CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209410Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103538

MEETING MINUTES

Osmotica Pharmaceutical US, LLC
Attention: Mark S. Aikman, PharmD
Vice President, Regulatory Sciences
1904 Eastwood Road
Lumina Station #2, Suite 205
Wilmington, NC 28403

Dear Dr. Aikman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Osmolex ER (Amantadine HCl Extended Release Tablets).

We also refer to the meeting between representatives of your firm and the FDA on November 2, 2016. The purpose of the meeting was to discuss the proposed NDA.

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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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 B
Meeting Category:	PreNDA
Meeting Date and Time:	November 2, 2016; 2:00 – 3:00 PM EST
Meeting Location:	FDA White Oak Campus; 10903 New Hampshire Ave. Silver Spring, MD; Building 22, Rm. 1309
Application Number:	IND 103538
Product Name:	Osmolex ER (Amantadine HCl Extended Release Tablets).
Indication:	Treatment of Parkinson's disease (b) (4)
Sponsor/Applicant Name:	Osmotica Pharmaceutical US, LLC
Meeting Chair:	Eric Bastings, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES
Eric Bastings, MD, Deputy Director
Gerald David Podskalny, DO, MPHS, Clinical Team Leader
Susanne Goldstein, MD, Clinical Reviewer
J. Edward Fisher, PhD, Supervisory Nonclinical Pharmacologist
Luann Mckinney, PhD, Nonclinical Pharmacologist
Xiangmin Zhang, PhD, Statistical Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Bilal AbuAsul, PhD, Clinical Pharmacology Reviewer
Ta-Chen Wu, PhD, Acting Biopharm Lead
Martin Rusinowitz, MD, CSS Reviewer
Tracy Peters, PharmD, Director of Labeling
Brenda Reggettz, PharmD, DNP RPM
Annie Nguyen, PharmD, DNP RPM
Stacy Metz, PharmD, Senior Regulatory Project Manager

SPONSOR ATTENDEES
Tina deVries, PhD, Osmotica Executive VP, Research & Development
Samer Kaba, MD, Osmotica VP, Global Clinical Development and Medical Affairs
Angela Dentiste, MBA, Osmotica VP, Clinical Operations
Mark Aikman, PharmD, Osmotica VP, Regulatory Science

George Spanos, PhD, Osmotica VP Analytical Services
(b) (4)

George Wagner, Vice President, Regulatory Affairs, Osmotica

1.0 BACKGROUND

Osmotica Pharmaceutical US LLC (Osmotica), has developed a new extended release dosage form, Amantadine HCl Extended Release (ER) Tablets (Osmolex ER), for once daily oral administration for treatment of Parkinson's disease. Osmotica has been in discussion with the Division regarding this product since the January 2009, Pre-IND Meeting. Osmotica and the Division have also held a December 2009, SPA discussion meeting, a January 2014, End-of-Phase 2 meeting (EoP2), and a July 2014, EoP2 CMC meeting.

All of these discussions centered on the use of Osmolex ER for the treatment of Levodopa-Induced Dyskinesia (LID). Two phase 3 studies in LID were completed; (b) (4) . Osmotica desires to seek approval of Osmolex ER for the treatment of Parkinson's disease. In support of this 505(b)(2) application, Osmotica intends to rely on the FDA's previous finding of safety and/or effectiveness for amantadine HCl capsules (discontinued Endo NDA 016020, Symmetrel Capsules). Osmotica Pharmaceutical US LLC is targeting the submission of an NDA for Osmolex ER (Amantadine HCl ER Tablets) in 4th quarter 2016.

FDA sent Preliminary Comments to Osmotica on October 31, 2016.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls Questions

Question 1:

Does the Agency agree with the proposed specifications for the drug substance and the drug product?

FDA Response to Question 1:

In general, the proposed test parameters for the drug substance appear reasonable. The acceptability of the analytical procedures and acceptance criteria is a matter for review. At this time, we note the following concerns and recommendations.

Drug Substance

- The current specification includes testing for Heavy Metals per USP <231>. We recommend that you transition to testing for Elemental Impurities consistent with ICH Q3D and USP <232>/<233>.

