

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205649

SUPPL #

HFD # 510

Trade Name Xigduo XR

Generic Name dapagliflozin and metformin HCl

Applicant Name Astra Zeneca

Approval Date, If Known October 29, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The Applicant requested 5 years of market exclusivity because at the time of submission (October 29, 2013), dapagliflozin was not previously approved. On January 8, 2014, the Division approved NDA 202293 - Farxiga (dapagliflozin).

The Applicant relied on safety and efficacy data submitted to NDA 202293 for the approval of this product, NDA 205649. Bioavailability and bioequivalence studies provided the bridge for approval.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years - please see the comments above

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021202 Glucophage XR (metformin extended-release)

NDA# 202293 Farxiga (dapagliflozin)

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

The Applicant completed several studies for safety and efficacy that were originally submitted to NDA 202293. They referenced them for this application. A complete list can

be provided if needed. No new clinical data was provided in this application.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
!

Date: October 27, 2014

Name of Office/Division Director signing form: Division of Metabolism and Endocrinology
Products/Jean-Marc Guettier
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ELIZABETH R CHEN
10/29/2014

JEAN-MARC P GUETTIER
10/30/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹	
NDA # 205649	
Proprietary Name: Xigduo XR Established/Proper Name: dapagliflozin and metformin XR Dosage Form: tablets	Applicant: AstraZeneca and Bristol-Myers Squibb
RPM: Elizabeth Chen	Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) Date of check: </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions	
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 29, 2014</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received
❖ Application Characteristics ³	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4 (New Combination)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: Approval (October 29, 2014)
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included See Approval letter dated 10-29-2014 for final labeling
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included –
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included See Approval letter dated 10-29-2014 for final labeling
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input type="checkbox"/> Included See Approval letter dated 10-29-2014 for final labeling
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	11-24-2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 01/22/2014 DMEPA: <input type="checkbox"/> None 10/06/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 10/23/2014 OPDP: <input type="checkbox"/> None 10/24/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	01/17/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 10/30/2014
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>09/03/2014</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	11/04/2013 (Acknowledge NDA) 11/24/2013 (Proprietary Name Granted) 01/10/2014 (No Filing Issues Identified) 01/23/2014 02/14/2014 (Meeting Request Granted) 02/19/2014 03/21/2014 03/26/2014 04/15/2014 (Transfer of Ownership) 04/23/2014 (Meeting Minutes/Mid-Cycle Communication) 04/30/2014 06/04/2014 07/18/2014 (Late-Cycle Meeting Background Package) 10/14/2014 10/29/2014 (3) (Late-Cycle Meeting Minutes; General Advice Letter; Approval)
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	N/A
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	04/07/2014
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	07/28/2014
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Guidance: 04/07/2014 - see Mid-cycle Communication for minutes

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10/29/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	10/29/2014
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review See CDTL Review dated 10/29/2014
• Clinical review(s) (<i>indicate date for each review</i>)	Filing: 12/19/2014 Primary: 07/11/2014
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Primary Clinical Review dated 07/11/2014, page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	07-05-2014
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	Filing: 12/10/2013 Primary: 06-20-2014

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	Filing: 12/26/2013 Primary: 07-14-2014
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	12/19/2013 8/26/2014 08-28-2014 10/17/2014
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Filing: 12/10/2013 Primary: 06-11-2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Filing: 12/11/2013 Primary: 04-04-2014 Biopharmaceutics: 07-02-2014 Memo: 09/25/2014
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> N/A	11/04/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>) N/A	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review) (Quality Review dated 04/04/2014, page 7)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: N/A • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment N/A	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter N/A	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

ELIZABETH R CHEN
10/30/2014

From: Chen, Elizabeth
To: ["Angioli, Mike"](#)
Subject: RE: Xigduo XR USPI (10-29-2014 @ 5:45)
Date: Wednesday, October 29, 2014 6:50:00 PM

Dear Mike,

Thank you. We note your agreement to the labeling dated 10/29/2014, and accept the revisions in the attachment.

