CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

CHEMISTRY REVIEW(S)

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF NEUROLOGY PRODUCTS

CMC MEMO

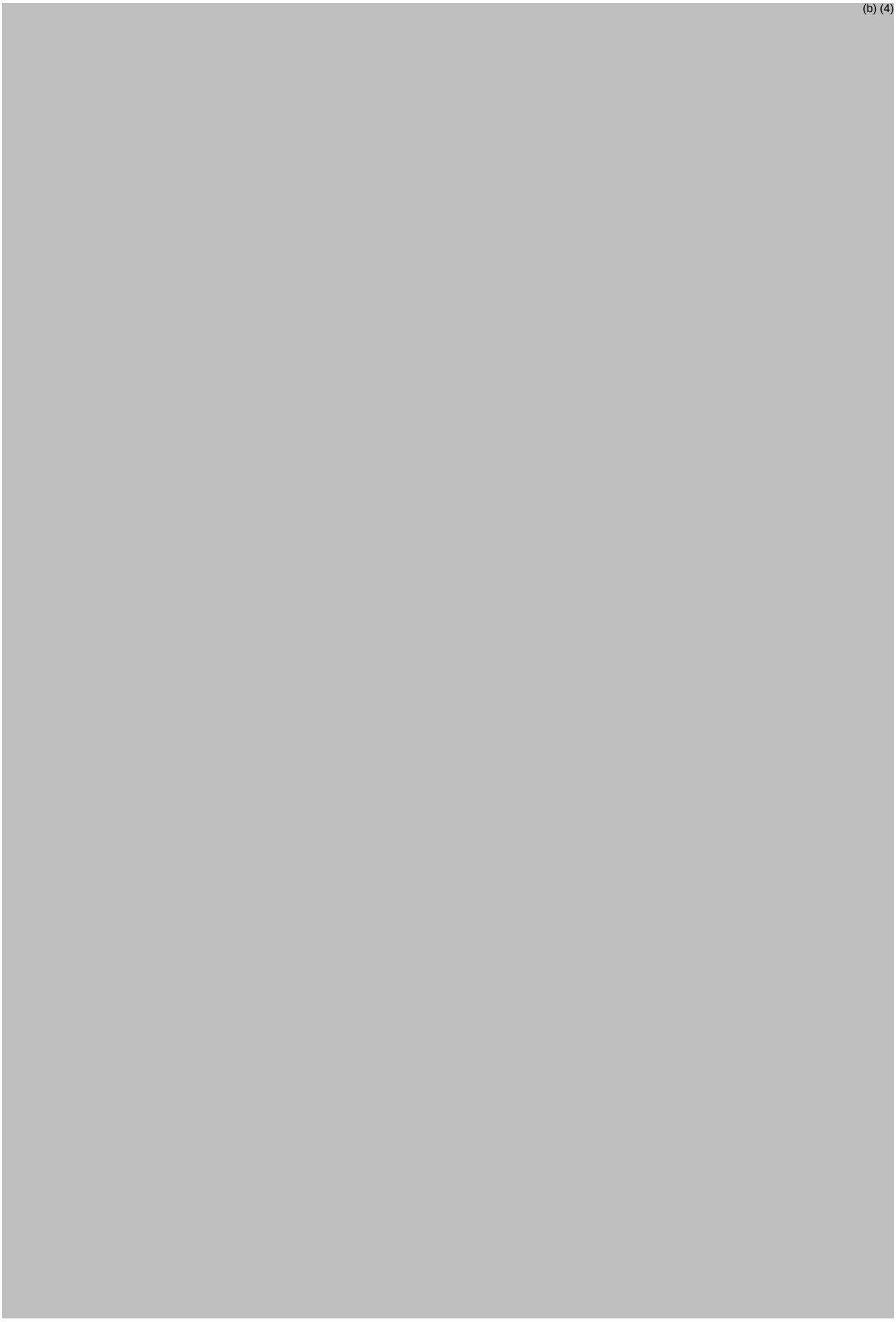
DATE:	11-JAN-2010
APPLICANT:	GlaxoSmithKline
TO:	NDA 22-399, Horizont (gabapenten enacarbil) ER Tablets
FROM:	Chhagan G. Tele, CMC Reviewer, ONDQA/DPA-1/Branch 1
SUBJECT:	Responses to the Questions raised in IR letter dated 28-DEC-2009 (amendment #0035, 08-JAN-2010)