- We recommend that you revise the limit for individual unknown impurities from not more than (NMT) (b) (4)% to NMT (b) (4)% consistent with the recommendation in ICH Q3A (R2) Impurities in New Drug Substances.
- Currently, assay is determined by titration per USP. Provide justification that the GC related compounds methods is specific for process impurities and potential degradants.

Drug Product

We do not agree with your proposed dissolution acceptance criteria at this time. As we conveyed to you at the EoP2 CMC meeting (July 9, 2014), (b) (4) Acceptability of the proposed dissolution acceptance criteria will be a review issue and determined at the NDA stage based on the totality of the data. Please investigate the root cause for the variability associated with the dissolution method.

Meeting Discussion:
No further discussion at the meeting.

Question 2:

Does the Agency concur that the stability data will support an expiration date of (b) (4) months for the 160 mg, 240 mg and 320 mg Amantadine HCl Extended Release Tablets?

FDA Response to Question 2:

The expiration dating period for the drug product will be determined during the review, based on the extent and quality of the stability data. We acknowledge that the long-term stability that is available for the NDA will include long-term stability data through 30 months in bottles and 24 months in blister packaging. However, per the recommendations in ICH Q1E Evaluation of Stability Data, the long-term data for the remaining batches, 18 months in bottles and blisters, would not support extrapolation beyond 30 months.

Meeting Discussion:
No further discussion at the meeting.

Question 3:

Does the Agency agree that the data are adequate to address concerns regarding the potential alcohol dose-dumping of the Drug Product?

FDA Response to Question 3:

We agree that the in-vitro dissolution profiles you have generated for up to 2 hours seem to indicate a lack of alcohol-induced dose-dumping of the proposed ER drug product. However, submit the complete dissolution profiles (i.e., up to 8 hours) within the NDA.

We note the increased drug release rate as a function of alcohol content in the dissolution media. In the NDA submission, discuss the potential clinical consequences (including labeling implications) of increased drug release with alcohol consumption.

Meeting Discussion:

The Sponsor inquired about the acceptability of partial dissolution profiles. FDA clarified the comment provided at the End of Phase 2 meeting recommending the Sponsor submit complete dissolution profiles beyond 2 hours for investigating the potential alcohol-induced dose-dumping. FDA is concerned about a potential for increased drug release at 2 hours post dose. FDA also recommended that the Sponsor provide supporting information with the NDA submission to address any clinical concern and labeling implications of increased drug release from the proposed ER drug product with alcohol consumption.

Question 4:

Does the Agency agree that that Amantadine HCl ER Tablets meet the requirement for an extended release designation?

FDA Response to Question 4:

The information you provided with respect to in vitro drug release profiles of all 3 strengths, bioavailability profile and steady-state pharmacokinetic performance (Studies OS320-PKP05, OS320-PKP06, and OS320-PK04) appear to support the extended release claim for your drug product. The final determination of the ER claim is a review issue.

Meeting Discussion:
No further discussion at the meeting.

2.2. Nonclinical Question

Question 5:

Does the Agency concur that no additional preclinical data are required for this application?

FDA Response to Question 5:

Based on the information provided, no additional nonclinical data will be needed; however, the adequacy of your application will be a matter of review.

Meeting Discussion:
No further discussion at the meeting.

2.3. Clinical Questions

Question 6:

Does the Agency concur that the data from of the steady state bioavailability study provide a bridge to the approved amantadine HCl capsule NDA?

FDA Response to Question 6:
As presented in your briefing packet, the Cmax and AUC for amantadine HCl ER and amantadine HCl oral syrup (RLD) appear within bioequivalence (BE) limits. However, there is a significant difference in Tmax between Amantadine HCl ER and the RLD (mean 7.5 hours for amantadine HCl ER vs. 2-3 hours for amantadine HCl oral syrup). You will need to address the possible pharmacodynamic effect and clinical implications of a delayed Tmax. In addition to the BE analyses for Cmax, AUC and Cmin, you should provide a point-by-point comparison for the PK profiles of the amantadine ER product and immediate release product, to further assess the similarities between the profiles.

Meeting Discussion:

FDA had concerns about the potential clinical implications of having a delayed Tmax with Osmolex versus amantadine IR. The Sponsor opined that the clinical effect of amantadine is better described by AUC rather than the time to dose response.