Regards,
Elizabeth

From: Angioli, Mike [mailto:Mike.Angioli@astrazeneca.com]
Sent: Wednesday, October 29, 2014 6:45 PM
To: Chen, Elizabeth
Cc: Kasbekar, Sanchali
Subject: Xigduo XR USPI (10-29-2014 @ 5:45)

Elizabeth,

See attached label with acceptance of FDA comments.

I will be here if you need to talk.

Regards,

Mike

301 398 0507

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From: [Angioli, Mike](#)
To: [Chen, Elizabeth](#)
Cc: [Kasbekar, Sanchali](#)
Subject: Xigduo XR USPI (10-29-2014 @ 5:45)
Date: Wednesday, October 29, 2014 6:45:19 PM
Attachments: [Draft Xigduo XR USPI --NDA 205649 USPI FDA edits \(10-29-2014\) \(2\) with AZ Comments \[track cahnges\] \(10-29-2014-545 PM\).doc](#)

Elizabeth,

See attached label with acceptance of FDA comments.

I will be here if you need to talk.

Regards,

Mike

301 398 0507

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/s/

ELIZABETH R CHEN
10/29/2014

From: Chen, Elizabeth
To: Mike.Angioli@astrazeneca.com
Subject: NDA 205649 - PMR list
Date: Tuesday, October 14, 2014 12:39:00 PM
Attachments: [XIGDUO XR - PMRs.doc](#)

Dear Mike,

Please see the attached form related to PMRs associated with the Xigduo XR (dapagliflozin and metformin extended-release) product. We would appreciate a response by COB on Monday, October 20, 2014.

If you have any questions regarding this communication, please feel free to contact me.

Regards,
Elizabeth

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
elizabeth.chen@fda.hhs.gov
PH: 240-402-3729

PMR/PMC list for NDA 205649
XIGDUO XR (dapagliflozin and metformin HCl) fixed-dose combination tablets

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A study to evaluate whether pediatric patients with type 2 diabetes mellitus or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Xigduo XR tablets. The study should evaluate tablets that are at least as large as the largest Xigduo XR tablet. Placebo tablets should be used if the study population consists of healthy subjects.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

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/s/

ELIZABETH R CHEN
10/14/2014

**PeRC PREA Subcommittee Meeting Minutes
September 3, 2014**

PeRC Members Attending:

Lynne Yao
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Peter Starke
Andrew Mulberg
Gregory Reaman
Daiva Shetty
Kevin Krudys
Lily Mulugeta
Robert Nelson

Agenda

(b) (4)

NDA	205649	Xigduo XR (dapagliflozin/metformin) Partial Waiver/Deferral/Plan	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate
-----	--------	--	---

(b) (4)

(b) (4)

Xigduo XR (Dapagliflozin/Metformin) Partial Waiver/Deferral/Plan

- NDA 205649 seeks marketing approval for Xigduo XR (dapagliflozin/metformin) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.
- The application triggers PREA as directed to new active ingredient.
- The application has a PDUFA goal date of October 29, 2014.
- *PeRC Recommendations:*
 - The PeRC agreed with a partial waiver for pediatric patients less than 10 years of age because studies would be impossible or highly impracticable.
 - The PeRC agreed with a deferral for pediatric patients aged 10 to less than 17 years because adult studies have been completed and the product is ready for approval.
 - Protocol submission, study completion, and final report submission dates should be consistent with the dates already established for the PREA requirement for dapagliflozin (Division to confirm those dates).
 - The PeRC recommended that evaluation of swallowability of this tablet be included in the PREA requirement because this tablet is very large (20 mm in diameter). The PeRC acknowledged that there is no clear policy for the requirement to perform swallowability studies; however, if the formulation is known to be very large (i.e., greater than 12-15 mm in diameter) then the PeRC agreed that evaluation of swallowability would be appropriate.

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/s/

JANE E INGLESE
09/15/2014

From: Chen, Elizabeth
To: [Jennings, Amy \(amy.jennings@bms.com\)](mailto:amy.jennings@bms.com)
Subject: NDA 205649 - Information Request
Date: Wednesday, June 04, 2014 2:48:00 PM

Dear Amy,

Please see the following information requests from the clinical reviewer. Please prioritize requests 3, 4, and 5, and provide the information by COB Friday (June 6). Requests 1, 2, and 6 should be answered by early next week.