Question 1: **The manufacturing process description in section m3.2.P.3.3 is not complete and therefore not acceptable. It does not include the design space, including the Quality Process Parameters ranges described in your Pharmaceutical Development section m3.2.P.2 and the description of the manufacturing equipment, including scale. Update the manufacturing section with adequate details or submit commercial master batch records to comply with 21 CFR 314.50 (d)(1)(ii)(c).**

GSK Response: GSK provided commercial master batch records for the drug product (batch size (b) (4) tablets) including Quality Process Parameters ranges and manufacturing equipment with (b) (4) as described in Pharmaceutical Development section m3.2.P.2.

Manufacturing Process

(b) (4)



GSK Response: As requested the comparability protocols listed in Section m3.2.S.2.1 for the post approval site changes for drug substance manufacture, release testing, and stability testing have been updated to state that with the proposed data package these changes will be submitted as a CBE-30 Supplement. The comparability protocol that was listed in Section 3 of m3.2.S.2.2 has been removed.

EVALUATION: **Adequate**. As requested, GSK agreed to submit a CBE-30 Supplement for the post approval site changes for drug substance manufacture, release testing, and stability testing. The comparability protocol for the post approval site changes for drug product manufacture has been removed and for the site changes for packaging, release testing and stability testing have been updated to state that with the proposed data package these changes will be submitted as a CBE-30 Supplement.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

CHHAGAN G TELE
02/05/2010

RAMESH K SOOD
02/05/2010

Horizant™
(gabapentin enacarbil) Extended Release Tablets
NDA 22-399

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: GlaxoSmithKline
Glaxo Wellcome House, Berkeley Avenue
Greenford, Middlesex, UB6 0NN UK

Indication: Gabapentin enacarbil is a novel transported pro-drug of gabapentin designed to overcome the pharmacokinetic limitations of gabapentin and is being developed at a 600 mg oral dose for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

Presentation: Horizant™ (gabapentin enacarbil) Extended Release Tablets are white oval shaped tablets of approximately (b) (4)", debossed on one side with "GS LFG". The drug product is packaged in (b) (4) bottles containing (b) (4)), 30, 60 and 180 count tablets. The bottles have (b) (4), and dessicant.

EER Status: Acceptable (24-Sep-09)

Consults: ONDQA Biopharmaceutics – Acceptable (S. Suarez, 27-Oct-09)
Environmental Assessment – Acceptable (R. Bloom, 22-Sep-09)
Methods Validation - Revalidation by Agency was not requested

Original Submission: 15-Sep-08 (withdrawn)

Resubmission: 09-Jan-09

Post-Approval Agreements: None

Drug Substance:
Gabapentin enacarbil (also called XP 13512) is a non-ester, pro-drug of gabapentin (a marketed drug). It has a molecular formula $C_{16}H_{27}NO_6$ and molecular weight 329.39. There is a single chiral center (b) (4), the drug substance is a racemic mixture. Gabapentin enacarbil is a white to off-white powder, soluble in (b) (4)

(b) (4). Gabapentin enacarbil is classified as a BCS Class 2 compound (low solubility, high permeability).

(b) (4)

The applicant provided adequate information regarding structure elucidation and confirmation, method of manufacture, in-process controls, test methods, container closure system, and stability testing of gabapentin enacarbil drug substance. The drug substance specification includes description (visual), identification (IR), drug related impurities (HPLC), residue on ignition (USP <281>), (b) (4) and assay (HPLC).

The applicant's proposed retest period of (b) (4) at temperatures up to25º C (77º F) is granted based on the provided stability data.

Conclusion: The drug substance is **satisfactory.**

Drug product:
Horizant™ tablets are extended release (b) (4) tablets containing 600 mg of gabapentin enacabril. The recommended dose is 1200 mg/day, to be taken orally at the evening with food. The drug product formulation contains commonly used, compendial excipients: dibasic calcium phosphate dihydrate, glycerol behenate, talc, colloidal silicon dioxide, sodium lauryl sulfate and magnesium stearate.

The manufacture of the drug product consists of (b) (4) The drug product specification includes description (visual), identification (HPLC and UV), assay (HPLC), impurities (HPLC), dissolution (USP apparatus 2, HPLC), uniformity for dosage units (HPLC), uniformity for (b) (4) tablets (HPLC), and microbial quality (USP <61>).

