June 7, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20552

CITIZEN PETITION

Dear Sir or Madam:

Epic Pharma, LLC is electronically submitting this Citizen Petition pursuant § 505(j)(2)(C) (the "FD&C Act") and in accordance with 21 C.F.R. 10.20, 10.30, and 314.93, to request the Commissioner of the Food and Drug Administration (the "Agency" and/or the "FDA") to determine that the drug product Buspirone Hydrochloride Tablets, USP, in the new strengths of 2.5 mg, 3.75 mg, and 12.5 mg, is suitable for submission in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

The petition requests the Agency to determine that the drug product, Buspirone Hydrochloride Tablets, USP, in the new strengths of 2.5 mg, 3.75 mg, and 12.5 mg per tablet, is suitable for submission in an ANDA.

This petition is based on the reference listed drug ("RLD") Bristol Myers Squibb Co Pharmaceutical Research Institute's BuSpar, 5 mg, 10 mg, 15 mg, and 30 mg per tablet strength. The RLD is approved under New Drug Application ("NDA") 018731 by Bristol Myers Squibb Co Pharmaceutical Research Institute and is listed in the discontinued section of the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, current edition ("Orange Book"). The applicable Reference Standard ("RS") currently listed in the prescription portion of the Orange Book is ANDA 202557 held by Accord Healthcare Inc. This petition seeks approval for a change in strength different from reference drugs. The strengths requested are 2.5 mg, 3.75 mg, and 12.5 mg per tablet.

B. Statement of Grounds

- The FDC Act § 505(j)(2)(C), with 21 C.F.R. 10.20, 10.30, and 314.93, permits the submission of an ANDA for a drug product that differs in strength from the listed drug after the FDA has approved a petition that seeks permission to file such an application. The FDC Act indicates such a petition must be approved by the Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product.

- The RLD, BuSpar (Buspirone Hydrochloride Tablets, USP), 5 mg, 10 mg, 15 mg, and 30 mg currently held by Bristol Myers Squibb Co Pharmaceutical Research Institute, is listed in the discontinued section of the current version of the Orange Book, indicating [there is a] "Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons". [Reference: 75 Fed. Reg. 64310, 64311 (Oct 18, 2010)].

- The RS currently listed in the prescription portion of the Orange Book is ANDA 202557 held by Accord Healthcare Inc. A copy of the current electronic edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* "Orange Book" for Buspirone Hydrochloride Tablets, USP is provided as Attachment 1. The proposed drug product represents the same tablet dosage form of low (2.5 mg and 3.75 mg) and intermediate (12.5 mg) strengths and contains the same active ingredient and labeling.

- According to the reference standard package insert (Attachment 2) held by Accord Healthcare Inc., it contains strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, and 30 mg. The 7.5 mg per tablet strength is not listed in the reference list drug package insert (Attachment 3). It was approved through suitability petition under Docket No. 98P-0967/CP1, February 1, 1999.

- According to RLD labeling and RS labeling, 5 mg, 7.5 mg, and 10 mg tablets are bisect scored, and 15 mg, and 30 mg tablets can be either bisected or trisected. The proposed 2.5 mg can be obtained by splitting the 5 mg tablet. The proposed 3.75 mg can be obtained by splitting the 7.5 mg tablet. The proposed 12.5 mg can be obtained by combining 5 mg with 7.5 mg tablets or 2.5 mg with 10 mg tablets. Since the proposed strengths can be obtained from existing multi-scored tablets, there shall not be safety or effectiveness concerns. The approval of proposed strengths would make it more convenient for healthcare providers and patients to have more precise doses across the entire dose range.

- The proposed 2.5 mg in strength is already within the dosing recommendations of the RLD's approved labeling. For example, as per the brand label, in combination drug therapy lower dose of buspirone is recommended at 2.5 mg b.i.d or q.d. Buspirone has been shown in vitro to be metabolized by CYP3A4. This finding is consistent with the in vivo interactions observed between buspirone and the following:

    - *Erythromycin:* In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in Cmax and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.
    - *Itraconazole:* In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in Cmax and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination,

a low dose of buspirone (eg, 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

- *Nefazodone:* In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in Cmax and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5 mg b.i.d. doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in Cmax were observed for nefazodone (8%) and its metabolite HO-NEF (11%). Subjects receiving buspirone 5 mg b.i.d. and nefazodone 250 mg b.i.d experienced lightheadedness, asthenia, dizziness, and somnolence, adverse events also observed with either drug alone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

- According to internal prescribing data provided by pharmacies, significant number of Buspirone HCl Tablet USP, 5 mg are prescribed to be combined with 7.5 mg to make 12.5 mg dose. Significant number of Buspirone HCl Tablet USP, 5 mg tablets are split to have 2.5 mg dose. These data confirm that there are patient needs to have low and intermediate strengths. The availability of 2.5 mg, 3.75 mg and 12.5 mg tablet strengths will provide a prescribing physician with a greater degree of flexibility to more smoothly and incrementally "adjust the dosage to individual patient needs." This will also reduce pharmacy level errors as results of incorrectly broken tablets or combined tablets providing incorrect product dosage. Since the proposed strengths also can be obtained by existing multi-scored tablets, it shall not raise questions of safety and effectiveness.

- The petition is seeking the strengths of 2.5 mg and 3.75 mg to act as low-dose, and 12.5 mg acts as intermediate-dose for patients. The proposed strengths would provide additional dosing flexibility and accuracy in the approved patient population.

- Accordingly, based on the information provided above, Epic Pharma, LLC respectfully requests the Commissioner find the proposed strengths of 2.5 mg, 3.75 mg, and 12.5 mg for Buspirone Hydrochloride Tablets, USP should raise no questions of safety or effectiveness. Therefore, the Agency should approve this petition.

C. Environmental Impact

The actions requested in this petition are subject to categorical exclusions under 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 is unfavorable to the petition.

If there are any questions concerning this citizen petition, please contact the undersigned by telephone at (347) 238-2729 or via email at RADept@epic-pharma.com.

Xiaofeng Meng

Digitally signed by Xiaofeng Meng
Date: 2022.06.07 09:58:27 -04'00'

Xiaofeng Meng
Chief Executive Officer
Epic Pharma, LLC

Attachments:

1. Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations* for Buspirone Hydrochloride Tablets, USP, accessed 06/01/2022
2. Approved labeling for Reference Standard Drug (ANDA 202557)
3. Approved labeling for Reference Listing Drug (NDA 018731)