In order to use BA/BE pathway, the Sponsor would need to rely on the similarity between the pharmacokinetic (PK) profiles of Osmolex and amantadine IR. This would require comparing the Osmolex PK parameters at multiple time points (partial AUC measurements) and to amantadine IR. Although the two drug products may not match on every time point, a justification should be provided for the time points at which Osmolex is disparate from amantadine IR.

Question 7:

Does the Agency concur that the renal impairment study (Study OS320-PKP07) supports dose adjustment recommendations for the label?

FDA Response to Question 7:

The acceptability of the proposed dose adjustments in renal impairment will be a matter of review. You should also provide PK modeling and simulations that support your dose adjustments in patients with different stages of renal impairment.

Meeting Discussion:
No further discussion at the meeting.

Question 8:
Does the Agency concur that the phase 1 studies provide sufficient data to support the filing of the NDA under section 505(b)(2)?

FDA Response to Question 8:

The phase 1 studies conducted seems sufficient to support the submission of an NDA under section 505(b)(2). However, please also refer to our response to Question 6. The acceptability of the data will be a matter of review.

Additional Clinical Pharmacology Comments,

You need to conduct in-vitro studies to evaluate whether amantadine is a substrate/inhibitor of major drug transporters. Please refer to the FDA guidance for drug interaction for additional details.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

Meeting Discussion:
No further discussion at the meeting.

Question 9:

Does the Agency agree with Sponsor's proposed indication of Parkinson's disease (b) (4) *for Osmolex ER?*

FDA Response to Question 9:

If you provide an adequate PK bridge to amantadine immediate-release oral capsules, your application may support a similar indication to that of Symmetrel for the treatment of Parkinson's disease.

The final indication language would be decided during the review of an NDA.

Meeting Discussion:

The RLD for comparison with Osmolex is amantadine IR syrup. However, this product has been withdrawn. The Sponsor has submitted a petition to have an FR notification placed stating that the withdrawal was not for safety or lack of efficacy. The sponsor is unsure that the FR notification posting will occur prior to filing of their NDA and is concerned this will lead to a refusal to file.

The Division stated they would have to consult with the (b)(2) committee and include a post-meeting response in this document.

Post Meeting Note:
A product does not have to be listed in the Federal Register as "not withdrawn for reasons of safety or efficacy" to be used as the RLD.

Question 10a:

Does the Agency agree with Sponsor's plan to include the safety data from studies OS320-3005 and OS320-3006 in the submission to supplement the safety data supporting this NDA?

FDA Response to Question 10a:

If you provide an adequate PK bridge to amantadine immediate-release oral capsules, it is unclear whether data from studies OS320-3005 and OS320-3006 would provide additional useful safety information (b) (4). This will be a matter for review.

Meeting Discussion:
No further discussion at the meeting.

Question 10b:

If the Agency agree that safety data from the phase 3 studies should be included in the NDA, does the Agency agree (b) (4)

FDA Response to Question 10b:
See answer to Question 10a.

Meeting Discussion:
No further discussion at the meeting.

Question 11:

Does the Agency agree with the plan of including CRFs of subjects who died, reported an SAE, or discontinued due to AEs with this submission?

FDA Response to Question 11:

Yes, we agree with your plan to include CRFs of subjects who died, reported a serious adverse event (SAE) or discontinued due to adverse event. You should also include narratives for all subject deaths, nonfatal SAEs, adverse events leading to withdrawal, dose reduction, or institution of concomitant therapy in your submission. In addition, you should include a tabular summary of all subjects who discontinued. Provide a tabular and written summary of all patients who reported an adverse event any time before discontinuing from the study, regardless of the reason given for discontinuation (e.g., lost to follow-up or consent withdrawn).

Meeting Discussion:

The Sponsor asked for clarification regarding the Division's request for additional safety summaries for patients who discontinued early from the clinical studies that will be submitted in the NDA. The division's clinical reviewers noted that a high proportion of patients in the amantadine ER group (approximately 30-40%) discontinued study participation early. The Division requested the Sponsor provide a summary and discussion of the temporal relationship between adverse events and patient discontinuation from the studies submitted in the NDA. The Sponsor still needs to submit narratives for patients who experienced and adverse event that led to discontinuation or withdrawal of study medication. The Division requests the sponsor analyze the potential relationship between the study drug and adverse events, such as the type of event and the time from adverse event to patients discontinuation, regardless of whether the event was classified as causing the patients to withdraw. The Division requests the Sponsor include written and tabular summaries of these analyses, but there is no need to create additional individual case narratives.