For the 30-count bottle, 60-count bottle, and 180-count bottle, a shelf life of 36 month is granted when stored at 25° C (77° F); excursions permitted 15° to 30° C (59° to 86° F), protected from moisture. The package label includes instructions to not remove desiccants and to dispense in original bottle.

Conclusion: The drug product is **satisfactory.**

Additional Items:

- The applicant's original name of Solzira was found to be unacceptable. The revised name of Horizant was deemed acceptable (L. Kelley, 20-Oct-09).

- All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

- The analytical methods used in the testing procedures are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

- Four comparability protocols for lowered reporting categories for post-approval changes to drug substance manufacture were submitted and approved. Three protocols provide for submission of site changes for drug substance manufacture, release testing, and stability testing as a CBE-30 supplement. The fourth protocol providing for filing of a change in (b) (4) as a CBE-0 supplement.

Overall Conclusion: From a CMC perspective, the application is recommended for **approval**.

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

CHRISTINE M MOORE
02/05/2010

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF NEUROLOGY PRODUCTS

CMC MEMO

DATE:	23-OCT-2009
APPLICANT:	GlaxoSmithKline
TO:	NDA 22-399, Solzira (gabapenten enacarbil) ER Tablets
FROM:	Chhagan G. Tele, CMC Reviewer, ONDQA/DPA-1/Branch 1
SUBJECT:	Overall Compliance, Environmental Assessment (EA), and CMC Recommendation

Establishment Evaluation

The CDER Office of Compliance (OC) issued an overall "Acceptable" recommendation for NDA 22-399 on 24-SEP-2009. A copy of the establishment evaluation report is attached.

Environmental Assessment

Review of the Environmental Assessment (consult conclusion and recommendation, Raanan Bloom, 22-SEP-09) concluded that no significant adverse environmental impacts are expected from the approval of this NDA. A Finding of No Significant Impact (FONSI) is recommended.

(b) (4)

Question 2: The following dissolution specification is recommended for gabapentin enacarbil ER tablets:

USP	Spindle Rotation Speed	Media Volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 mM potassium phosphate monobasic buffer at pH7.4 with 1% SLS	4 hours: (b) (4) 8 hours: 12 hours 24 hours

a) Your proposed dissolution method appears to be over-discriminating and not clinically relevant. The method discriminates between two batches that have equal in vivo performance. Consider developing a more clinically relevant dissolution method that is not over-discriminating.
b) Provide stability data from the three primary batches to support the dissolution specification at the recommended time intervals.

GSK Response: GSK provided response regarding methodology and dissolution specification (amendment sequence #0031, dated 15-OCT-09).

Response to Question 2a: GSK agreed that the dissolution method is over-discriminating for the in-vivo performance and accepted the Agency's concern that the method is over discriminating and will review the dissolution data once more experience is gained from the launch of the product and a greater number of commercial batches have been manufactured. At that time, if warranted, GSK agreed to assess if any dissolution method changes are required. GSK therefore proposed to continue with the more discriminating dissolution method through product approval and launch.

GSK agreed to adopt the recommended specification sampling times, but with the revised acceptance criteria for the 8 and 12 hour sampling time points. The proposed revised specification is listed in Table 1. It is indicated by the applicant that the proposed dissolution specification for Gabapentin Enacarbil ER Tablets, 600 mg, is based on the *in-vitro* dissolution performance of tablet batches used in (b) (4) and in the pivotal phase 3 clinical studies.

Table 1: GSK Proposed Dissolution Specification for Gabapentin Enacarbil ER Tablet

Proposed Specification	
Time (hrs)	% Released (b) (4)
4	
8	
12	
24	

- Dissolution data for bioequivalent batches: The clinical study (b) (4) compared two batches of the same formulation, manufactured at the same scale, from the intended commercial site of manufacture. These batches (3049975R and 3053361R) have the fastest and the slowest *in-vitro* release profile of all the current clinical trial supply batches using the current 24-hour dissolution method. These batches were shown to be bioequivalent. The mean tablet dissolution for these batches at 8 hours and 12 hours ranged from 45 - 67% and 65 - 85%, respectively, and the individual tablet dissolution test values ranged from (b) (4) respectively.

