CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218139Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND157262

MEETING REQUEST-
WRITTEN RESPONSES

Novitium Pharma L.L.C
Attention: Muthusamy Shanmugam
70 Lake Drive
East Windsor, NJ 08520

Dear Mr. Shanmugam:

Please refer to your pre-investigational new drug application (PIND) file for terazosin.

We also refer to your submission dated August 24, 2021, containing a meeting request. The purpose of the requested meeting was to discuss the clinical requirements and the regulatory filing pathways for a 505(b)2 NDA for terazosin oral solution.

Further reference is made to our Meeting Granted letter dated September 1, 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 your meeting questions.

If you have any questions, call Sydney Tran, Regulatory Project Manager at 301-796-1587

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Clinical Team Leader
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-IND
Application Number: 157262
Product Name: terazosin
Indication: treatment of symptomatic benign prostatic hyperplasia
Sponsor Name: Novitium Pharma L.L.C.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Novitium requested this type B PIND meeting to discuss and obtain the Agency's guidance on the clinical requirements and the regulatory filing pathway for the use of terazosin oral solution in the treatment of symptomatic benign prostatic hyperplasia (BPH) and hypertension. Novitium's objective is to develop a new dosage form for terazosin.

2.0 QUESTIONS AND RESPONSES

Opening FDA Remark: As previously communicated to you in our meeting acknowledgement letter, we defer responses for the hypertension indication. Regarding the hypertension indication, request a separate PIND meeting with the Division of Cardiology and Nephrology (DCN). The following responses and comments pertain only to the benign prostatic hyperplasia (BPH) indication.

2.1. Clinical

Question 1:
Does the FDA agree with the company position (b) (4)

[redacted]

FDA Response to Question 1:
No, we do not agree. A Biopharmaceutics Classification System (BCS)-based biowaiver is applicable only to immediate-release, solid oral dosage forms or suspensions for systemic delivery. Therefore, the proposed oral liquid dosage form

(solution) does not qualify for a BCS-based biowaiver. We refer you to FDA's Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers. https://www.fda.gov/media/148472/download

To bridge your product to the reference product for a 505(b)(2) NDA, we recommend a three-way, crossover, relative bioavailability (BA) study with the following treatment arms: (1) test product oral terazosin solution (fasting); (2) reference product oral terazosin capsule (fasting); and (3) test product oral terazosin solution (fed). Include statistical comparison of the PK parameters of the reference and test products under fasting conditions for purposes of comparative BA bridging (Arm 1 vs Arm 2) and to assess the effect of food on your proposed oral solution (Arm 1 vs Arm 3).

From the clinical safety perspective, we are concerned that absorption of terazosin may be faster and greater for the oral solution compared to the oral capsule. Syncope and orthostatic hypotension are known adverse reactions to terazosin. If C_{max} and/or T_{max} differ between the products, and maximum terazosin concentrations are greater or achieved faster for the investigational product, the frequency and/or severity of syncope and orthostatic hypotension may be worse for the investigational product. For this reason, your relative bioavailability (BA) study protocol should address the following:

- Safety monitoring:
  Vital signs should be monitored every 15 minutes after dose ingestion until 1 to 2 hours after the expected peak pharmacodynamic effect. The peak pharmacodynamic effect is expected to occur at approximately 2 to 3 hours after ingestion of terazosin oral capsules and may be sooner following terazosin oral solution. Provide details for vital sign assessments in your final protocol.

- Pharmacokinetics (PK) sampling and analysis:
  For both the reference and proposed products, the blood sampling scheme should include adequate time points, including time points close to the T_{max} to characterize C_{max} and timepoints spaced to characterize the elimination phase.

- Dose selection:
  For patient safety and accurate BA determination, address the following dose-related issues in your relative BA protocol:

  - The terazosin labeling recommends initiating therapy at the lowest dose (1 mg) then gradually increasing the dose as tolerated to achieve the desired clinical effect. Titration is meant to minimize the frequency of hypotensive adverse reactions. When initiating or re-starting therapy with terazosin, a "first-dose" syncopal effect is also known.

  - (b) (4) For dose selection in the relative BA study, consider dose

proportionality for the peak concentration (C_{max}) and total exposure (AUC) for the entire dosage range you seek for approval.

Submit your protocol for FDA review and feedback before you conduct the study.

Question 2:
We understand that the change in dosage form (from an oral capsule to an oral solution) triggers the requirement for paediatric assessments under the Paediatric Research Equity Act (PREA). We further note that the package insert labelling for the Jubilant product contains no dosing instructions for paediatric patients. The label indicates that safety and effectiveness in pediatric patients have not been determined. Therefore, based on the Reference Standard labelling, it can be inferred that Terazosin does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

Given that the package insert labelling does not contain dosing instructions for paediatric patients, does the Agency agree that it is not necessary for Novitium to conduct additional paediatric studies to assess safety and efficacy and to develop paediactric dosing instructions for its proposed drug product?

