

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216774Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

IND 139539

**MEETING REQUEST-
WRITTEN RESPONSES**

Teva Pharmaceuticals USA, Inc.
Attention: Alberto Rivalta
Director, Regulatory Affairs
2945 West Corporate Lakes Blvd
Suite B
Weston, FL 33331

Dear Mr. Rivalta:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eltrombopag choline.

We also refer to your submission dated April 22, 2021, containing a meeting request. The purpose of the requested meeting was to gain agreement on proposed eCTD submission content plan, discuss dissolution method, and gain agreement and guidance in regard to several questions pertaining to Chemistry, Manufacturing and Controls.

Further reference is made to our Meeting Granted letter dated May 10, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 19, 2021, background package.

If you have any questions, call May Zuwannin, Regulatory Project Manager at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Written Responses



WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: 139539

Product Name: eltrombopag choline

Indication: The treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
The treatment of thrombocytopenia in adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy (b) (4)
(b) (4)
(b) (4)
(b) (4)

Sponsor Name: Teva Pharmaceuticals USA, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Teva is planning the submission of a 505(b)(2) for an application which incorporates an active ingredient of a different salt. An approved drug product (Promacta) incorporates eltrombopag olamine as the active ingredient, whereas Teva proposes an application which incorporates eltrombopag choline as the active ingredient.

Teva is requesting the Agency's review and agreement of Teva's proposed eCTD submission content plan for eltrombopag choline tablets, 9 mg, 18 mg, 36 mg, and 54 mg. Also, feedback on the dissolution method is being requested. Additionally, Teva would like to gain the Agency's agreement and guidance as it relates to several questions pertaining to Chemistry, Manufacturing and Controls (CMC).

2.0 QUESTIONS AND RESPONSES

Question 1: Does the Agency agree that the proposed eCTD submission content plan (Sequence # 0019) contains the necessary sections/modules needed for acceptance of this application? In particular, we draw your attention to the Module 2 Summaries section. If not, can the Agency specifically identify any sections/modules which the

Agency feels are currently omitted, but must be included in order for the application to be considered substantially complete for acceptance of the application?

FDA Response: The Summary of Biopharmaceutic Studies and Associated Analytical Methods should be placed in Section 2.7.1. The Proposed eCTD Table of Contents for the planned submission contains the Introduction in Section 2.7.

Refer to the [Comprehensive Table of Contents Headings and Hierarchy](#) and the [M4 Organization of the Common Technical Document for Registration of Pharmaceuticals for Human Use Guidance for Industry](#) for more details on each section referred in the FDA Response.

From a technical perspective (and not content related), all other sections proposed in the eCTD-IND Table of Contents are acceptable.

Question 2: As part of the January 27, 2021 written responses provided by the Agency for PIND 139539, the Agency recommended to provide the dissolution method development and validation report, and request acceptability of the dissolution method.

(b) (4)

The dissolution method development report was previously provided in Sequence # 0019, section 3.2.P.2 and the dissolution validation report and its addendum is provided in section 3.2.P.5.3. Does the Agency agree that this dissolution method is suitable for the quality control of the Teva's Eltrombopag Choline Tablets?

FDA Response: No. We acknowledge your proposed dissolution method for quality control of your product. Based on the preliminary review of the provided dissolution method report in the package, the proposed dissolution method conditions ^{(b) (4)} **seem to be not supportive.**

(b) (4)

Question 3: As it applies to this application, are there any general considerations or recommendations from the Agency that would facilitate acceptance of this application and ensure that the application contains the necessary information to support the Agency's review?

FDA Response: We do not recommend that you submit an NDA until the dissolution issue is resolved and the results have been shared with the Agency.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ In addition, you may contact the Division of Pediatric and

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).²

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

505(b)(2) REGULATORY PATHWAY

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).³ In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov).⁴

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific

³ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.regulations.gov>

appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your

proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
06/16/2021 03:45:54 PM