- Dissolution data for phase 3 clinical supplies: Mean dissolution profiles of Gabapentin Enacarbil ER Tablets, 600 mg, tested in the phase 3 clinical studies are provided. The mean dissolution for pivotal study clinical supplies at 8 hours and 12 hours ranged from 41 - 68% and 61 - 82%, respectively, and the individual tablet dissolution test values ranged from (b) (4) respectively.

Note: A teleconference was held (21-OCT-09) between the FDA (Drs. Patrick Marroum, Sandra Suarez Sharp, Ramesh Sood, Chhagan Tele, and Don Henry) and the applicant (GSK team). The dissolution acceptance criteria for 8 and 12 hour time points were negotiated (b) (4) respectively) based on dissolution data for bioequivalence batches (3049975R and 3053361R). GSK provided revised drug product specification (amendment 0032 dated 23-OCT-09). Based on Dr Suarez Sharp's review, dated 26-NOV-2009, the revised specification is acceptable.

Table 2: Revised Specification for XP13512 ER Tablets (600 mg strength)

Test	Acceptance Criteria
Description	(b) (4)
Identification of XP13512 by HPLC-RT[1]	
Identification of XP13512 by HPLC-UV[1]	
Assay (HPLC)	
Uniformity of Dosage Units by Weight Variation[1]	
Degradation Products (%w/w) (b) (4)	
Individual Unspecified Degradation Products[2] **(% w/w)**	
Total Degradation Products[3] (%w/w)	
Dissolution	Complies with USP <711>

Time (hrs)	% Released
4	(b) (4)
8	
12	
24	

Notes:
1. Performed at release only.
2. Report all unspecified degradation products individually ≥0.05% w/w with the corresponding relative retention time. Includes only drug product related degradation products. Known drug substance (b) (4) impurities are not included.
3. Total degradation products is the sum of all degradation products above or equal to 0.05% w/w. Known drug substance (b) (4) impurities are not included.

Response 2b: The applicant provided stability data for non-debossed and Commercial Image tablets following storage for up to 24 months and 12 months, respectively, at 2 - 8° C, 25° C/60% RH, and 30° C/65% RH and 6 months at 40° C/75% RH. Full details of the primary stability batches under examination are given in Table 3. The batches of product were manufactured using the proposed commercial composition and manufacturing process. The product was packaged in (b) (4) bottles with desiccant and (b) (4). Both (b) (4)

(b) (4)

desiccant. These packs are of identical composition and sizes to that proposed for the commercial product. It is noted that when the stability protocol for the non-debossed tablets was finalized, the 12 hour dissolution method described in the EOPII Briefing Package (IND 71,352 Serial Number 0054) had been chosen for dissolution testing at all time points for the 25° C/60% RH and 30º C/65% RH storage conditions. In addition, samples of non-debossed tablets, stored at 25° C/60% RH and 30° C/65% RH, were to be tested with the 24 hour dissolution method at 6, 12, 24, and 36 months. The sponsor also indicated that after the 9 month time point, a decision was made to replace the 12 hour dissolution method with the 24 hour dissolution method for release and stability testing. Therefore, per the protocols, stability data for the non-debossed Tablets was not provided for the 24 hour dissolution method at the 3 and 9 month time points. Also, due to an oversight, testing with the 24 hour dissolution method was not performed at the 3 month time point for samples of Commercial Image Tablets stored at 25° C/60% RH and 30° C/65% RH.

Table 3: Details of Stability Batches of XP13512 ER Tablets (600 mg strength, Non-Debossed and Commercial Image)

Product Strength	600 mg (Non-Debossed)	600 mg (Non-Debossed)	600 mg (Non-Debossed)	600 mg (Commercial Image)	600 mg (Commercial Image)	600 mg (Commercial Image)
Stability Study Number	CIN-AD-P-631	CIN-AD-P-631	CIN-AD-P-631	CIN-AD-P-866	CIN-AD-P-866	CIN-AD-P-866
Drug Product Batch Number	**3056084R**	**3056085R**	**3056086R**	**3062644R**	**3062645R**	**3062646R**
Input Drug Substance Batch Number	(b) (4)					
Site of Drug Substance Manufacture						
Batch Size (kg)						
Pilot/Production Scale[1]						
Site of Manufacture	Patheon	Patheon	Patheon	Patheon	Patheon	Patheon
Date of Manufacture	February 2007	February 2007	February 2007	October 2007	October 2007	October 2007
Site of Packaging	Patheon	Patheon	Patheon	Patheon	Patheon	Patheon
Date of Packaging	March 2007	March 2007	March 2007	Nov 2007	Nov 2007	Nov 2007
Pack	Table 2	Table 2	Table 2	Table 3	Table 3	Table 3
Date Stability Started	Mar 2007	Mar 2007	Mar 2007	Dec 2007	Dec 2007	Dec 2007
Data Presented (Months)	24	24	24	12	12	12