1. The ISS notes that per the SAP, hepatic adverse events were only summarized for the Dapa+Met Pool (ST and ST+LT), but not the Dapa+Met Placebo-controlled Pool (ST and ST+LT). Provide a summary of hepatic adverse events for the placebo- controlled pool.
2. Specify the Patient ID numbers and provide narratives for subjects with either AST or ALT > 5, 10 and 20 X ULN and subject for subjects with ALT > 3x ULN and with T Bili > 1.5 X ULN for the dapa+met pool (ST,ST+LT) and the placebo controlled pool (ST and ST+ LT).
3. Provide a table depicting the incidence of major and minor hypoglycemia events in the 8 placebo controlled trials (ST and ST+LT) to the primary endpoint. Also provide this table for the dapa+met alone placebo controlled pool. Specify any SAEs, or events of withdrawal due to hypoglycemia for both the dapa+met alone and dapa+met placebo control pooled. Provide PT ID numbers with a brief summary of events and narratives (or specify location of narrative in the submission). See Table 6 of the proposed label as an example.
4. For genital infections and urinary tract infections, summarize the following additional information for the dapa+met placebo controlled pool (ST and ST+LT): incidence of discontinuations from study, percent of subjects with a prior predisposing history, the incidence of subjects requiring treatment and the incidence of subjects requiring additional treatment. Specify any SAEs, or events of withdrawal for the dapa+met placebo control pool. Provide PT ID numbers with a brief summary of SAE events and withdrawal events and include narratives (or specify location of narrative in the submission).
5. Provide a Table summarizing baseline demographics and baseline diabetes characteristics for the dapa+met placebo controlled pool (ST and ST+LT). See Table 9-12 in the ISS for an example.
6. Provide a summary of incidence of SAES and adverse events leading to withdrawal for adverse events of interest (renal impairment, volume depletion, UTI, genital infection, liver events, and hypoglycemia). Provide subject ID numbers and narrative information.

Please let me know if you have any questions.

Regards,
Elizabeth

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
elizabeth.chen@fda.hhs.gov
PH: 240-402-3729

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/s/

ELIZABETH R CHEN
06/04/2014

From: Chen, Elizabeth
To: [Jennings, Amy \(amy.jennings@bms.com\)](mailto:amy.jennings@bms.com)
Subject: NDA 205649 - Information Request (placebo-controlled datasets)
Date: Wednesday, April 30, 2014 7:07:00 PM

Dear Amy,

Please see the below information request from our clinical reviewer:

1. Please provide tables of common adverse events representing the placebo controlled dapa + Met ST and ST + LT treatment groups. This table should include data for placebo + met, dapa 5 + met, dapa 10 + met and total dapa + met and should be in descending order of events.
2. For genital infections and urinary tract infections, specify the incidence for females and males per treatment group in the dapa + met placebo-controlled pool.
3. For the dapa + met placebo-controlled pool, provide the incidence of hypoglycemia per treatment group for subjects on background sulfonylurea or insulin therapy.
4. For the dapa + met placebo-controlled pool, provide the incidence of renal events by age (< 65 and > 65) for adverse events of renal impairment or failure and adverse events of renal impairment or failure in subjects with eGFR Category Subgroup ≥ 60 mL/min/1.73 m². (See Table 30 & 31 of ISS)
5. For adverse events of volume depletion, provide a Table (similar to table 27 of the ISS) for the dapa + met placebo-controlled pool. This table should include the incidence of volume depletion based on age (<65 years of age and ≥ 65 years of age), subjects using loop diuretics and not using loop diuretics, and for subgroups of subjects with eGFR ≥ 30 and < 60 ml/min, and ≥ 60 ml/min.

Please provide this information as soon as possible. If you have any questions or require clarification on any of the requests, please feel free to contact me.

Regards,
Elizabeth

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
elizabeth.chen@fda.hhs.gov
PH: 240-402-3729

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/s/

ELIZABETH R CHEN
04/30/2014



NDA 205649

MID-CYCLE COMMUNICATION

AstraZeneca AB
c/o Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated October 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 7, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Pamela Lucarelli
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: April 7, 2014, 11:45 AM to 1:00 PM

Application Number: NDA 205649

Product Name: Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets

Indication: treatment of type 2 diabetes mellitus

Applicant Name: Astra-Zeneca

Meeting Chair: Karen Mahoney, M.D.