Question 12:

Does the Agency agree that Osmotica should provide the Amantadine HCl ER Tablet label in PLR format?

FDA Response to Question 12:

Yes, the Prescribing Information you will include in your marketing application must conform to the Physician's Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements.

Meeting Discussion:
No further discussion at the meeting.

Question 13:

Does the Agency agree that a review of the published literature currently available would be sufficient to support the pregnancy section of the label?

FDA Response to Question 13:

Your plan to provide a thorough review of the published literature is sufficient to support the information you will propose in the Pregnancy (8.1) and Lactation (8.2) subsections, and also either the inclusion of information in or omission of the Females and Males of Reproductive Potential (8.3) subsection. The acceptability of the information included in the submission will be a matter of review.

You also must establish that reliance on the studies described in the literature or on other studies is scientifically appropriate. Please refer to the 505(b)(2) Regulatory Pathway section in this document.

Meeting Discussion:
No further discussion at the meeting.

Question 14:

Does the Agency agree that relative bioavailability, dose proportionality and food effect information from the phase 1 studies should be added to the existing immediate release product pharmacokinetic information in the proposed label?

FDA Response to Question 14:

It is premature to discuss labeling issues related to your product and/or the RLD. This would be a matter for review in an NDA.

Meeting Discussion:
No further discussion at the meeting.

2.4. Administrative Questions

Question 15:

Does the Agency concur that the previously approved Initial Pediatric Study Plan and waiver of PREA requirements continue to be acceptable?

FDA Response to Question 15:
Yes. However, you need to request a waiver from PREA requirements in the Pediatric Plan included in your NDA. Please refer to the PREA Requirements section in this document.

Meeting Discussion:
No further discussion at the meeting.

Question 16:

Does the Agency agree that NDA 016020 (Symmetrel Capsules) is appropriate as the sole listed drug product on form 356h for acceptance and approval of this 505(b)(2) NDA?

FDA Response to Question 16:

You have identified NDA 16020 for Symmetrel (amantadine) immediate-release oral capsules, which is no longer marketed, as the listed drug upon which you intend to rely to support approval of your proposed product, an extended-release tablet formulation of amantadine. However, your scientific bridge is a comparison of the relative bioavailability (BA) of your proposed product to

an ANDA product for a different dosage form of amantadine, i.e., ANDA 75060 (Wockhardt) amantadine oral syrup, a marketed listed drug identified in the Orange Book as a reference standard. Please explain how the results of a comparison of your proposed product to ANDA 75060 support reliance on our finding of safety and effectiveness for Symmetrel oral capsules.

A satisfactory finding from your relative BA study and scientific explanation bridging NDA 16023 for Symmetrel to the amantadine oral syrup product may provide justification for reliance on our finding of safety and effectiveness of NDA 16023 for Symmetrel. Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

Meeting Discussion:
See Meeting Discussion for Question 9.

Question 17:

Is this data format approach acceptable, and does the Division have additional specific data format requests?

FDA Response to Question 17:

Please refer to the information in Data Standards for Studies and Office of Scientific Investigations (OSI) Requests in the Other Important Information section of this document.

Meeting Discussion:
No further discussion at the meeting.

3.0 OTHER IMPORTANT INFORMATION

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.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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 (Catalog) (See http://www fda.gov/forindustry/datastandards/studydatastandards/default htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), 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 will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635 htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459 htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

