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SUBMITTED VIA REGULATIONS.GOV

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir/Madam:

The undersigned, on behalf of a client, submits this Suitability Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. § 314.93 and 21 C.F.R. §§ 10.20 and 10.30, to request that the Commissioner of the U.S. Food and Drug Administration ("FDA") declare that the drug product Diclofenac Potassium Tablets, 12.5 mg, is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

Petitioner requests that FDA declare that Diclofenac Potassium Tablets, 12.5 mg, is suitable for submission as an ANDA.[1] As designated in FDA's *Approved Drug Products*

[1] Petitioner previously petitioned FDA seeking a determination for the same drug product, *see* ANDA Suitability Petition, Docket No. FDA-2023-P-4464 (Oct. 10, 2023). FDA denied the Suitability Petition, determining that the proposed change in strength raises questions of safety and effectiveness. Specifically, FDA found that "the requested change to the drug product/your proposed product, Diclofenac Potassium Tablets, 12.5 mg, would, at the least, necessitate significant labeling changes to address the newly introduced safety or effectiveness problem posed by the proposed strength, which differs from the listed drug product." FDA, ANDA Suitability Petition Response, Docket No. FDA-2023-P-4464, at 1 (Apr. 30, 2024). Petitioner did not request FDA reconsideration of the petition decision under 21 C.F.R. § 10.33, because a request for reconsideration must be based solely on the information contained in the original petition, and, as discussed below, Petitioner has additional information for FDA to consider.

with Therapeutic Equivalence Evaluations ("Orange Book"), the Reference Listed Drug ("RLD") upon which this petition is based is Novartis Pharmaceutical Corp.'s CATAFLAM (diclofenac potassium) Tablets, which is approved for prescription use under New Drug Application ("NDA") 020142 in 25 mg and 50 mg strengths.[2] The Petitioner seeks to introduce a new 12.5 mg strength for prescription use.

B. Statement of Grounds

FDC Act § 505(j)(2)(A)(iii) provides for the submission of an ANDA for a drug product that differs in strength from that of the listed drug provided FDA has first approved a petition permitting the submission of such an application.

CATAFLAM, approved under NDA 020142, contains either 25 mg or 50 mg of diclofenac potassium in a tablet dosage form. A copy of the current Orange Book entry for CATAFLAM Tablets, 25 mg and 50 mg, is included in ***Attachment 1***. The proposed drug product also contains diclofenac potassium in a tablet dosage form, but in a 12.5 mg strength. The petition is thus seeking a change in tablet strength to 12.5 mg from that of the RLD (25 mg and 50 mg).

The proposed change in strength is consistent with the dosing recommendations of the RLD's approved labeling. For example, the Prescribing Information for CATAFLAM Tablets, 50 mg (NDA 020142)—which is approved for the treatment of primary dysmenorrhea, for relief of mild to moderate pain, for relief of the signs and symptoms of osteoarthritis, and for relief of the signs and symptoms of rheumatoid arthritis—states the following under "Dosage and Administration":

> Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).
>
> After observing the response to initial therapy with CATAFLAM, the dose and frequency should be adjusted to suit an individual patient's needs.

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[2] CATAFLAM (diclofenac potassium) Tablets, 25 mg and 50 mg (NDA 020142), are listed in the *Discontinued Drug Product List* section of the Orange Book. FDA previously determined that the drug product was not withdrawn for safety or effectiveness reasons. *See* FDA, Notice, 68 Fed. Reg. 65,074 (Nov. 19, 2003) (25 mg); 82 Fed. Reg. 19,735, 19,736 (Apr. 28, 2017) (50 mg).

> For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg three times a day. With experience, physicians may find that in some patients an initial dose of 100 mg of CATAFLAM, followed by 50-mg doses, will provide better relief.
>
> For the relief of osteoarthritis the recommended dosage is 100 to 150 mg/day in divided doses, 50 mg twice a day or three times a day.
>
> For the relief of rheumatoid arthritis the recommended dosage is 150 to 200 mg/day in divided doses, 50 mg three times a day or four times a day.

Prescribing Information, CATAFLAM Tablets, 50 mg (NDA 020142), Dosage and Administration (Apr. 2021), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020142s029lbl.pdf (***Attachment 2***). The availability of a new 12.5 mg tablet strength will provide a prescribing physician with the ability to "[u]se the lowest effective dose for the shortest duration consistent with individual patient treatment goals."