Note:
1. Typical production scale is (b) (4)

Table 4: Summary of Stability Data of Non-Debossed XP13512 ER Tablets (Batch #s 3056084R, 3056085R, and 3056086R) 14, 60, 180 count/bottle

Parameter	**Test Results**				
	Initial	**2-8º C (24 months)**	**25º C/60% RH (24 months)**	**30º C/75% RH (24 months)**	**40º C/75% RH (6 months)**
Description		Conform	Conform	Conform	Conform
Assay (% range)	(b) (4)				
Degradation Products (% range)					
(b) (4)		(b) (4)			
Individual Unspecified Degradation Products					
(b) (4)		(b) (4)			

(b) (4)	(b) (4)
Total degradation products	
Dissolution (mean % range) 24 months at 2-8º C, 30º C/75% RH, 25º C/60% RH and 6 months at 40º C/75% RH	
4 h (b) (4)	(b) (4)
8 h	
12	
24	

NP: Not Performed, ND: Not Detected, * The proposed dissolution specification was not in place at time of testing. L2 testing was not performed.

EVALUATION: Adequate. Results are provided for non-debossed tablets stored up to 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH and 6 months at 40° C/75% RH. Data demonstrated that the gabapentin enacarbil drug product is stable. No change in description was observed for non-debossed XP13512 ER tablets after storage at 2-8° C, 25° C/60% RH, and 30° C/65% RH after 24 months or 40° C/75% RH after 6 months. Storage at accelerated storage conditions enhances degradation compared to other storage conditions (see increase in (b) (4) in table above).

Assay

Initial: in the range of 97.4-98.8%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 96.4-99.8%, after 6 months at accelerated: in the range of 96.1-98.0%

Total Degradation Products

Initial: in the range of (b) (4)%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65%: in the range of < (b) (4)%, after 6 months at accelerated: in the range of (b) (4)%

Dissolution

4 h: Initial: mean 27%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: 25-30%, after 6 months at accelerated: in the range of 29-33%

8 h: Initial: mean 60%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 55-63%, after 6 months at accelerated: in the range of 58-66%

12 h: Initial: mean 79%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 74-82%, after 6 months at accelerated: in the range of 76-83%

24 h: Initial: mean 97%, after 24 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 93-97%, after 6 months at accelerated: in the range of 94-100%

Table 5: Summary of Stability Data of Commercial Image XP13512 ER Tablets (Batch #s 3062644R, 3062645R, and 3062646R) (b) (4) 60, 180 count/bottle

Parameter	Test Results				
	Initial	2-8º C (12 months)	25º C/60% RH (12 months)	30º C/75% RH (12 months)	40º C/75% RH (6 months)
Description		Conform	Conform	Conform	Conform
Assay (% range)	(b) (4)				
Degradation Products (% range)					
(b) (4)					
Individual Unspecified Degradation Products					
(b) (4)					

	(b) (4)

Dissolution (mean of % range) 12 months at 2-8º C, 30º C/75% RH, 25º C/60% RH and 6 months at 25º C/60% RH	
4 h	(b) (4)
8 h	
12	
24	

NP: Not Performed, ND: Not Detected, * The proposed dissolution specification was not in place at time of testing. L2 testing was not performed.

EVALUATION: Adequate. Results are provided for commercial tablets following storage for up to 12 months at 2-8° C, 25° C/60% RH, 30° C/65% RH, and 40° C/75% RH. Data demonstrated that the gabapentin enacarbil commercial drug product is stable. No change in description was observed for commercial image XP13512 ER tablets after storage at 2-8° C, 25° C/60% RH, 30° C/65% RH after 12 months, and 40° C/75% RH for 6 months. Storage at accelerated storage conditions enhances degradation compared to other storage conditions (see increase in (b) (4) in table above).