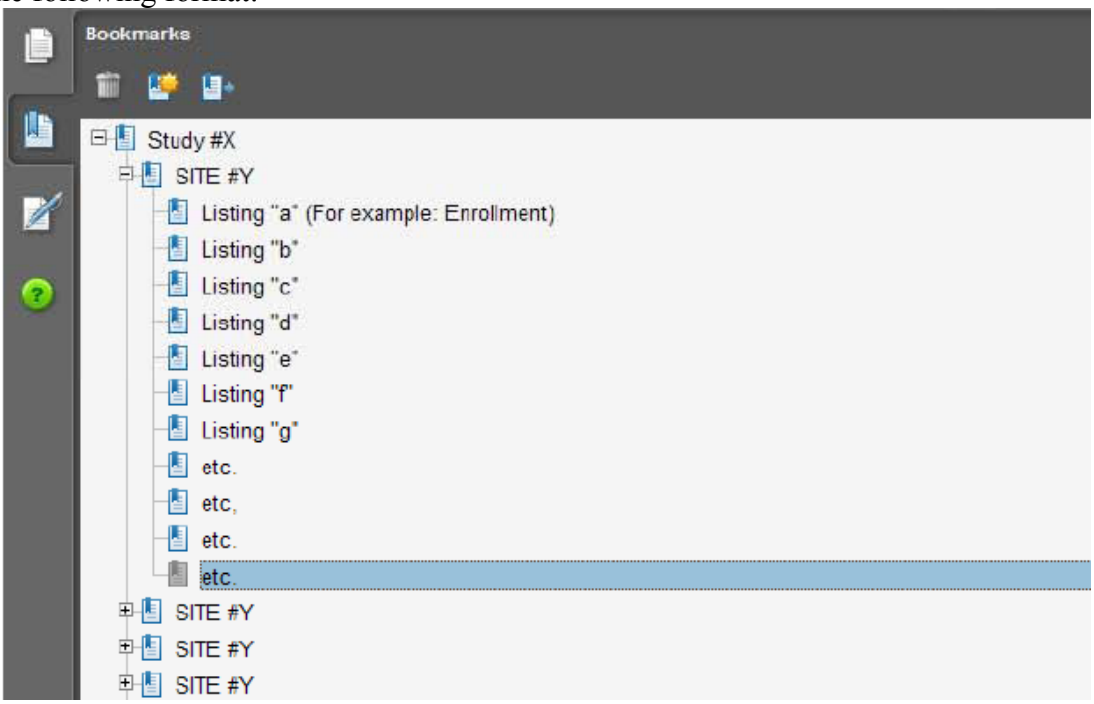
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No items require further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

No attachments and handouts.

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

/s/

ERIC P BASTINGS
12/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103538

MEETING MINUTES

Osmotica Pharmaceutical Corp
Attention: Mark S. Aikman, PharmD, Vice President, Regulatory Sciences
1205 Culbreth Dr., Suite 200
Wilmington, NC 28405

Dear Dr. Aikman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amantadine Hydrochloride Extended Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 9, 2014. The purpose of the meeting was to gain Agency concurrence on CMC and Regulatory information for Phase 3 clinical program and subsequent new drug application submission.

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, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
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 B
Meeting Category:	End-of-Phase 2 CMC
Meeting Date and Time:	July 9, 2014; 11:00 am – 12:00 pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 103538
Product Name:	Amantadine Hydrochloride Extended Release Tablets
Indication:	Treatment of Levodopa-Induced Dyskinesia (LID) in Patients with Parkinson's disease
Sponsor/Applicant Name:	Osmotica Pharmaceutical Corp.
Meeting Chair:	Olen Stephens
Meeting Recorder:	Teshara G. Bouie

FDA ATTENDEES
Olen Stephens, Ph.D., Acting Branch Chief
Martha Heimann, Ph.D., CMC Lead
Shastri Bhamidipati, Ph.D., Review Chemist
Sandra Suarez-Sharp, Ph.D., Biopharmaceutics Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

SPONSOR ATTENDEES

Praveen Tyle, Ph.D.	President & Chief Executive Officer
Mark Aikman, PharmD	Vice President, Regulatory Sciences
Tak-Yee Lee, Ph.D.	Vice President, Project & Program Management
George Spanos, Ph.D.	Global Head, Analytical Services

1.0 BACKGROUND

IND 103538 is being developed for the treatment of Levodopa-Induced Dyskinesia (LID) in Patients with Parkinson's disease. On May 8, 2014, the sponsor requested a meeting gain Agency concurrence on CMC and Regulatory information for Phase 3 clinical program and subsequent new drug application submission. Background packages were received on June 6, 2014. Preliminary responses were sent to the sponsor on July 3, 2014. On July 8, 2014, the Sponsor amended their meeting request to discuss only questions 5 and 7 and to provide stability data (b) (4)

2. DISCUSSION

Question 1 – Does the Agency concur with the tentative specifications for Amantadine Hydrochloride drug substance as in Table 1?

