CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205054Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205054

MEETING MINUTES

Saxon International Associates
Attention: Mr. Peter Saxon
US Agent: GP Pharm, SA
10 DeBary Place
Summit, NJ 07901

Dear Mr. Saxon:

Please refer to your New Drug Application (NDA) dated July 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutrate Depot® (leuprolide acetate) (b) (4) 22.5 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 7, 2015. The purpose of the meeting was to discuss the Complete Response letter dated May 29, 2015, and next steps for application approval.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Wheeler, Senior Regulatory Project Manager at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Post CR Letter
Meeting Date and Time:	October 7, 2015, 2:30PM-4PM
Meeting Location:	White Oak, Building 22, Room 1415
Application Number:	NDA 205054
Product Name:	leuprolide acetate
Indication:	Prostate cancer
Sponsor/Applicant Name:	GP Pharm, SA
Meeting Chair:	V. Ellen Maher, MD
Meeting Recorder:	Charlene Wheeler, MSHS

FDA ATTENDEES

Geoffrey Kim, MD	Director, DOP1
Amna Ibrahim, MD	Deputy Director, DOP1
V. Ellen Maher, MD	Clinical Team Leader, DOP1
Max Ning, MD, PhD	Medical Officer, DOP1
Tamy Kim, PharmD	ADRA, OHOP
Xiao Hong Chen, PhD	Quality Assessment Lead, ONDP
Li-Shan Hsieh, PhD	Chemistry Reviewer
Ali Al-Hakim, PhD	Chemistry Reviewer
Olen Stephens, PhD	Branch Chief, ONDP, Division 1, Branch II
Hui Zhang, PhD	Biostatistics Reviewer, DBV
Todd Palmby, PhD	Pharm/Tox Supervisor, DHOT
Qi Liu, PhD	Clinical Pharmacology Team Leader
Pengfei Song, PhD	Clinical Pharmacology Reviewer
Shenghui Tang, PhD	Biostatistics Team Leader
Christy Cottrell	Chief Project Management Staff, DOP1
Charlene Wheeler, MSHS	Senior Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Antonio Parente, PhD, MBA	Executive President
Berta Ponsati, PhD	CEO
Gemma Gambus, MD, PhD	Medical Director
Neil Shore, PhD	Principal Investigator
Mayte Vazquez, PhD	Regulatory Affairs Manager

Peter Saxon	US Agent
Rosa Sanahuja	Clinical Operations Manager

1.0 BACKGROUND

On July 31, 2014, GP Pharm SA submitted a New Drug Application (NDA) for Lutrate® Depot (leuprolide acetate for injection), (b) (4) 22.5 mg/vial, under the provisions of 505(b)(2). The proposed indication for this NDA was "palliative treatment of advanced prostate cancer". The application was reviewed under the Standard Review Designation.

On May 29, 2015, a Complete Response (CR) letter was issued to the Applicant. In the letter, the review division clearly specified the reasons for this CR action and provided pertinent recommendations to address the identified deficiencies. For details, see the CR letter.

For this Type A meeting, the Applicant aims to discuss the CR letter and clarify the next steps required for approval of this NDA. In the submitted meeting package, the Applicant provided their rationale and/or additional information for the intended discussion topics.

2. DISCUSSION

2.1. Clinical

Question 1: Pertains to comment 1 in the Complete Response Letter.

In the approval of gonadotropin releasing hormone agonists for the palliative treatment of advanced prostate cancer, testosterone levels serve as a surrogate marker of efficacy. When all available testosterone levels are used in the analysis, (b) (4) *Lutrate Depot 22.5 mg failed to achieve and maintain castrate testosterone levels in an acceptable percentage of patients.* (b) (4) *In study GP/C/05/PRO, Lutrate Depot 22.5 mg achieved and maintained castrate testosterone levels between Days 28-168 in 83.9% of patients. Further, the results of these studies are difficult to interpret since there may have been marked variations in dose due to the extent of overfill in each Lutrate vial.*

To address this deficiency, you should optimize your formulations of (b) (4) *Lutrate Depot 22.5 mg and conduct additional clinical trials to demonstrate the safety and efficacy of your products.*

Taking into consideration that Acute on Chronic and Breakthroughs are known and expected punctual testosterone elevations occurring during androgen deprivation therapy, key time points (KTP) at the end of each dose interval was defined as primary endpoint to evaluate the efficacy of the study drug in both clinical trials. In addition, at the Pre-NDA meeting held in October 2012, the Agency requested to the Sponsor to provide the primary endpoint of the phase 3 studies as written in the protocol: The proportion of patients with castrate testosterone levels (testosterone < 50 ng/dL) at key time points (b) (4)

(b) (4) days 28, 84 and 168 for LUTRATE DEPOT 22.5 mg 3 month formulations.

Does the Agency concur on the primary endpoint?

FDA Response: No, all testosterone levels should be used in the primary endpoint. Evaluation of the effectiveness of a GnRH analog for the palliative treatment of prostate cancer is based on the unequivocal demonstration of the achievement and maintenance of castration with the analog.

