CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219122Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 155653

MEETING REQUEST-
WRITTEN RESPONSES

VistaPharm, Inc.
Attention: Billie J. Wiltison
Senior Director, Regulatory Affairs
7265 Ulmerton Road
Largo, FL 33771

Dear Mr. Wiltison:

Please refer to your pre-investigational new drug application (PIND) file for sitagliptin hydrochloride oral solution.

We also refer to your submission dated June 11, 2021, containing a meeting request. The purpose of the requested meeting was to receive advice on the regulatory requirements and overall development program to support submission of a 505(b)(2) new drug application for the proposed product, sitagliptin hydrochloride oral solution.

Further reference is made to our Meeting Granted letter dated June 16, 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 June 11, 2021, background package.

If you have any questions, call Liz Godwin, Senior Regulatory Project Manager at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy Director (Acting)
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
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: PIND 155653

Product Name: sitagliptin hydrochloride oral solution
Proposed Indication: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Sponsor Name: VistaPharm, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

VistaPharm, Inc. (VistaPharm) is developing a new oral solution dosage form and new salt form of sitagliptin hydrochloride as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. As VistaPharm's product will differ from the proposed listed drug Januvia (sitagliptin phosphate) by dosage form and salt form, the Sponsor intends to submit a marketing application for their proposed product under the 505(b)(2) regulatory pathway.

On March 16, 2021, FDA issued an Exempt letter informing VistaPharm that their planned comparative bioavailability study met all the requirements for exemption from the IND regulations.

On June 11, 2021, VistaPharm submitted a combined type B Pre-IND meeting request and background package to receive advice on the regulatory requirements and their overall development program to support submission of a 505(b)(2) new drug application (NDA) for their proposed product.

The meeting was granted on June 16, 2021, as Written Responses Only.

2.0 QUESTIONS AND RESPONSES

Your questions are repeated below with our responses followed in bold font.

2.1. Regulatory/Administrative/Other

Question 1: Does the Agency agree that a 505(b)(2) regulatory pathway is appropriate for seeking approval for the proposed product, Sitagliptin Hydrochloride Oral Solution?

Does the Agency agree that JANUVIA (sitagliptin) tablets is an appropriate listed drug?

FDA Response to Question 1: **If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.**

We typically do not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Januvia (sitagliptin phosphate) tablets (NDA 021995) appears acceptable.

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Question 2: Does the Agency agree that a co-packaged dosing device is not necessary for the safe and effective use of Sitagliptin Hydrochloride Oral Solution, 25 mg/mL?

FDA Response to Question 2: **We agree that your proposal to not include a co-packaged dosing device is reasonable based on the available information regarding your proposed product.**

Question 3: Does the Agency agree that similar to the listed drug, the proposed product labeling should consist of Prescribing Information, Medication Guide, carton and immediate container labeling? Does the Agency foresee the need for any additional labeling pieces?

FDA Response to Question 3: **Your plan to submit Prescribing Information, Medication Guide, carton and container labeling is reasonable, however this is ultimately a review issue. Refer to the Prescription Drug Labeling Resources website[1] for additional details.**

Question 4: Does the Agency agree that VistaPharm does not need to establish a pregnancy exposure registry for the proposed drug product?

FDA Response to Question 4: **We agree that no pregnancy exposure registry is needed.**

2.2. Chemistry, Manufacturing, and Controls

Question 5: The active ingredient in the proposed drug product formulation is (b) (4). Does the Agency agree that if the proposed liquid drug product is (b) (4) in appearance, it can still be characterized as a solution dosage form?

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

FDA Response to Question 5: **Your proposal to characterize the drug product as a solution dosage form appears reasonable based on the provided information.**

Question 6: Are the proposed controls related to the liquid drug product's appearance acceptable to the Agency?

FDA Response to Question 6: **The proposed controls related to the drug product appearance appear to be reasonable. Confirm that the (b) (4) analytical methods and acceptance criteria are compliant with United States Pharmacopeia (b) (4) or shown to be equivalent.**

Additional microbiology comments for the future NDA submission:

1. **Note that the intended non-sterile aqueous drug product (Sitagliptin Hydrochloride Oral Solution, 25 mg/mL) should be tested for microbiological quality at commercial release and on the commercial stability program according to the USP test methods or methods validated as equivalent. The tests include total microbial enumeration (per USP <61>), absence of specified microorganisms (per USP <62>) and absence of Burkholderia cepacia complex (per USP <60>), with the acceptance criteria as recommended in USP <1111> for a non-sterile aqueous oral dosage form. Therefore, the release and stability tests of the intended drug product should include descriptions of these three tests and the acceptance criteria.**

