June 3, 2019

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Citizen Petition Requesting Therapeutic Equivalence Rating Assignment for NDA 209552

Request Aurobindo Pharma Limited's Argatroban in Sodium Chloride Injection, 50 mg/ 50 mL approved under 505(b)(2) NDA 209552 be assigned a therapeutic equivalence rating of 'AP' to the pharmaceutically equivalent Reference Listed Drug Argatroban in Sodium Chloride Injection, 50 mg/50 mL NDA 022434, held by Eagle Pharmaceuticals, Inc.

Dear Sir/Madam,

The undersigned submits this petition on behalf of Aurobindo Pharma Ltd. pursuant to 21 CFR §10.30 requesting the Commissioner of the Food and Drug Administration to designate Aurobindo Pharma's Argatroban in Sodium Chloride Injection, 50 mg/50 mL approved under 505(b)(2) NDA 209552 as therapeutically equivalent with an 'AP' rating to the Reference Listed Drug (RLD) Argatroban in Sodium Chloride Injection, 50 mg/50 mL NDA 022434, held by Eagle Pharmaceuticals, Inc.

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration designate Aurobindo Pharma Ltd.'s Argatroban in Sodium Chloride Injection, 50 mg/50 mL approved under 505(b)(2) NDA 209552 as therapeutically equivalent with an 'AP' rating to the RLD Argatroban in Sodium Chloride Injection, 50 mg/50 mL NDA 022434, held by Eagle Pharmaceuticals, Inc.

B. Statement of Grounds

FDA has approved three NDAs for pharmaceutically equivalent versions of Argatroban in Sodium Chloride Injection, 50 mg/50 mL:

- Eagle Pharma's Argatroban in Sodium Chloride Injection, 50 mg/50 mL (NDA 022434)
- Hikma's Argatroban Injection, 50 mg/50 mL (NDA 203049)
- Aurobindo Pharma's Argatroban in Sodium Chloride Injection, 50 mg/50 mL (NDA 209552)

Aurobindo Pharma's formulation approved under 505(b)(2) NDA 209552 is qualitatively and quantitatively same as the formulation of Sandoz's Argatroban in Sodium Chloride Injection 125 mg/125 mL approved under NDA 022485 (which was used as the basis of submission of our NDA). Aurobindo Pharma Ltd. submitted a 505(b)(2) application due to the difference in the fill volume (50 mL vs. 125 mL). Our NDA 209552 was approved on November 27, 2018.

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NDA 020883 currently held by Novartis Pharmaceuticals Corp. is the RLD referenced in the 505(b)(2) applications submitted by Sandoz (NDA 022485), Eagle Pharma (NDA 22434) and Hikma (NDA 203049). Thus, these three previously-approved 505(b)(2) NDAs and 505(b)(2) variations on these approvals (including Aurobindo's NDA) all refer to the original innovator product approved under NDA 020883. This is indicated in their approval documents which are posted on the Agency's website as linked below.

Eagle 505(b)(2) NDA 022434
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022434_argatroban_toc.cfm

Sandoz 505(b)(2) NDA 022485
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022485_argatroban_toc.cfm

Hikma 505(b)(2) NDA 203049 *(Original approval for 250 mg/2.5 mL)*
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203049_argatroban_toc.cfm

(S-004 (for 50 mg/50 mL presentation)
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/203049Orig1s004.pdf

The Eagle 505(b)(2) NDA 022434 was granted a waiver of *in-vivo* bioequivalence testing based on formulation comparison to the RLD 020883, and certain *in-vitro* comparison data. The Sandoz 505(b)(2) NDA 022485 was also granted a waiver of *in-vivo* bioequivalence testing pursuant to 21 CFR §320.22(d)(3) based on formulation comparison to the RLD 020883, and certain *in-vitro* comparison data. Aurobindo's NDA 209552 (citing Sandoz's NDA 022485 as RLD) was granted a waiver of *in-vivo* bioequivalence testing pursuant to 21 CFR §320.22(d)(1) based on formulation comparison to the Sandoz product.

Additionally, please note that pending suitability petition FDA-2014-P-0813 submitted dated June 14, 2014 requested FDA determination that an ANDA could be submitted for Argatroban Injection, 1 mg/mL in the strength of 50 mg/50 mL citing Sandoz's approved 505(b)(2) NDA 022485. To date the Agency has not taken action with respect to this suitability petition. However, had it been approved, an ANDA could have been submitted for this product.

