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June 19, 2024

VIA ELECTRONIC SUBMISSION 6/18//24

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, pursuant to Section 505U)(2)(C) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR 10.30 and 314.93 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Rosuvastatin Calcium Orally Disintegrating Tablets (ODT), in strengths of 5 mg, 10 mg, 20 mg, and 40 mg are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Rosuvastatin Calcium Orally Disintegrating Tablets, in strengths of 5 mg, 10 mg, 20 mg and 40 mg are suitable for submission as an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Crestor® (Rosuvastatin Calcium) Tablets, 5 mg, 10 mg, 20 mg and 40 mg approved under NDA 021366 currently held by IPR Pharmaceuticals as designated in the Orange Book (see copy of the page from the current Electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Attachment 1)).. Therefore, the petitioner seeks only a change in dosage form from that of the reference listed drug product, from conventional tablets to orally disintegrating tablets.

B. Statement of Grounds

The Federal Food, Drug, and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in dosage form from that of the listed drug provided that FDA has approved a petition declaring that the proposed difference does not raise any questions of safety or effectiveness.

The RLD, Crestor® (rosuvastatin calcium) Tablets by IPR Pharmaceuticals is a conventional tablet product containing 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin calcium in each tablet.. The proposed drug product will be an orally disintegrating tablet dosage form, containing 5 mg, 10 mg, 20 mg, or 40 mg of Rosuvastatin Calcium. This petition is thus seeking a change in dosage form of the RLD to an orally disintegrating tablet from that of a conventional oral tablet.

The proposed product will utilize the same dosing schedule as that of the RLD and the only difference will be that the ODT product will be recommended to be dissolved in the mouth prior to swallowing. The current dosing instructions in the approved labeling of the RLD are as follows:

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Dosage and Administration:

2.1 General Dosage and Administration Information

Administer CRESTOR orally as a single dose at any time of day, with or without food. The tablet should be swallowed whole. Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating CRESTOR, and adjust the dosage if necessary. If a dose is missed, advise patients not take an extra dose. Resume treatment with the next dose.

2.2 Recommended Dosage in Adult Patients

The dosage range for CRESTOR is 5 to 40 mg orally once daily. The recommended dose of CRESTOR depends on a patient's indication for usage, LDL- C, and individual risk for cardiovascular events.

2.3 Recommended Dosage in Pediatric Patients

Dosage in Pediatric Patients 8 Years of Age and Older with HeFH: The recommended dosage range is 5 mg to 10 mg orally once daily in patients aged 8 years to less than 10 years and 5 mg to 20 mg orally once daily in patients aged 10 years and older.

Dosage in Pediatric Patients 7 Years of Age and Older with HoFH: The recommended dosage is 20 mg orally once daily.

2.4 Dosing in Asian Patients

Initiate CRESTOR at 5 mg once daily due to increased rosuvastatin plasma concentrations. Consider the risks and benefits of CRESTOR when treating Asian patients not adequately controlled at doses up to 20 mg once daily *[see Warnings and Precautions (5.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

2.5 Recommended Dosage in Patients with Renal Impairment

In patients with severe renal impairment (CL_{cr} less than 30 mL/min/1.73 m^2) not on hemodialysis, the recommended starting dosage is 5 mg once daily and should not exceed 10 mg once daily *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

2.6 Dosage and Administration Modifications Due to Drug Interactions

CRESTOR Dosage Modifications Due to Drug Interactions
Table 1 displays dosage modifications for CRESTOR due to drug interactions *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Table 1: CRESTOR Dosage Modifications Due to Drug Interactions

Concomitantly Used Drug	**CRESTOR Dosage Modifications**
Cyclosporine	Do not exceed 5 mg once daily.
Teriflunomide	Do not exceed 10 mg once daily.
Enasidenib	Do not exceed 10 mg once daily.
Capmatinib	Do not exceed 10 mg once daily.
Fostamatinib	Do not exceed 20 mg once daily.
Febuxostat	Do not exceed 20 mg once daily.
Gemfibrozil	Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 10 mg once daily.

Tafamidis	Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 20 mg once daily.
Antiviral Medications	
○ Sofbuvir/velpatasvir/voxilaprevir ○ Ledipasvir/sofosbuvir	Concomitant use not recommended.
○ Simeprevir ○ Dasabuvir/ombitasvir/paritaprevir/ritonavir ○ Elbasvir/Grazoprevir ○ Sofosbuvir/Velpatasvir ○ Glecaprevir/Pibrentasvir ○ Atazanavir/Ritonavir ○ Lopinavir/Ritonavir	Initiate at 5 mg once daily. Do not exceed 10 mg once daily.
Darolutamide	Do not exceed 5 mg once daily.
Regorafenib	Do not exceed 10 mg once daily.

C. Pediatric Waiver Request

In September of 2007, Congress reauthorized the Pediatric Research Equity Act of 2003 (PREA) that amended the Federal Food, Drug, and Cosmetic Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such study would provide beneficial health data for that patient population. The Act specifically requires that a request for a new dosage form is subject to a pediatric evaluation. The act also provides for a waiver from such requirement if the drug:

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients;

(II) is not likely to be used in a substantial number of pediatric patients.

Labeling for the proposed product will be include the same indications and dosing recommendationsfor all ages of pediatric patients for whom the drug is indicated (down to 7 years of age). While the RLD labeling contains information stating that the product "has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age, use of statins in patients younger than 10 years of age may be ill advised due to the potential impact on development of the central nervous system and other body systems.

It appears that the only recommended use of this product in pediatric patients is for heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia. The label goes on to state: “Safety and effectiveness of CRESTOR as an adjunct to diet to reduce LDL-C have been established in patients 8 years of age and older with HeFH. Use of CRESTOR for this indication is based on one 12-week controlled trial with a 40-week open-label extension period in 176 pediatric patients 10 years of age and older with HeFH and one 2-year open-label, uncontrolled trial in 175 pediatric patients 8 years of age and older with HeFH. In the 1-year trial with a 12-week controlled phase, there was no detectable effect of CRESTOR on growth, weight, BMI (body mass index), or sexual maturation in patients aged 10 to 17 years.”

In addition, the label states: “The safety and effectiveness of CRESTOR as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established pediatric patients 7 years of age and older with HoFH. Use of CRESTOR for this indication is based on a randomized, placebo-controlled, cross-over study in 14 pediatric patients 7 years of age and older with HoFH. The safety and effectiveness of CRESTOR have not been established in pediatric patients younger than 8 years of age with HeFH, younger than 7 years of age with HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).”

The petitioner hereby requests that a full waiver from the conduct of pediatric studies be granted for this petition to permit a subsequent ANDA filing, as the proposed product is not likely to be used in a substantial number of pediatric patients. Furthermore, the drug product is already appropriately labeled for use in pediatric patients aged 7 or 8 years of age and older based on indication, HoFH or HeFH. FDA has previously granted an Orphan Designation for the pediatric HoFH indication and subsequently granted 7 years of ODE for pediatric HoFH where that exclusivity period expired on May 27, 2023. Therefore, the pediatric HoFH indication qualifies for the PREA orphan exemption at 505B(k) of the FD&C Act.

D. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

E. Economic Impact

The petitioner does *not* believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

F. 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,

Gene Nakagawa
President
Newcastle Bioscience LLC
gene@newcastlebio.com

Attachments:

1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing, accessed 6/19/24
2. Draft insert labeling for proposed product
3. Approved labeling for reference-listed drug, Lipitor (atorvastatin calcium) Tablets by Pfizer.