Assay

Initial: in the range of 98.3-99.6%, after 12 months at 2-8° C, 25° C/60% RH, 30° C/65% RH: in the range of 96.7-100.7%, after 6 months at accelerated: in the range of 96.1-98.0%

Total Degradation Products

Initial (b) (4)%, after 12 months at 2-8° C, 25° C/60% RH, 30° C/65% RH: in the range of < (b) (4), after 6 months at accelerated: in the range of (b) (4)%

Dissolution

4 h: Initial: mean 33%, after 12 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: 29-35%, after 6 months at accelerated: in the range of 29-36%

8 h: Initial: mean 64%, after 12 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 62-70%*, after 6 months at accelerated: in the range of 62-67%

12 h: Initial: mean 83%, after 12 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 80-88%*, after 6 months at accelerated: in the range of 71-84%

24 h: Initial: mean 98%, after 12 months at 2-8° C, 25° C/60% RH, and 30° C/65% RH: in the range of 92-99%, after 6 months at accelerated: in the range of 92-96%

(b) (4)

Comparability Protocol Decision to be sent in the Action Letter

The applicant provided comparability protocol for the post approval site changes for drug substance manufacture, release testing, and stability testing with the proposed data package that will be submitted in the Annual Report. However, FDA inspection of the proposed site is needed in addition to the proposed data package, which needs to be submitted in a CBE-30 supplement.

CMC Recommendation

From the CMC point of view, NDA 22-399 for Solzira (gabapentin enacarbil) ER Tablets is recommended **APPROVAL.**

ATTACHMENT

NDA 22-399: Overall Acceptable Recommendation from the Office of Compliance

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22399/000	**Sponsor:**	GLAXO GRP LTD
Org. Code:	120		5 MOORE DR
Priority:	1S		RESEARCH TRIANGLE PARK, NC 27709
Stamp Date:	15-SEP-2008	**Brand Name:**	SOLZIRA
PDUFA Date:	09-NOV-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	GABAPENTIN ENACARBIL
District Goal:	10-SEP-2009	**Product Number; Dosage Form: Ingredient; Potency**	001; TABLET, EXTENDED RELEASE; GABAPENTIN ENACARBIL; 600MG

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	C. TELE	Review Chemist	301-796-1762
	R. SOOD	Team Leader	301-796-1466

Overall Recommendation: ACCEPTABLE on 24-SEP-2009 by S. FERGUSON (HFD-322) 301-796-3247

Establishment: **CFN:** 1033964 **FEI:** 1033964

GLAXOSMITHKLINE INC
1011 NORTH ARENDELL AVE

ZEBULON, NC 275971217

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-SEP-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JAN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:			
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-JAN-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 1510437	**FEI:** 1510437	
	PATHEON PHARMACEUTICALS INC 2110 E GALBRAITH RD		
	CINCINNATI, OH 452371625		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, EXTENDED RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-SEP-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

MARTHA R HEIMANN
10/27/2009
Checked in for Chhagan Tele

RAMESH K SOOD
10/27/2009

NDA 22-399

Solzira™ (gabapentin enacarbil) Extended Release Tablets

GlaxoSmithKline

Chhagan G. Tele, Ph.D.
Division I/Branch 1
Office of New Drug Quality Assessment

Division of Neuropharmacological Drug Products
Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-399

2. REVIEW #: 1

3. REVIEW DATE: 27-AUG-2009

4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (withdrawn 12-NOV-08)	15-SEP-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmitted	09-JAN-2009
Amendment (BC) 0008	23-MAR-2009
Amendment (BC) 0014	29-MAY-2009
Amendment (BC) 0025	26-AUG-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Glaxo Group Limited d/b/a GlaxoSmithKline
Address:	Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN UK
Representative:	Debra H. Lake, M.S., Manager, Regulatory Affairs Five Moore Drive P.O. Box 13398, Research Triangle Park, NC 27709
Telephone:	(919) 483-9500

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Solzira™ (the proposed tradename)
   b) Non-Proprietary Name/USAN: gabapentin enacarbil
   c) Code Name/# (ONDQA only): GSK Code: GSK1838262, XenoPort: XP13512
   d) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: 1
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1); Solzira™ (gabapentin enacarbil) ER Tablets (600 mg Strength)

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: For the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)