Using all available time points, the rate of castration maintenance was approximately 85% (b) (4) formulation, indicating that the (b) (4) formulations did not maintain castration despite the (b) (4) % dose overfill in the clinical batches.

We would like to remind you that the interpretability of clinical data also depends on the CMC acceptability of a study product or formulation. See response to Question 8.

Meeting Discussion: No discussion took place at the meeting.

Question 2: In addition to the primary endpoint, different sensitivity and comparative analyses are presented in the meeting package to support the efficacy of (b) (4) 3 month (L3M) formulations. For these analyses the Sponsor has applied the same efficacy end-points used by other LHRH agonist US marketed products as well as sensitivity analysis criterion proposed by FDA reviewers in their Assessment Reports. Results are discussed in the context of previously approved drug products.

Does the Agency concur that the results of these analyses reinforce the primary endpoint?

FDA Response: No. Sensitivity analyses should not be used to salvage a study with unreliable findings. See response to Question 1.

Meeting Discussion: No discussion took place at the meeting.

Question 3: Regarding study GP/C/05/PRO, the sponsor after an in-depth review of testosterone chromatograms has detected abnormal spikes that are not in line with the clinical and pharmacodynamic patient's profile observed in the study. Specifically, most of these chromatograms presented some interference. Therefore the Sponsor approached FDA for an opinion on sample reanalysis and decided to proceed accordingly.

The results obtained are presented and discussed in this meeting package and will be updated in the NDA re-submission.

Does the Agency agree that with this approach?

FDA Response: No, we do not agree. See response to Question 1. The decision to reanalyze selected samples was your choice. However, the reanalysis of selected samples is

biased and is not acceptable. If you plan to resubmit the reanalysis results, you should reanalyze all the samples rather than only 31 samples in your Study GP/C/05/PRO with a fully validated new method. You should provide adequate long-term stability data to cover the storage period of these samples to ensure that lack of testosterone degradation due to storage.

Given the identified issues concerning the quality of the (b) (4) Lutrate formulations, a complete reanalysis of the samples from this study may be unable to constitute a basis for re-evaluation of the efficacy of the Lutrate 22.5 mg formulation.

Meeting Discussion: FDA clarified that all samples should be re-analyzed with the new validated methodology.

Comments Added After the Meeting:

The quality of your product is not acceptable and, therefore, the results of your testosterone assays are uninterpretable.

While you met the pre-specified endpoint of your studies, it is necessary to analyze data from the clinical trials of the numerous GnRH agonists in the same way. Using our current method, a Kaplan-Meier analysis, these trials did not meet the current standard for approval of a GnRH agonist. The current standard is that the lower bound of the 95% confidence interval for the point estimate of the percentage of patients who maintained castrate testosterone levels during the treatment period should not be below 90%.

We remain concerned about the reanalysis of testosterone samples that have been stored for a prolonged period. We are also concerned that reanalysis of a portion of the samples may introduce bias in the results. Finally, the quality of your product is not acceptable and, therefore, the results of your testosterone assays are uninterpretable.

2.2. Product Quality

Question 4: Pertains to comment 2 in the Complete Response Letter.

The batch formula cannot accurately reflect drug product composition because batches were manufactured with different amounts of excipients. Provide a batch formula that reflects the proposed composition of the drug product registration batches.

Does the Agency concur with the company position and agree that all batches included in the application were manufactured using same batch formula?

FDA Response: No, FDA cannot concur. The manufacturing process described in the NDA (b) (4) This is not an acceptable practice as it does not accurately reflect the actual batch formula.

Meeting Discussion: FDA stated the wide range of leuprolide microspheres loaded into the vials would result in an unacceptable range in the rate release controlling excipients. The [redacted] **The Applicant acknowledged an understanding of the concerns underlying the deficiency comment and will provide data to address this deficiency. FDA emphasized that when responding to this deficiency, the Applicant should provide clear and detailed information regarding the manufacturing process (including batch records) to substantiate the claim** [redacted]

Question 5: Pertains to comment 3 in the Complete Response Letter.

[redacted]

Does the Agency concur with the Company Position and agree that the revised control for [redacted]?

FDA Response: No, the revised controls [redacted] **are not acceptable.** [redacted]

Meeting Discussion: No discussion took place at the meeting.

Question 6: Pertains to comment 4 in the Complete Response Letter.

You did not provide new information about overfill; however, you referenced Section 3.2.P.2.3.2.4 regarding the justifications provided in the original NDA. Provide justifications but NOT calculations to estimate the amount of product loss during drug delivery and subsequent amount of overfill needed to compensate for this loss.

Does the Agency concur with the Company position and agree that the information provided justify the excess product introduced into the vials?

FDA Response: FDA does not accept the justification for the large overfill in the drug product. As stated above, significant improvements remain to be made with regard to the formulation and manufacturing process. After further development, the improved product should allow for a significantly reduced overfill volume.

Meeting Discussion: No discussion took place at the meeting.