Aurobindo Pharma's Argatroban in Sodium Chloride Injection, 50 mg/50 mL is pharmaceutically equivalent to the Reference Listed Drug (RLD), NDA 022434 (Argatroban in Sodium Chloride Injection) held by Eagle Pharmaceuticals, Inc.

A side-by-side pharmaceutical comparison of NDA 209552 (Aurobindo Pharma) and the RLD NDA 22434 (Eagle Pharma) is provided in Table 1:

Table 1: Side-by-Side Pharmaceutical Equivalence Comparison of NDA 209552 and NDA 022434

Attribute	Aurobindo Pharma's NDA 209552	Eagle Pharma's RLD NDA 022434	Comparison
Strength	50 mg/50 mL	50 mg/50 mL	Same
Route of Administration	Intravenous	Intravenous	Same
Dosage form	Injectable	Injectable	Same
Active Ingredient	Argatroban	Argatroban	Same

Attribute	Aurobindo Pharma's NDA 209552	Eagle Pharma's RLD NDA 022434	Comparison
Indications	Argatroban Injection is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adult patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI)	Argatroban Injection is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adult patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI)	Same
Excipients	Sodium Chloride 9 mg/mL Sorbitol 3 mg/mL Water for Injection q.s.	Sodium Chloride 8 mg/mL Lactobionic acid 2 mg/mL L-Methionine 2 mg/mL Sodium Hydroxide to adjust pH Water for Injection q.s.	Formulation differences do not affect bio-availability

Approved Drug Products with Therapeutic Equivalence Evaluations, ("The Orange Book"), defines *pharmaceutically equivalent* drug products as follows:

1. Contain identical amounts of the same active drug ingredient in the same dosage form and route of administration
2. Meet compendial or other applicable standards of strength, quality, purity and identity

The Orange Book defines *therapeutically equivalent* drug products as follows:

1. Are approved as safe and effective.
2. Contain identical amounts of the same active drug ingredient in the same dosage form and route of administration
3. Meet compendial or other applicable standards of strength, quality, purity and identity
4. Are bioequivalent
5. Are adequately labeled
6. Were manufactured under cGMP

Aurobindo Pharma Limited's approved 505(b)(2) NDA 209552 Argatroban in Sodium Chloride Injection, 50 mg/50 mL meets all of the above-listed requirements.

According to the Orange Book Preface to the 39th Edition, therapeutically equivalent drug products can differ in certain other characteristics, such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration date/time, minor aspects of labeling and storage conditions.

Table 1 demonstrates that the Eagle Pharma's RLD and Aurobindo Pharma's NDA drug products are identical with the exception of the excipients used. These changes in excipients do not affect bio-availability based on multiple waivers of *in-vivo* bioequivalence granted by the Agency.

Based on all the above-mentioned reasons, Aurobindo Pharma Limited hereby requests the Agency to grant our NDA 209552, Argatroban in Sodium Chloride Injection a therapeutic equivalence rating of 'AP' to the RLD Argatroban in Sodium Chloride Injection, 50 mg/50 mL NDA 022434, held by Eagle Pharmaceuticals, Inc.

A TE code is necessary so that Aurobindo Pharma Limited's application will be exempt from, or can otherwise obtain refund of, any PDUFA program user fees that FDA may assess with respect to NDA 209552 for Fiscal Year 2020 and future fiscal years.

C. Environmental Impact

Issuance, amendment, or revocation of procedures for submission of applications for product development, testing and investigational use, and approval are categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR § 25.30(h).

D. Economic Impact

Information regarding economic impact will be submitted upon request by the commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all the 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.

Please contact the undersigned at AuroMedics Pharma LLC, 279 Princeton-Hightstown Road, East Windsor, NJ 08520, if you have any questions regarding this submission.

Sincerely,
AuroMedics Pharma LLC
(U.S. Agent for Aurobindo Pharma Limited)

Vincent P. Andolina

Digitally signed by Vincent P. Andolina
DN: c=US, st=NJ, l=East Windsor, o=AuroMedics Pharma LLC, cn=Vincent P. Andolina, email=vandolina@aurobindousa.com
Date: 2019.06.03 16:40:19 -04'00'

Vincent P. Andolina
Vice President, Regulatory Affairs