Meeting Recorder: Elizabeth Chen, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director
Karen Mahoney, M.D., Clinical Team Leader
Kaveeta Vasisht, M.D., Pharm.D., Clinical Reviewer
Pamela Lucarelli, Chief, Project Management Staff
Elizabeth Chen, Pharm.D., Regulatory Project Manager

Office of Clinical Pharmacology

Lokesh Jain, Ph.D., Clinical Pharmacology Team Leader
Suryanarayana Sista, Ph.D., Clinical Pharmacology Reviewer

APPLICANT ATTENDEES

AstraZeneca

Dave Lange, Assoc Director Regulatory Affairs
Russ Esterline, Ph.D., VP Global Product Development, Cardiovascular & Metabolic Diseases
GMD
Eva Johnsson, M.D., Ph.D., Medical Science Director, Cardiovascular & Metabolic Diseases
GMD
Kristina Johnsson, M.D., Ph.D., Senior Patient Safety Physician
Jennifer Sugg, M.S., Statistical Science Director, Biostatistics, GMD
Robert Sepelyak, Project Manager, Pharmaceutical Development

Bristol-Myers Squibb

Amy Jennings, Ph.D., Group Director, Cardiovascular/Metabolics, Global Regulatory & Safety
Sciences – US
Jim List, M.D., Ph.D., Vice President, Diabetes Development

Agata Ptaszynska, M.D., Group Director, Global Clinical Research, CV/Met
Lisa Ying, Ph.D., Director, Global Biometric Sciences
Giridhar Tirucherai, Ph.D., Director, Clinical Pharmacology & Pharmacometrics - CV/Met

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues with an impact on approvability have been identified at this time.

Although not a significant approvability issue, in response to your inquiry regarding morning versus evening dosing of the dapagliflozin-metformin fixed-dose combination product, the Division continues to support morning dosing. This is due to concern for a risk of adverse events associated with excessive urination at night, and an observation of an imbalance in adverse events for evening versus morning with dapagliflozin administration.

3.0 INFORMATION REQUESTS

Please submit new combined labeling that is consistent with the recently approved dapagliflozin single product labeling.

We appreciate your prompt response to all information requests conveyed during the teleconference. There are no additional information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late-cycle meeting is currently planned to take place on Monday, July 28, 2014, from 12:00 PM to 1:00 PM.

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/s/

PAMELA LUCARELLI
04/23/2014



NDA 205649

TRANSFER OF NDA OWNERSHIP

AstraZeneca AB
c/o Bristol-Myers Squibb
Attention: Amy Jennings, Ph.D.
Group Director, Global Regulatory & Safety Sciences-US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

We acknowledge your correspondence, dated and received, February 28, 2014, notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: dapagliflozin and metformin extended release tablets 5/500 mg,
5/1000 mg, 10/500 mg, 10/1000 mg

NDA Number: 205649

Name of New Applicant: AstraZeneca AB

Name of Previous Applicant: Bristol-Myers Squibb

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate AstraZeneca as the applicant of record for this application.

DRUG MASTER FILE LOA

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

REPORTING REQUIREMENTS

All changes to the information in the NDA from that described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. However, changes in the name of the manufacturer, packer, or distributor in the drug product's label or labeling may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R CHEN

04/15/2014

From: Chiang, Raymond
To: ["amy.jennings@bms.com"](mailto:amy.jennings@bms.com)
Cc: [Chen, Elizabeth](#)
Subject: Re: NDA 205649
Date: Wednesday, March 26, 2014 4:02:00 PM

Hi Amy,

I'm covering for Elizabeth while she is on leave.

Please see information requests from the FDA medical officer. She said that she needs this information as soon as possible.

Please confirm receipt of this email.