11. DOSAGE FORM: ER Tablets

12. STRENGTH/POTENCY: 600 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN: gabapentin enacarbil

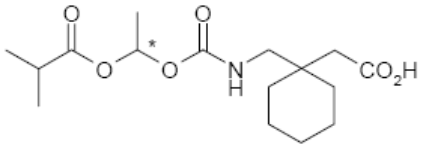
Non-Proprietary Name: (1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl) amino]methyl}cyclohexyl)acetic acid

Chemical Formula: $C_{16}H_{27}NO_6$

Molecular Weight: 329.39

CAS registry #: 478296-72-9

Structure:



XP13512 contains one chiral center. The compound exists as a racemate of S-(XP17814) and R-(XP17815) enantiomers.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS
			(b) (4)	4	N/A	LOA 08-FEB-08
				4	N/A	LOA 13-FEB-08

(b) (4)			
	4	N/A	LOA 31-MAR-08
	4	N/A	LOA 14-FEB-08
	4	N/A	LOA 08-FEB-08
	4	N/A	LOA 09-MAY-08
	4	N/A	LOA 08-FEB-08
	4	N/A	LOA 08-FEB-08
	4	N/A	LOA 07-FEB-08
	4	N/A	LOA 31-MAR-08
	4	N/A	LOA 15-FEB-08
	4	N/A	LOA 07-FEB-08
	4	N/A	LOA 21-FEB-08

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71,352 (effective 13-DEC-2004) Tablets	Commercial IND (RLS)
		(b) (4)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		Shawnte L. Adams (HFD-322)
Pharmtox	Pending		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Pending		
EA	Consultation requested	03-AUG-09	Raanan Bloom
Microbiology	N/A	N/A	N/A

NOTE #1: NDA 22-399 for Solzira™ (gabapentin enacarbil) Extended Release Tablets for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) was submitted on 15-SEP-08 and withdrawn (12-NOV-08) for the concerns about clinical study XP060. GSK resubmitted this NDA on 09-JAN-09.

The Chemistry Review for NDA 22-399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view NDA 22-399 for Solzira™ (gabapentin enacarbil) ER Tablets is recommended **APPROVABLE** from the CMC standpoint due to the following pending issues:

1) The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.

2) A consult review of the environmental assessment (OPS/PARS) is pending.

3) The applicant provided comparability protocol for the post approval site changes for drug substance manufacture, release testing, and stability testing with the proposed data package that will be submitted in the Annual Report. However, FDA inspection of the proposed site is needed in addition to the proposed data package, which needs to be submitted in a CBE-30 supplement. We will send this decision to the applicant for submitting this information in CBE-30 in the action letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and drug substance(s)

Gabapentin was initially developed by Parke-Davis (now Pfizer) as Neurontin® Capsules for treatment of epilepsy under NDA 20-345. It is currently marketed in three dosage forms, i.e., capsule, tablet, and oral solution, for treatment of epilepsy and post-herpetic neuralgia. Gabapentin enacarbil (XP13512) is a non-ester, orally administered, prodrug for gabapentin developed by XenoPort for treatment of restless legs syndrome (RLS) under IND 71,352. In April 2008, XenoPort licensed the product to GSK. In the current NDA, GSK proposed marketing of gabapentin enacarbil as extended release tablets containing 600 mg of the active ingredient (equivalent to 312 mg gabapentin). The recommended dose is 1200 mg/day, to be taken orally at evening with food. The design intent for XP13512 ER Tablets (600 mg strength) was to produce an extended release (ER) tablet formulation for XP13512 to provide relief of the symptoms of primary restless legs syndrome, using a manufacturing process suitable for a (b) (4) Phase II clinical trials. The same commercial formulation for XP13512 ER Tablets, 600 mg was used in all Phase 1, 2, and 3 clinical studies.

Drug Product

Adequate information on components and composition of the proposed commercial drug product for unit dose formulation for 600 mg strength is provided. Common excipients (colloidal silicon dioxide,

dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc) of USP/NF compendial grades are used to manufacture drug product. The proposed commercial tablet formulation is qualitatively identical to the tablets used for Phase 3 clinical trials and will be manufactured at the same site. Two changes to the commercial drug product have been made since the manufacture of pivotal clinical supplies. These are the addition of a debossed image and (b) (4). These changes are characterized by the applicant as minor. The manufacture of the drug product consists of manufacturing process as: (b) (4) The drug product will be manufactured by Patheon Pharmaceuticals at the Cincinnati, Ohio facility using (b) (4)