FDA Preliminary Response: We agree that the proposed specification for Amantadine Hydrochloride appears appropriate.

Discussion: *No further discussion at the meeting.*

Question 2 – Does the Agency have any concern with the qualitative and quantitative composition of the drug product intended for Phase 3 and subsequent NDA registration?

FDA Preliminary Response:
(b) (4) the approval of the strengths not tested in pivotal phase 3 trials should be based on in vivo bioequivalence testing. The FDA is willing to entertain a bracketing approach proposal to address this requirement.

Otherwise, we do not have any concern with the qualitative and quantitative composition of the drug product intended for Phase 3 and subsequent NDA registration if they are in compliance with Inactive Ingredient Guide (IIG). Please be advised that adequacy of the formulation is a subject matter of NDA review.

Discussion: *No further discussion at the meeting.*

Question 3 – Does the Agency concur that the proposed manufacturing process and process controls are appropriate to support consistent manufacture of the drug product for Phase 3 clinical materials and subsequent NDA registration?

FDA Preliminary Response: We agree that the proposed manufacturing process and process controls appear to be appropriate for manufacture of the drug product for Phase 3

clinical materials and subsequent NDA registration pending review of data in the NDA as to drug product quality.

Discussion: *No further discussion at the meeting.*

Question 4 – Does the Agency concur with the tentative specifications for the amantadine hydrochloride extended release tablets for Phase 3 clinical materials and subsequent NDA registration as in Table 3?

FDA Preliminary Response:
In general, the proposed specifications for the drug product appear suitable. However, it is premature to comment on the acceptability of the proposed dissolution acceptance criteria. Refer to the additional biopharmaceutics comments section for points to consider on the selection of the dissolution acceptance criteria of your proposed product.

Discussion: *No further discussion at the meeting.*

Question 5 – Osmotica will conduct stability studies of 3 batches of each product strength packaged in HDPE bottles. (b) (4) does the Agency concur that stability data of (b) (4) following ICH conditions is adequate in the NDA?

FDA Preliminary Response: In the absence of data, we recommend that you file the NDA with the following stability data for the blister configuration: three batches of the highest and lowest strengths and one batch of the intermediate strength. The shelf life of the blisters and bottle configurations will be evaluated separately.

Discussion: (b) (4)

Question 6 - (b) (4)

(b) (4)

Additional Comments

We have the following comments regarding the biopharmaceutics information (not limited to) that should be provided in your NDA.

1) **Dissolution Method:** Include the dissolution method report supporting the selection of the proposed test. The report should include the following information:
   a. The pH solubility profile;
   b. Detailed description of the in dissolution method being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the*

equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least (b)(4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least six samples per testing variable;

c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the amount of drug release with time; and

d. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables.
In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

Discussion: *No further discussion at the meeting.*

2) Dissolution acceptance criteria: For the selection of the dissolution acceptance criteria of your product, the following points should be considered:

a. The in vitro dissolution profiles should encompass the timeframe over which at least (b)(4)% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.

b. The dissolution profile data from the bio-batches (clinical & PK) should be used for the setting of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values).

c. The establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set, in addition to the early release criterion at 30 min (b)(4).
The specification ranges should be based on the overall dissolution data generated at these times and should be based on average in vitro release data for each lot under study, equivalent to USP Stage 2 testing (n=12).

d. In general, the selection of the dissolution specification ranges is based on mean target value (b)(4)% and NLT (b)(4)% for the last specification time-point. (b)(4)

e. The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Note that the final determination on the acceptability of the dissolution method is a review issue that may be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Discussion: *No further discussion at the meeting.*

3) **In Vitro Alcohol Dose-Dumping Study:** When evaluating for the potential of alcohol-dose dumping, you should conduct in vitro drug release testing initially using the highest strength and you may have to follow-up with an in vivo study, depending on the result of the in vitro testing. You should discuss the result of your in vitro study with the Agency prior to the NDA submission.