Thanks,

Ray

1. Please specify if there is a table listing non-fatal SAEs in NDA submission? If this table is not present provide a table listing non-fatal SAES by SOC and PTs (similar to Appendix 1013) for the Dapagliflozin + Metformin Pool (ST) and Dapagliflozin + Metformin Pool (ST + LT), as well as the Dapagliflozin + Metformin Placebo-controlled Pool (ST) and Dapagliflozin +Metformin Placebo-controlled Pool (ST+LT).
2. Provide an additional table specifying subject ID numbers or narrative locations for non-fatal SAEs by system organ class and preferred terms.

Raymond S. Chiang, MPT, MS, MS
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Email: Raymond.Chiang@fda.hhs.gov

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/s/

RAYMOND S CHIANG
03/26/2014

From: Chen, Elizabeth
To: [Jennings, Amy \(amy.jennings@bms.com\)](mailto:amy.jennings@bms.com)
Subject: NDA 205649 - Information Request for Dosing Meeting
Date: Friday, March 21, 2014 4:32:00 PM

Dear Amy,

I have the following request for information from one of the reviewers related to the upcoming meeting on timing of dose for Xigduo XR. Please respond by March 28th, 2014.

Please provide the following clarifications with respect to data submitted in your recent Type C meeting request briefing package.

1. For summary Table 7 [Summary of 24-week Safety in MB102013 (ST)] and Table 8 [Summary of 102-week Safety in MB102013 (ST+LT)], please provide the cumulative percentage of subjects with events in the following treatment groups: Placebo, All dapagliflozin QAM (includes 2.5, 5 and 10 mg treated subjects), and All dapagliflozin QPM (combines 2.5, 5 and 10 mg treated subjects). Provide a second table excluding the dapagliflozin 2.5 mg dose from the All dapagliflozin QAM and QPM treatment groups. This second table will represent only the combined 5 mg and 10 mg treatment groups.
2. In Tables 7 and 8, you have provided the percentage of subjects with specific preferred term events. Clarify the number of events per preferred term listed in both Table 7 and Table 8 for events of hypoglycemia, fracture, volume depletion, nocturia, falls and dizziness. In addition, clarify the number of events per subject listed in Table 7 and Table 8 for events of hypoglycemia, fracture, volume depletion, nocturia, falls and dizziness.
3. Provide narrative or available clinical information for the following events listed in Tables 7 and 8 (death, SAE, AE leading to discontinuation, dizziness, nocturia, volume depletion).

Regards,
Elizabeth

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
elizabeth.chen@fda.hhs.gov
PH: 240-402-3729

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ELIZABETH R CHEN
03/21/2014

From: [Vasisht, Kaveeta](#)
To: [Chen, Elizabeth](#)
Cc: [Mohamadi, Ali](#)
Subject: DAPA/Met IR
Date: Thursday, February 06, 2014 9:30:38 AM

Hi Elizabeth,

Can you send the following:

Please detail which clinical trials are new to the dapagliflozin/ metformin FDC NDA that have not been previously submitted for review under the dapagliflozin NDA. Also specify if any new data has been submitted with the FDC NDA that has not been previously submitted.

From: [Jennings, Amy](#)
To: [Chen, Elizabeth](#)
Subject: RE: NDA 205649
Date: Wednesday, February 12, 2014 10:19:11 AM

Hi Elisabeth,

Was nice speaking with you yesterday. Per our discussion on info you were seeking,

All of the clinical data supporting the efficacy and safety of dapagliflozin when used with metformin was previously submitted to the dapa NDA 202-293 up through the 30-month update (30MU) provided in the dapa NDA 202-293 resubmission. This includes the 12 studies focused on in the dapa/met XR FDC NDA (see Table 1 in the SCS) and the all phase 2b/3 pool used to assess rare events. We used the same datacuts for these studies provided in the dapa/met XR FDC NDA as used in the 30MU for the dapa NDA. In the dapa/met XR FDC NDA, additional analyses were provided using 2 new pools which are subsets of data already existing in the dapa NDA 202-293: dapa+met pool (9 of these studies) and dapa+met placebo pool (8 of these studies).

In addition to the data supporting the safety and efficacy of dapagliflozin, five biopharmaceutics studies contributed relative bioavailability (BA) or bioequivalence (BE) data for the dapagliflozin/metformin XR FDC development program (see Table 1 of the clinical overview).