Question 7: Pertains to comment 5 in the Complete Response Letter.

The chemical physical properties of the drug substance have to be generated from the actual drug substance batches produced from manufacture. Provide chemical and physical properties of the drug substance from your manufactured batches.

Does the Agency concur with the Company position and agree that the studies conducted support the request included in the Complete Response Letter?

FDA Response: The data submitted in Annex 12 appears to respond to the complete response deficiency regarding drug substance characterization. Review of this data will occur after NDA resubmission. At that time, clarify and confirm that the characterization data originates from a single batch manufactured with the commercial process intended for the marketed product in the US.

Meeting Discussion: No discussion took place at the meeting.

Question 8: Pertains to comment 6 in the Complete Response Letter.

The stability of the three primary batches of drug substance and drug product is not acceptable because no stability data for the drug substance were provided in the NDA.

We consider the provided drug product stability data to only be supportive since they were obtained from annual reports. In addition, these data were collected from drug product batches obtained from marketed product available in foreign countries and packaged in a different packaging configuration.

Based on the above information, expiry dating for the drug substance and drug product cannot be established. Provide a stability study and related test data of the three primary batches of the drug substance and drug product.

Does the Agency agree that the stability data included in the application supports the shelf-life and storage conditions of the drug product to be commercialized in the US?

FDA Response: The data submitted in the meeting package appears to be the same data already reviewed for NDA 205054, which received a Complete Response. As outlined above, significant formulation and manufacturing process deficiencies were identified that lead to drug product batches with inconsistent quality. Any resubmission of NDA 205054 will require thorough pharmaceutical development to improve the manufacturing process (b) (4) **Once this development is complete, new registration and stability batch data will be necessary to support resubmission of the NDA. Future communications regarding the adequacy of data packages to resolve the CMC Complete Response deficiencies should include a summary of activities to improve the formulation and manufacturing process as well as manufacturing data (executed batch records) to document changes made since the original NDA submission.**

Meeting Discussion: FDA clarified that the data needed to address the deficiency in the stability data would include three freshly manufactured drug substance batches, with full characterization, used to manufacture the drug product stability batches using the current manufacturing process.

The Applicant will follow up with a proposal for consideration that will be submitted as a meeting request for written responses.

Question 9: Pertains to comment 7 in the Complete Response Letter.

(b) (4)

Does the Agency agree with the limit proposed for the release curve 4 hour time point?

FDA Response: No, the FDA does not agree with the justifications for the *in vitro* release acceptance criteria. As stated in the response to Question #8, FDA has identified several concerns regarding the manufacturing process and formulation. Addressing these concerns will require pharmaceutical development that will improve the product's consistency and quality. New batch and stability data for lots manufactured with the new process and formulation will be required in the NDA resubmission. Additionally, BA/BE data may be necessary depending on the degree of formulation/manufacturing changes implemented in the pharmaceutical development. As such, the current *in vitro* release method may not be applicable to the new lots. When the NDA is resubmitted, the revised *in vitro* release method and its acceptance criteria should be discriminatory and clinically relevant.

Meeting Discussion: No discussion took place at the meeting.

2.3. Regulatory

Question 10: Pertains to comment 8 in the Complete Response Letter.

(b) (4)

Does the Agency agree with the company position (b) (4) should be included in the application?

FDA Response: No. Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness (b) (4)

Meeting Discussion: No discussion took place at the meeting.

FDA Post Meeting Minute Addendum: Upon further review of your justification regarding patent certification to patent (b) (4) **since you are not relying on the Lupron Depot** (b) (4) **strength for approval, you will not be required to certify** (b) (4)

Question 11: Pertains to comment 9 in the Complete Response Letter.

As stated in our PreNDA meeting minutes dated October 24, 2012, if you rely 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. You should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. (b) (4)

(b) (4)

(b) (4)

Alternatively, you may demonstrate similarity to the listed drug by conducting comparative studies between your proposed product and Lupron Depot, such as comparative physico-chemical tests and bioassays, nonclinical data, pharmacokinetic (PK)/pharmacodynamics (PD) data, and clinical studies.

Does the Agency agree with the company position?

FDA Response: Your bridge appears to be acceptable.

Meeting Discussion: No discussion took place at the meeting.

2.4. Clinical

Question 12: Pertains to the Safety comment in the Complete Response Letter.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

Should the safety assessment and report of study (b) (4) be included in NDA 205054? In case it is, please confirm if standardized data sets in accordance with CDISC SDTM should be included in the application.

FDA Response: You should submit safety data from new clinical studies if you plan to resubmit the application.

The safety data from Study (b) (4) is not needed for resubmission.

Meeting Discussion: No discussion took place at the meeting.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance

below. The PSP 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 PSP 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 PSP, including a PSP 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. 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 http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues require further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor will submit a Type C meeting request for CMC	Sponsor	N/A

6.0 ATTACHMENTS AND HANDOUTS

See attached.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLENE N WHEELER
10/29/2015

VIRGINIA E MAHER
10/29/2015

29 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page