

This warning is as important in the OTC setting as it is when diclofenac topical gel 1%, is prescribed. Inclusion of the warning in OTC labeling can provide critical information underlying a consumer's decision to purchase diclofenac topical gel 1% versus another treatment for rheumatoid arthritis, as well as when to use the diclofenac product. Inclusion of the warning would likely also inform a consumer's communication with their health care provider. In particular, the warning improves the likelihood that a consumer will tell a health care provider about their use of diclofenac topical gel 1%, when being examined for a possible infection.

Petitioner therefore requests that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel, 1% (NDA 22112) be revised to include, in the Drug Facts/Warning section, the following:

> **Diagnosis of infection warning**: By reducing inflammation and possibly bringing down a fever that you have, this product may make it more difficult for a health care provider to detect whether you have an infection.

5. Sec. 5.14 - Sun Exposure

Section 5.14 of the Warnings and Precautions section of the prescription labeling states that patients should avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicate that topical diclofenac treatment resulted in an earlier onset of ultraviolet induced skin tumors.

No such precaution appears in the OTC labeling. Petitioner therefore requests, with respect to the Drug Facts/Warning section that states in relevant part:

> **When using this product**
> - avoid contact with eyes, nose, or mouth
> - If eye contact occurs, rinse thoroughly with water

[10] https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19 - last visited March 24, 2020.

that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1% (NDA 22112), be revised to include a third bullet as follows:

When using this product

- avoid contact with eyes, nose, or mouth
- If eye contact occurs, rinse thoroughly with water
- Minimize or avoid exposure to natural or artificial sunlight on treated areas

6. Sec. 7 - Drug Interactions, in particular, concomitant use of diclofenac and digoxin

Section 7 of the prescription labeling consists of a single chart titled "Clinically Significant Drug Interactions with Diclofenac." The portion of the chart regarding digoxin cautions that the concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin, and that physicians should monitor serum digoxin levels if the two drugs are used concomitantly.

Petitioner accordingly requests that, in the pertinent portion of the Drug Facts/Warning section that states:

Ask a doctor before use if

- you have problems or serious side effects from taking pain relievers or fever reducers
- stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic
- you are under age 18 years. It is not known if this drug works or is safe in children under age 18 years

FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1% (NDA 22112), be revised by inserting an additional bullet after the fifth bullet ("you are taking a diuretic") so that the section reads:

Ask a doctor before use if

- you have problems or serious side effects from taking pain relievers or fever reducers
- stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke

- you are taking a diuretic
- you are taking digoxin
- you are under age 18 years. It is not known if this drug works or is safe in children under age 18 years

7. Sec. 8.3 - Females of Reproductive Potential, Infertility

Section 8.3 of the prescription drug labeling states that the use of prostaglandin-mediated NSAIDs, including diclofenac gel, may delay or prevent rupture of ovarian follicles that has been associated with reversible infertility in some women. *See also* Section 17 (Patient Counseling). Section 8.3 further states that women having difficulties conceiving or who are undergoing investigation of infertility should consider withdrawal of NSAIDs, including diclofenac gel.

There are no warnings in the OTC labeling, however, regarding infertility.

Petitioner therefore requests that FDA require that the labeling of OTC Voltaren Arthritis Pain (diclofenac sodium) topical gel 1% (NDA 22122) be revised so that an additional bullet is added in the Drug Facts/Warning section so that portion that begins "**Stop use and ask a doctor if**," reads:

Stop use and ask a doctor if

- pain gets worse or lasts more than 21 days
- redness or swelling is present in the painful area
- you are a woman experiencing difficulty conceiving, or are undergoing investigation of infertility
- fever occurs
- skin irritation occurs
- any new symptoms appear. These could be signs of a serious condition
- […]

C. Conclusion

Petitioner is aware that OTC labeling may not always mirror the information contained in prescription labeling, and that oral NSAIDs have been previously switched from prescription to OTC status. Petitioner, however, does have concerns about the adequacy of portions of the recently approved OTC labeling from a safety perspective.

Given the limitations of space when drafting OTC labeling, Petitioner has taken care to suggest proposed changes that are as succinct as possible and in many instances are just a few words. As noted above, should the Agency, upon reexamination, conclude that diclofenac gel 1% is still an appropriate product to be sold over the counter, Petitioner defers to the Agency regarding the precise language of any requested revision as long the underlying meaning is preserved, as well as the most appropriate label placement of the revision.

III. ENVIRONMENTAL IMPACT

Under 21 C.F.R. § 25.31, this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

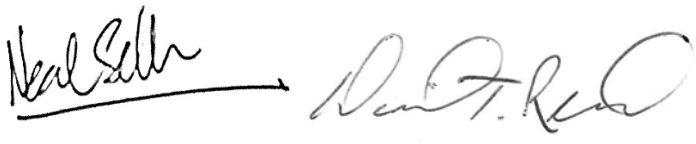
IV. ECONOMIC IMPACT

Under 21 C.F.R. § 10.30, economic impact information will be provided if requested by the Commissioner following review of this petition.

V. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information, known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



A. Neal Seth David T. Read

Attachments:
Exhibit A (diclofenac gel 1% prescription labeling)
Exhibit B (diclofenac gel 1% OTC labeling, approved on February 14, 2020)