2. **Purified water is indicated as an ingredient for the final drug product formulation. Note that non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC), which have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional (b) (4) systems. Thus, despite the presence of otherwise adequate (b) (4) systems, BCC strains can survive and even proliferate in product during storage. For additional information on BCC see PDA J Pharm Sci Tech 2011; 65(5): 535-43. In order to control for the presence of BCC in your product you should consider identifying potential sources for introduction of BCC during the manufacturing process, and in the NDA submission, you should identify these sources and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Therefore, indicate the risk assessment and process controls to mitigate BCC contamination during the manufacturing processes.**

3. **Because the intended product is a multi-dose formulation and [redacted] include antimicrobial effectiveness testing (AET) per USP <51> (or equivalent method) [redacted]**

2.3. Nonclinical

Question 7: Does the Agency agree that no new non-clinical studies are required based on the change in salt form from sitagliptin phosphate to sitagliptin hydrochloride?

FDA Response to Question 7: **We are unable to agree definitively that no new nonclinical studies are required prior to reviewing the quality data. Further toxicological assessment, if needed, would be based on bridging differences in the quality profile (e.g., degradant and impurity profile) or other attributes between your product and the listed drug, as appropriate.**

Question 8: Does the Agency agree that no new non-clinical studies are required based on the proposed use of [redacted] as a sweetener in the formulation?

FDA Response to Question 8: **Based on the qualitative and quantitative information provided on the individual components in [redacted] we do not anticipate the need for any new nonclinical studies to evaluate use of [redacted] as a sweetener in the drug product formulation.**

2.4. Clinical

Question 9: Does the Agency agree that the proposed comparative bioavailability study design and acceptance criteria are acceptable to demonstrate a clinical "bridge" to support reliance on FDA's previous findings of safety and effectiveness for the listed drug?

FDA Response to Question 9: **Your proposed approach to compare the relative bioavailability of the sitagliptin oral solution 25 mg/mL to the listed drug using the single 100 mg dose administered under the fasted state is reasonable with respect to the study design elements to establish the clinical bridge. Also see responses to Question #10 & #11.**

Question 10: Does the Agency agree that a comparative bioavailability study in the fasting state only is acceptable given that the listed drug is not labeled with a known food effect (can be taken with or without food)?

FDA Response to Question 10: **We recommend that you introduce an additional arm in the proposed fasted bioequivalence (BE) study to evaluate**

pharmacokinetics (PK) of your product under fed condition to also understand the food effect. Alternatively, you could plan a separate food effect study. Although the listed drug is not labeled with a known food effect, the change in dosage form for your product could impact the food effect.

Question 11: If the proposed fasting study shows comparable bioavailability, does the Agency agree that no additional clinical studies are needed to support approval?

FDA Response to Questions 10 & 11: **We cannot provide agreement at this time about whether additional clinical studies will be needed to support approval of your future NDA. In principle, we agree that if you establish an adequate scientific bridge from the listed drug to your product, including relative bioavailability then a safety and efficacy study would not be needed to support approval.**

2.5. PREA Requirements

Question 12: VistaPharm intends to propose the same indication and conditions of use (in adults) as the listed drug based on a demonstration of bioequivalence with the listed drug. As the listed drug received a pediatric study waiver for ages birth to 10 years and recently completed the deferred pediatric study in the older cohort, it is VistaPharm's belief that additional studies in the pediatric population will not be required for the proposed sitagliptin product and plan to propose this approach in an iPSP as required under PREA. Does the Agency agree with this approach?

FDA Response to Question 12: **Your proposed plan seems reasonable. However, we are unable to provide full agreement until review of a submitted initial pediatric study plan (iPSP). Per the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*[2], you should submit the iPSP no later than 210 calendar days before submitting a marketing application.**

Additional Comment:

1. **We note that you do not indicate if you plan to use a proprietary name for your product in the background package. However, if you intend to have a proprietary name for your product, we recommend that you submit your request for FDA review of your proposed proprietary name during the Pre-IND or IND phase of your drug development program.**

   The content requirements for such a submission can be found in the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

[2] 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.

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*. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

4.0 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.

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

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 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

[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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]

5.0 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]

6.0 505(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).[8] 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.[9]

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

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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
[8] 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.
[9] http://www.regulations.gov

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 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.

7.0 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/

LISA B YANOFF
08/10/2021 04:45:53 PM