    a. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
    b. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
    c. Conduct an statistical test (e.g. f2 testing) to assess the similarity (or lack thereof) in the dissolution profiles.
        - Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.
        - The report should include the complete data (i.e., individual, mean, SD, comparison plots, similarity results, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

    Discussion:
    The Sponsor inquired about the relevance in conducting the in vitro alcohol interaction study for a product that also has IR characteristics. The FDA responded that to address the concern, the study could be conducted using the ER core only; however, it was recommended that the study also includes the evaluation of the final drug product as a whole to account for any potential effect of the IR layer on the outcome of the results.
    Alternatively, the sponsor was advised to submit their justification explaining why dose-dumping may not be an issue for their proposed product. The sponsor should also consider both the safety and efficacy impact of dose-dumping in their justification.

4) **Extended Release Designation Claim:** The following information should be submitted to support the extended release designation claim (refer also to CFR 320.25f):
    - The BA profile established for the drug product rules out the occurrence of any dose dumping;
    - The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release

drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA;
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
- The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

Discussion: *No further discussion at the meeting.*

Additional Discussion:
The Agency questioned what kind of controls are in place to ensure proper drilling of the extended release cores. The Sponsor stated controls for drilling the hole include (b) (4) *The Agency requested this control information be submitted in the NDA.*

The sponsor requested advice regarding food affect, dose proportionality, and PK at steady state plans. The Agency stressed to the sponsor that Clinical Pharmacology should provide advice on these plans, not ONDQA. The sponsor's clinical pharmacology questions should be submitted to the Division of Neurology Products.

The sponsor questioned if they could get accelerated approval since this will be the first product with this indication. They would like to submit the CMC information first. The Agency informed the Sponsor that it's premature to respond to this request and clinical input is required to make this decision.

The Sponsor questioned why they have to conduct the in vitro alcohol dose-dumping study in three different media. The Agency responded that testing in three media are only required when the dissolution method for quality control purposes has not been established. Otherwise, the FDA current recommendation is to conduct the testing in the QC and 0.1N HCl medium.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Action Item/Description	Owner
(b) (4)	FDA: completed and advice included under discussion for Q7
	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

TESHARA G BOUIE
07/14/2014

OLEN M STEPHENS
07/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103538

MEETING MINUTES

Osmotica Pharmaceutical Corp.
Attention: Mark S. Aikman, PharmD
Director, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Dr. Aikman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amantadine HCl Extended Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 15, 2014. The purpose of the meeting was to discuss the overall development program that includes two Phase 3 studies.

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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-796-2139.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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 B
Meeting Category:	End of Phase 2
Meeting Date and Time:	January 15, 2014, 3:00 – 4:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	103538
Product Name:	Amantadine HCl Extended Release Tablets
Indication:	Treatment of Levodopa-Induced Dyskinesias in patients with Parkinson's disease
Sponsor/Applicant Name:	Osmotica Pharmaceutical Corp.
Meeting Chair:	Eric Bastings, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES
Eric Bastings, MD, Deputy Director
Dave Podskalny, DO, MPHS, Clinical Team Leader
Susanne Goldstein, MD, Clinical Reviewer
Martha Heimann, PhD, CMC Team Leader
Angela Men, PhD, Clinical Pharmacology Team Leader
Kristina Dimova, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Leader
Ohid Siddiqui, PhD, Statistical Reviewer
Aaron Sherman, DNP
Stacy Metz, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES
Praveen Tyle, PhD, President & Chief Executive Officer
Mark Aikman, PharmD, Vice President, Regulatory Sciences
Gene Wright, PharmD, PhD, Vice President, Head of Global Clinical Development
Angela Dentiste, MBA, Vice President, Clinical Operation
Lan-Chi Nguyen, MS, RAC, Sr. Manager, CMC Documentation
(b) (4) Consultant
(b) (4) Consultant

1.0 BACKGROUND

This is a 505(b)(2) application for Amantadine HCl Extended Release Tablets for Treatment of Levodopa-Induced Dyskinesias in Patients with Parkinson's disease. On September 17, 2013, Osmotica Pharmaceutical Corp. requested a Type B EOP2 meeting to discuss the overall development program that includes two Phase 3 studies. The meeting package was submitted on December 17, 2013. The preliminary responses were sent to the sponsor on January 13, 2014. The sponsor provided pre meeting responses on January 14, 2014 and those responses have been incorporated into this document.