FDA Response to Question 2:
It is premature for the Agency to agree that it is not necessary to conduct additional pediatric studies to assess safety and efficacy and to develop pediatric dosing instructions for the proposed drug product. Submit an iPSP for review. Refer to the **PREA Requirements** section of this letter for additional details.

2.2. Chemistry, Manufacturing, and Controls

Question 3:

(b) (4)

FDA Response to Question 3:
No, we do not agree. Submit 12 months of long-term and six months of accelerated stability data in your NDA. All stability data intended for use in the determination of the expiration dating period of your drug product should be submitted within 30 days from the initial date of submission of your application.

2.3. Regulatory

Question 4:

In line with the FDA Guidance for Industry on Determining Whether to Submit an ANDA or a 505(b)(2) Application, does the FDA agree with the company's position to file this application as a 505(b)(2) application?

FDA Response to Question 4:
A 505(b)(2) application would be an acceptable approach, at this time, based on the information provided.

Question 5:
The Orange Book indicates that Abbott NDA 020347 for Terazosin Capsules, was discontinued from the market, but was not discontinued for reasons of safety or efficacy. We intend to designate NDA 020347 as the Reference Listed Drug on which our 505(b)(2) NDA will rely, while using the designated Reference Standard (RS) approved under ANDA 075317. Does the Agency agree with the selection of the RLD and RS to support this 505(b)(2) NDA?

FDA Response to Question 5:
Although the Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed drug product, your proposal to rely on NDA 020347 [Hytrin (terazosin hydrochloride) capsules] appears acceptable.

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug and will support the scientific appropriateness of reliance through a comparative bioavailability study (see response to Question 1), we recommend you use the ANDA product designated as the reference standard in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug. Jubilant Cadista Pharmaceuticals' ANDA 075317 is designated as the reference standard in the Orange Book for terazosin hydrochloride oral capsules.

Refer to the **505(b)(2) REGULATORY PATHWAY** section of this letter for additional details.

Question 6:
As the introduction of a new dosage form will not increase exposure to terazosin, we therefore intend to provide an exemption from the provision of a Phase I Environmental Risk Assessment and from providing specify study data.

Does the FDA agree with the company position to provide an exemption from a Phase I Environment Risk Assessment?

FDA Response to Question 6:
We agree. However, you should submit a request for a categorical exclusion in your IND and future NDA.

Question 7:
Considering the change in dosage form from capsules to oral solution, does the agency agree that we use the same prescribing information of Terazosin Capsules Reference Standard approved under ANDA 075317 held by applicant Jubilant Cadista Pharmaceuticals Inc., with changes involving the proposed drug product's specific information related to description and how supplied section. Does the Agency agree that no additional data would be required in the prescribing information for submission and approval of the NDA?

FDA Response to Question 7:
It is premature for the Agency to agree that future labeling would involve updating the reference standard's labeling in the Description and How Supplied sections (Sections 11 and 16, respectively) only.

A 505(b)(2) applicant that seeks to rely on FDA's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and/or effectiveness as reflected in the FDA-approved labeling for the listed drug. However, the applicant must provide labeling in the Physician Labeling Rule (PLR)/Pregnancy Lactation Labeling Rule (PLLR) format regardless of whether the labeling for the listed drug is in the PLR/PLLR format. To update labeling, 505(b)(2) applicants should review literature along with other publicly available information in order to inform their labeling and to provide the best information for healthcare providers.

Any information related to the new dosage form must also be updated in the labeling, which could include PK characteristics (Section 12), changes to the dosage regimen/administration instructions (Section 2), and/or any new information obtained during clinical studies (Sections 6 and 14).

According to 21 CFR 201.56(a)(2), the labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular way. The labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

Additional labeling and regulation guidance may be found at the links below.

https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.56

Additional FDA Comments

Considering the change in dosage form from capsules to oral solution, this product is a re-formulation. Conduct a short-term, repeat-dose bridging study to establish relative safety of the new formulation and to evaluate the nonclinical pharmacokinetics/toxicokinetics of the oral solution. We recommend a 28-day bridging study in the rat to evaluate the safety of the reformulated product.

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 Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further

[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.

guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the

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[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

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[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download

STUDIES IN HUMANS MAY NOT BE CONDUCTED UNDER THIS PIND

Before you may conduct studies in humans, you must submit a full Investigational New Drug Application (IND, see 21 CFR Part 312[1]) by amending this PIND with the required information. Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND. Send your IND submission in eCTD format through the ESG. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov[8].

505(b)(2) REGULATORY PATHWAY

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).[9] 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.[10]

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

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[8] http://www.fda.gov/ectd

[9] 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.

[10] http://www.regulations.gov

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 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)**

(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

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.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

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/

MARK S HIRSCH
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