FDA has separately determined that the proposed Diclofenac Potassium Tablets, 12.5 mg, drug product "would, at the least, necessitate significant labeling changes to address the newly introduced safety or effectiveness problem posed by the proposed strength, which differs from the listed drug product," CATAFLAM, *see* FDA, ANDA Suitability Petition Response, Docket No. FDA-2023-P-4464, at 1 (Apr. 30, 2024); however, FDA has not specifically identified how the proposed drug product "would jeopardize the safe or effective use of the product," how it would "necessitate significant labeling changes," or even what "newly introduced safety or effectiveness problem" there is in this case. *Id.* Regardless, Petitioner believes that there is sufficient evidence that the proposed change in strength from that of the RLD does not, in fact, raise questions of safety or efficacy for the proposed drug product. As such, FDA should conclude that clinical investigations are not necessary to demonstrate safety or effectiveness of the proposed drug product. In particular, Petitioner relies on the following:

- A study of low-dose diclofenac potassium (*i.e.*, 12.5 mg) showed that it has a rather good safety/tolerability profile—very similar to that of non-prescription ibuprofen. *See* Nicholas Moore, Diclofenac Potassium 12.5mg Tablets for Mild to Moderate Pain and Fever; A Review of Its Pharmacology, Clinical Efficacy and Safety, Clin Drug Invest 2007; 27 (3): 163-195 (***Attachment 3***).

- A study of Diclofenac Potassium Tablets, 12.5 mg, confirmed that it is well absorbed after oral administration, and that it is bioequivalent to 25 mg (dose-adjusted), thereby affirming effectiveness. The data indicate that there is no evidence of decreased bioavailability when diclofenac potassium is administered at a dose of 12.5 mg. *See* Burkhard Hinz, et al., Bioavailability of diclofenac potassium at low doses, Br. J. Clin. Pharmacol. 59:1, 80-84 (2005) (***Attachment 4***).

- The European Union's European Medicines Agency ("EMA") has separately concluded that a Diclofenac Potassium Tablets, 12.5 mg, drug product is permissible for dosing patients where dosing and administration provides for doses (*e.g.*, 50 mg) that can be divided by 12.5 mg. *See* EMA, Summary of Product Characteristics ("SmPc"), Diclofenac Potassium 12.5 mg Tablets (Aug. 2023) for PL 36687/0214 (***Attachment 5***).[3] The SmPc: (1) indicates that diclofenac is rapidly and completely absorbed from film-coated tablets and the plasma concentrations show a linear relationship to the size of the dose; (2) mentions that undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms; (3) mentions that caution is indicated in the elderly on basic medical grounds; and (4) recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight. *See id.*

There are no proposed changes in labeling with the exception of the change in strength sought in this petition. The uses, indications, warnings, and directions for use will remain the same as that of the RLD—as is the safety and effectiveness profile as noted above. Approved labeling for CATAFLAM Tablets (NDA 020142) is included as ***Attachment 2***. Draft labeling for the proposed drug product is included as ***Attachment 7***. Therefore, the Petitioner requests that FDA find that a change in tablet strength from 25 mg and 50 mg of diclofenac potassium raises no questions of safety or effectiveness.

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FDC Act by requiring certain applications for a drug submitted under FDC Act § 505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. *See* FDC Act § 505B(a)(1)(A)(i). Specifically, PREA applies to all applications for a new active ingredient, dosage form,

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[3] Petitioner also notes that the Australian Therapeutic Goods Administration ("TGA") has determined that Diclofenac Potassium Tablets, 12.5 mg, is a permissible non-prescription medicine "[f]or the temporary relief of muscular and rheumatic pain, backache, period pain, headache and dental pain, fever, painful symptoms of colds and flu (including aches and pains, sore throat pain)." TGA, Public Summary, Diclofenac Potassium 12.5 mg Film Coated Tablet (May 2024) (***Attachment 6***).

indication, route of administration, or dosing regimen. *See id.* ANDAs submitted under an approved suitability petition for a change in strength are not subject to PREA requirements. *See* FDA, Draft Guidance for Industry, Pediatric Drug Development: Regulatory Considerations—Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act, at 9 (May 2023). Petitioner asserts that PREA is not applicable to the proposed Diclofenac Potassium Tablets, 12.5 mg, drug product because the proposed change concerns only a new strength. As such, PREA should not serve as an impediment to the Agency granting this petition.

C. Environmental Impact

A claim for categorical exclusion of the requirements for an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

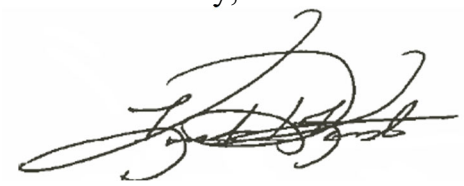
D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is submitted only when requested by the Commissioner. This information will be promptly provided, if so requested.

E. 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.

Sincerely,



Kurt R. Karst

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Attachments