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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 Buspirone HCl Oral Solution, 2 mg/mL, is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

The petitioner requests that FDA declare that Buspirone HCl Oral Solution, 2 mg/mL, is suitable for submission as an ANDA. As designated in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Reference Listed Drug ("RLD") upon which this petition is based is Bristol-Myers Squibb's BUSPAR (buspirone HCl) Tablets, which is approved for prescription use under New Drug Application ("NDA") 018731 in 5 mg, 10 mg, 15 mg, and 30 mg strengths.[1] The petitioner seeks to introduce a new 2 mg/mL oral solution dosage form for prescription use.

[1] BUSPAR Tablets, 5 mg, 10 mg, 15 mg, and 30 mg (NDA 018731), are currently listed in the *Discontinued Drug Product List* section of the Orange Book. FDA previously determined that the drug products were not withdrawn for safety or effectiveness reasons.
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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 and dosage form from that of the listed drug provided FDA has first approved a petition permitting the submission of such an application.

BUSPAR approved under NDA 018731 contains either 5 mg, 10 mg, 15 mg, or 30 mg of buspirone HCl in a tablet dosage form. A copy of the current Orange Book entry for BUSPAR Tablets, 5 mg, 10 mg, 15 mg, and 30 mg (NDA 018731), is included in ***Attachment 1***. The proposed drug products also contain buspirone HCl, but in an oral solution dosage form in a 2 mg/mL strength. The petition is thus seeking a change in dosage form to solution (oral)—and the accompanying strength of 2 mg/mL—from that of the RLD (tablets in 5 mg, 10 mg, 15 mg, and 30 mg strengths).

The proposed change in dosage form (and the accompanying strength) is consistent with the dosing recommendations of the RLD's approved labeling. For example, the prescribing information for BUSPAR Tablets provides the following dosing information: "The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 mg to 30 mg per day were commonly employed." Prescribing Information, BUSPAR Tablets, Dosage and Administration (Nov. 2010), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018731s051lbl.pdf (***Attachment 2***).

The availability of a new oral solution in a 2 mg/mL strength is consistent with the dosing instructions for the RLD (NDA 018731). Moreover, the availability of a new oral solution in a 2 mg/mL strength will provide a prescribing physician with a greater degree of flexibility in achieving proper dosing for a specific patient's needs. The proposed changes in dosage form and the accompanying strength from that of the RLD do not raise

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See FDA, Notice, Determination That BUSPAR (Buspirone Hydrochloride) Tablets, 10 Milligrams, 15 Milligrams, and 30 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 64,310 (Oct. 19, 2010); *see also* FDA, Notice, Determination That AQUAMEPHYTON (Phytonadione) Injectable and Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 81 Fed. Reg. 61,220 (Sept. 6, 2016) (concerning BUSPAR Tablets, 5 mg).

questions of safety or efficacy for the proposed drug product. Therefore, FDA should conclude that clinical investigations are not necessary to demonstrate safety or effectiveness of the proposed drug products.

There are no proposed changes in labeling with the exception of changes in dosage form (and accompanying strength) sought in this petition. The uses, indications, and warnings will remain the same as that of the RLD. Approved labeling for BUSPAR Tablets, 5 mg, 10 mg, 15 mg, and 30 mg (NDA 018731) is included as ***Attachment 2***. Draft labeling for the proposed drug products is included as ***Attachment 3***. Therefore, the Petitioner requests that FDA find that a change in dosage form to a solution (oral) in a 2 mg/mL strength of buspirone HCl 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, indication, route of administration, or dosing regimen. *See id.* Thus, while ANDAs submitted under an approved suitability petition for a change in strength are not subject to PREA requirements, ANDAs for a change in dosage form are 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) ("PREA Regulatory Guidance").

Nevertheless, Petitioner requests a full PREA waiver here. FDA will waive PREA requirements when studies in pediatric patients are impossible or highly impracticable; there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups; or when the drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (2) is not likely to be used in a substantial number of pediatric patients. *See* PREA Regulatory Guidance, at 12.

BUSPAR Tablets is approved for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. As further noted in the BUSPAR Tablets Prescribing Information: "The efficacy of BuSpar has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (GAD). Many of the patients enrolled in these studies also had coexisting depressive symptoms and BuSpar relieved anxiety in the presence of these coexisting depressive symptoms." Prescribing Information, BUSPAR Tablets, Indications and Usage (Nov. 2010). On July 19, 2001, FDA approved a supplemental NDA (NDA

018731/S-043) to add pediatric use information to the BUSPAR Tablets Prescribing Information stating:

> The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6-week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses studied were 7.5 mg to 30 mg b.i.d. (15–60 mg/day). ***There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults***. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.

Prescribing Information, BUSPAR Tablets, Pediatric Use (Nov. 2010) (emphasis added).

As noted above from the BUSPAR Tablets Prescribing Information, neither of the placebo-controlled pediatric clinical trials in pediatric patients ranging from 6 to 17 years of age yielded evidence that buspirone HCl is active against the symptoms of pediatric GAD. It is reasonable to extrapolate from that clinical finding that buspirone HCl also would not be effective in younger pediatric patients. As such, a PREA waiver would be appropriate here because there is evidence strongly suggesting that buspirone HCl would be ineffective or unsafe in all pediatric age groups.

A PREA waiver also would be appropriate here because buspirone HCl does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients. The pediatric clinical trials noted above and identified in the BUSPAR Tablets Prescribing Information already speak to the lack of any meaningful pediatric therapeutic benefit, thereby making it unlikely that the buspirone HCl will be used in a substantial number of pediatric patients. In addition, Petitioner notes that in May 2023, FDA approved LEXAPRO (escitalopram) Tablets (NDA 021323) for the treatment of GAD in pediatric patients 7 years and older. Thus, there is an existing therapy for pediatric patients, and one that, given the failed pediatric clinical studies of buspirone HCl, provides a meaningful therapeutic benefit over buspirone HCl.

Because a PREA waiver is justified here, Petitioner asserts that PREA should not serve as an impediment to the Agency granting this petition seeking permission to submit an ANDA for Buspirone HCl Oral Solution, 2 mg/mL.

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