2.0 DISCUSSION

2.1. Clinical Questions

(b) (4)

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

FDA Response:
Yes.

Meeting Discussion:
No further discussion at the meeting.

Question 5:
Does the Agency agree with the proposal for establishing the dosing guideline for Amantadine HCl ER Tablets for patients with renal impairment?

FDA Response:
Due to the severe cardiac toxicity caused by overdose of this drug, you need to study amantadine ER pharmacokinetics in patients with renal impairment or contraindicate the drug in this patient population. (b) (4) *to support dosing recommendation for patients with moderate/severe renal impairment in labeling, you should* (b) (4) *conduct dedicated studies in this patient population.*

Sponsor Pre-meeting Comments:

(b) (4)

(b) (4)

Meeting Discussion:
The sponsor asked for clarification about the dosing recommendations for patients with moderate/severe renal impairment. (b) (4)

The Agency accepted the sponsor's proposal to conduct a dedicated study in patients with severe renal impairment and use simulations to support dosing in patients with moderate renal impairment. (b) (4)

The Division asked the sponsor to submit the protocol for review and propose dosing adjustments in patients with renal impairment, similar to those in the Symmetrel label using the ER tablet strengths (160 mg, 240 mg, 320 mg).

Question 6:
Does the Agency agree that this program of clinical pharmacology studies is sufficient to support the NDA submission?

FDA Response:
On face, the planned clinical pharmacology studies are acceptable; however, you need to provide a list of prohibited co-medications and alcohol restrictions subjects must adhere to during these studies.

According to the Pre-IND package (2009), (b) (4) *; please confirm whether this still applies. In addition, please clarify whether the same Amantadine HCl ER formulation (as the one used in the Phase 2 trial) will be used in the phase 3 trials.*

We recommend the following clinical pharmacology studies:

- *An in vitro alcohol dumping study. Whether an in-vivo alcohol dumping study is needed will depend on the results of the in-vitro study.*
- *A BE study may be needed if there are substantial changes between the clinical trial and to-be-marketed formulation.*

Meeting Discussion:
No further discussion at the meeting.

2.2. Regulatory Questions

Question 7:

According to the Draft Guidance "How to Comply with the Pediatric Research Equity Act", September 2005, Parkinson's disease is on the example list of adult-related conditions that may qualify for a waiver of clinical studies in pediatric subjects. Osmotica requests a full waiver of pediatric studies. Does the Agency agree?

FDA Response:

The waiver letter you have submitted is insufficient. You must submit an initial Pediatric Study Plan (iPSP) within 60 days of this EOP2 meeting. You must include justification for your request for a waiver for the pediatric studies required under PREA. Please refer to the following guidance for additional information:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf

Meeting Discussion:

No further discussion at the meeting.

Question 8:

Is there any additional guidance from the Agency on the Amantadine HCl Extended Release Tablets program to support NDA submission?

FDA Response:

We have the following additional comments about Clinical Protocol OS320-3005:

(b) (4)

Meeting Discussion:
No further discussion at the meeting.

STATISTICAL COMMENTS
In this submission, you have included a study protocol for the study OS320-3005. The study has three arms: 320mg, 240mg, and placebo. The proposed included statistical analysis plan is not acceptable.

Sponsor Pre Meeting Comments:
In general, Osmotica is in agreement with the Division's comments. However, Osmotica seeks some minor clarifications which will be addressed in the meeting.

Meeting Discussion:
The sponsor should submit a Statistical Analysis Plan (SAP) for the pivotal studies. The SAP should describe how the sponsor plans to adjust for drop-outs in the studies, as well as imputation methods for the "worst case scenario".

CMC COMMENTS
We do not have specific comments at this time; however, we recommend that you request a CMC only meeting to discuss your commercial development plans.

Meeting Discussion:
The sponsor expressed appreciation and will follow up with a CMC meeting request.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a web page 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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 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. 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 you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product or a non-U.S. approved version of the product) as the comparator.

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative bioavailability study, it is recommended you use the ANDA product designated as the RLD in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not 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

There were no issues that required further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes. The sponsor pre meeting comments were incorporated into this document.

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

/s/

ERIC P BASTINGS
02/11/2014