I hope this addresses your question. Please let me know if you need further clarification.

Regards
Amy

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/s/

ELIZABETH R CHEN
02/19/2014



NDA 205649

MEETING REQUEST GRANTED

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xigduo XR (dapagliflozin and metformin HCL extended release) tablets.

We also refer to your January 24, 2014, correspondence requesting a meeting to discuss the timing of dosing for Xigduo XR. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: April 7, 2014

Time: 11:45 AM to 12:15 PM

Phone Arrangements: Domestic dial in: 866-217-3840
Conference code: 6773821

CDER Participants:

Jean-Marc Guettier, M.D.	Division Director (Acting)
Karen Mahoney, M.D.	Diabetes Team Leader
Kaveeta Vasisht, M.D.	Clinical Reviewer
Lokesh Jain, Ph.D.	Clinical Pharmacology Team Leader
Suryanarayana Sista, Ph.D.	Clinical Pharmacology Reviewer
Pamela Lucarelli	Chief, Project Management Staff
Elizabeth Chen, Pharm.D.	Regulatory Project Manager

Submit background information for the meeting (three paper copies or one electronic copy to the application and 4 desk copies to me) at least 1 month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by March 7, 2014, we may cancel or reschedule the meeting.

Submit the 4 desk copies to the following address:

Elizabeth Chen
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3109
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (240) 402-3729.

Sincerely,

[See attached electronic signature page]

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R CHEN
02/14/2014

From: [Jennings, Amy](#)
To: [Chen, Elizabeth](#)
Subject: RE: NDA 205649 - FDA Information Request
Date: Thursday, January 23, 2014 8:45:18 AM

Thanks Elisabeth,
I will forward to the team and get back to you asap
Amy

From: Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]
Sent: Thursday, January 23, 2014 8:45 AM
To: Jennings, Amy
Subject: NDA 205649 - FDA Information Request

Dear Dr. Jennings,

Please refer to your New Drug Application (NDA) dated October 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets.

We have the following requests for information from the Quality reviewer:

1. Provide a schematic drawing (with dimensions) for each of the four strength tablets.
2. The drug product specification criterion for total dapagliflozin impurities of (b) (4) % was selected based on (b) (4) :
dapagliflozin drug substance impurities (b) (4) %, (b) (4) % and unspecified others (b) (4) %. However, you state in Section 3.2.P.5.5, "There are no impurities in the drug product which are carried through from the commercially manufactured dapagliflozin propanediol drug substance". Lower the acceptable limit for total dapagliflozin impurities in the drug product specifications to ≤ (b) (4) % or provide further justification for your proposed limit especially considering that, as you state, "The dapagliflozin-related total impurities detected during stability studies across batches stored at 25°C/60%RH and 30°C/75%RH have changed little, if at all, from the initial values of ≤ (b) (4) %" in Section 3.2.P.5.6.

If you have any questions about this request, please feel free to contact me.

Regards,
Elizabeth

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

elizabeth.chen@fda.hhs.gov

PH: 240-402-3729

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/s/

ELIZABETH R CHEN
01/23/2014



NDA 205649

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated October 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets.

We also refer to your amendments dated October 31, and November 18, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is **October 29, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **September 10, 2014**. In addition, the planned date for our internal mid-cycle review meeting is **April 3, 2014**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. The dapagliflozin [REDACTED] (b) (4) [REDACTED]. Provide the location in the NDA of the supporting stability data or amend the application with the data.
2. In support of the biowaiver request for the two middle strengths (10/500 and 5/1000 mg tablets), provide the following information:
 - Comparisons of 10/500 mg strength to both of 5/500 (the lowest strength) and 10/1000 mg (the highest strength) i.e., three mean dissolution profiles in the same figure (e.g., Figure 3.1.1A, page 88 under Module 2.7.1) and three mean dissolution data in the same table (e.g., Table 3.1.1A, page 90 under Module 2.7.1) per each dissolution medium (pH1.2, 4.5, and 6.8) per each drug (API) should be reconstructed and submitted. The similarity factor (f_2) values should be provided if available.
 - Comparisons of 5/1000 mg strength to both of 5/500 (the lowest strength) and 10/1000 mg (the highest strength), i.e., three mean dissolution profiles in the same figure and three mean dissolution data in the same table per each dissolution medium (pH1.0, 4.5, and 6.8) per each drug (API) should be reconstructed and submitted. The similarity factor (f_2) values should be provided if available.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request [REDACTED] (b) (4).
Once we have reviewed your request, we will notify you if [REDACTED] (b) (4) request is denied and a pediatric drug development plan is required.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
01/10/2014



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 205649

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492-7660

Attention: Amy A. Jennings, PhD
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated and received October 29, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dapagliflozin and Metformin HCl Extended-Release Tablets, 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg and 10 mg/1000 mg.

We also refer to your correspondence, submitted and received October 31, 2013, requesting review of your proposed proprietary name, Xigduo XR. We have completed our review of the proposed proprietary name, Xigduo XR, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your October 31, 2013, submission are altered prior to approval of the application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Chen at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
11/24/2013



NDA 205649

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: dapagliflozin and metformin HCl tablets

Date of Application: October 29, 2013

Date of Receipt: October 29, 2013

Our Reference Number: NDA 205649

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 28, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R CHEN
11/04/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205649

LATE-CYCLE MEETING MINUTES

AstraZeneca AB
C/o Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated October 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 28, 2014.

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

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 28, 2014, 11:30 AM to 1:00 PM
Meeting Location: Teleconference

Application Number: NDA 205649
Product Name: Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets
Indication: treatment of type 2 diabetes mellitus
Applicant Name: Astra-Zeneca

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director
Karen Mahoney, M.D., Clinical Team Leader
Mukesh Summan, Ph.D., Nonclinical Reviewer
Pamela Lucarelli, Chief, Project Management Staff
Elizabeth Chen, Pharm.D., Regulatory Project Manager

Office of Biostatistics

Wei Liu, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology

Jaya Vaidyanathan, Ph.D., Clinical Pharmacology Reviewer
Suryanarayana Sista, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Christine Chamberlain, Pharm.D., Safety Evaluator, Division of Pharmacovigilance
Sarah Vee, Safety Evaluator, Division of Medication Error Prevention and Assessment
Amarilys Vega, Medical Officer, Division of Risk Management

APPLICANT ATTENDEES

AstraZeneca

Ian Hunt, Ph.D., Vice President, Global Regulatory Affairs, Patient Safety and Quality
Mike Angioli, M.S., Senior Director, Global Regulatory Affairs, Patient Safety and Quality
Russ Esterline, Ph.D., VP Global Product Development, Cardiovascular & Metabolic Diseases
GMD
Eva Johnsson, M.D., Ph.D., Medical Science Director, Cardiovascular & Metabolic Diseases
GMD
Kristina Johnsson, M.D., Ph.D., Senior Patient Safety Physician
Jennifer Sugg, M.S., Statistical Science Director, Biostatistics, GMD

Bristol-Myers Squibb

Amy Jennings, Ph.D., Group Director, Cardiovascular/Metabolics, Global Regulatory & Safety Sciences – US

Jim List, M.D., Ph.D., Vice President, Diabetes Development

Agata Ptaszynska, M.D., Group Director, Global Clinical Research, CV/Met

Lisa Ying, Ph.D., Director, Global Biometric Sciences

David Boulton, Ph.D., Director, Clinical Pharmacology & Pharmacometrics - CV/Met

1.0 BACKGROUND

NDA 205649 was submitted on October 29, 2013 for dapagliflozin and metformin extended-release (Xigduo XR).

Proposed indications: treatment of type 2 diabetes mellitus

PDUFA goal date: October 29, 2014

FDA issued a Background Package in preparation for this meeting on July 18, 2014.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion: None.

2. Information Requests

As of July 14, 2014, we are awaiting receipt of your response to an information request from the Division of Medication Error Prevention and Analysis (DMEPA). The request was conveyed to you on July 7, 2014.

Discussion: The request was received by the applicant, the information was returned to DMEPA, and DMEPA considered the response acceptable.

3. Postmarketing Requirements/Postmarketing Commitments

We agree that your cardiovascular outcomes trial which was agreed upon for dapagliflozin will be adequate to fulfill the requirement for evaluation of the cardiovascular risk of your dapagliflozin-metformin fixed-dose combination. We also agree that the pediatric studies which were agreed upon for dapagliflozin can be used to fulfill your Pediatric Research Equity Act requirement for your dapagliflozin-metformin fixed-dose combination.

Discussion: No other discussion.

4. Labeling Issues

Discussion: There was discussion regarding the applicant's (b) (4) from the proposed Full Prescribing Information (FPI). The Division is concerned that the information included (b) (4)

(b) (4)
The Division does not consider the data adequate to support such a claim. (b) (4)

(b) (4). The issue of whether any of the information (b) (4) can be included in the FPI will be discussed in further labeling meetings.

5. Review Plans

Secondary and signatory reviews are continuing, and additional issues may be identified. Labeling review continues. After we receive your revised labeling, additional labeling comments will likely follow.

Some inspection results are pending at this time.

Discussion: None.

6. Wrap-up and Action Items

The proposed trade name – Xigduo XR – has been conditionally approved, and the applicant may submit final carton and container labeling using this trade name.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

JEAN-MARC P GUETTIER
10/29/2014



NDA 205649

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

AstraZeneca AB
c/o Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated October 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 28, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 28, 2014, 11:30 AM to 1:00 PM
Meeting Location: Teleconference

Application Number: NDA 205649
Product Name: Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets
Indication: treatment of type 2 diabetes mellitus
Applicant Name: Astra-Zeneca

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

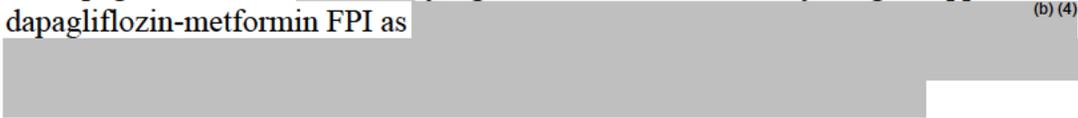
No issues related to risk management have been identified to date.

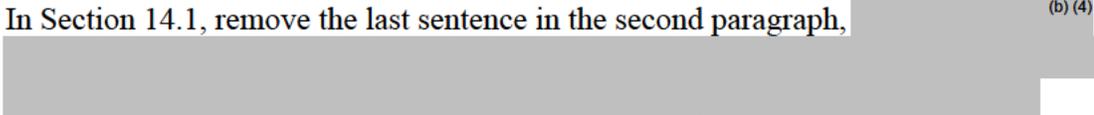
PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents;
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. We note several areas in the Full Prescribing Information (FPI) where the phrase from the dapagliflozin FPI “statistically significant reduction in body weight” appears in the dapagliflozin-metformin FPI as (b) (4)

2. Remove (b) (4)

3. In Section 14.1, remove the last sentence in the second paragraph, (b) (4)

This phrase, or similar phrases, should also be removed from other areas of the FPI where it occurs.
4. Labeling review is continuing and additional labeling comments may be conveyed.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 25, 2014. The resubmitted labeling will be used for further labeling discussions. At the end

of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Information Requests – 5 minutes
As of July 14, 2014, we are awaiting receipt of your response to an information request from the Division of Medication Error Prevention and Analysis. The request was conveyed to you on July 7, 2014.
3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
We agree that your cardiovascular outcomes trial which was agreed upon for dapagliflozin will be adequate to fulfill the requirement for evaluation of the cardiovascular risk of your dapagliflozin-metformin fixed-dose combination. We also agree that the pediatric studies which were agreed upon for dapagliflozin can be used to fulfill your Pediatric Research Equity Act requirement for your dapagliflozin-metformin fixed-dose combination.
4. Preliminary labeling issues – 10 minutes
See above
5. Review Plans – 5 minutes
Secondary and signatory reviews are continuing, and additional issues may be identified. Labeling review continues. After we receive your revised labeling, additional labeling comments will likely follow.
Some inspection results are pending at this time.
6. Wrap-up and Action Items – 5 minutes

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/s/

JEAN-MARC P GUETTIER
07/18/2014