Information about controls of critical steps in the manufacture of registration batches of the Solzira Tablets is provided. In-process tests (b) (4) were performed to maintain consistent manufacture of the drug product. The specifications for tablets included: Description (Appearance: visual), Identification (UV, HPLC), Assay (HPLC), Impurities (HPLC), Content Uniformity (HPLC), and Dissolution. The release specification for assay of gabapentin enacarbil tablets by HPLC is (b) (4)% of label claim. A specific, stability indicating HPLC method and acceptance criteria have been developed for determination of identification, assay, and purity of gabapentin enacarbil in Solzira Tablets. This method has been validated with respect to specificity, linearity, working range, accuracy, method precision, limit of quantitation, and robustness. The purity acceptance criteria conformed to the limits of purity/degradation products observed during release and ongoing stability studies of Solzira Tablets. Content Uniformity was performed using weight variation. The proposed specification for Content Uniformity conforms to compendial USP <905> criteria. Tablet dissolution results are quantitated by validated HPLC using gradient aqueous phosphate-acetonitrile mobile phase. XP13512 ER Tablets will be packaged in 30-, 60-, and 180-count, (b) (4) bottles with (b) (4) Each bottle configuration includes (b) (4) desiccant packet filled with (b) (4) The proposed container closure system was chosen to (b) (4)

Batch analysis data for three pilot scale commercial image batches of XP13512 ER Tablets (600 mg strength) are provided, which were manufactured according to the proposed commercial process at the commercial site and tested by the proposed commercial methods. Batch details and analysis data are also provided for three additional pilot scale non-debossed batches of XP13512 ER Tablets manufactured according to the proposed commercial process, at the commercial site, and tested by the proposed commercial methods. These batches differ from the tablets in debossing and (b) (4) Control of drug product is evidenced by the low variability of release data. This is true for assay, degradation products, uniformity of content, and dissolution. Consistent results were also obtained for appearance and identification tests. The data, therefore, lead to the inference that drug product quality is consistent through the scale employed in the manufacturing process for gabapentin enacarbil drug product.

In an amendment 0014 dated 29-MAY-09, the applicant provided information about testing of four batches of XP13512 ER Tablets (600 mg strength) in three different pH media (0.1 N HCl, pH 5.0 buffer, and pH 6.8 buffer) in accordance with FDA Guidance for Industry documents and as discussed at the Pre-NDA meeting (16-APR-08). The data provideded by the applicant supported the conclusion that there is no change in dissolution performance between the reference batch and the commerical image batches in three different biorelevant dissolution media. The similarity factor (f_2) test met the requirement of (b) (4) (calculated f_2 range: Medium A: 77-97, Medium B: 72-91, and Medium C: 86-91). As expected, the extent of dissolution was reduced in 0.1 N HCl (Media A). Complete dissolution was achieved in 20 mM KH_2PO_4 buffer, pH 5.0 and pH 6.8, 0.2% SLS (Media B and C).

Initially, 6 months stability data from three batches of commercial image Solzira Tablets and 12 months stability data from three batches of non-debossed gabapentin enacarbil ER tablets. In amendment 0014 (BC) dated 29-MAY-09, 24 months updated stability data for three non-debossed batches and 12 months updated stability data for three commercial image batches was provided. Samples were placed in chambers at 2-8° C, 25° C/60% RH, 30° C/65% RH, and 40° C/75% RH. All batches were manufactured at pilot scale using the commercial process and equipment at the commercial manufacturing site and packaged in the proposed commercial packs. The commercial image tablets have identical size and composition to the non-debossed tablets, with the exception of two changes: the addition of the debossed image and (b) (4). The overall quality of the batches of drug product placed on formal stability studies is intended to be representative of the material to be made for routine production at Patheon, Cincinnati. The samples were tested for appearance, assay, degradation products, and dissolution. Dissolution was performed using USP dissolution apparatus 2 (paddle) at 50 rpm with 900 mL pH 7.4 phosphate buffer medium. Microbial Limit Testing was also performed on all clinical and non-debossed stability batches manufactured at the commercial manufacturing facility. All results for Total Aerobic Microbial Count were well below the allowable limit of 1000 cfu/g. Results from all batches demonstrated zero counts for the Total Yeast and Mold Count. The applicant proposed (b) (4) The test results for the drug product remained within the shelf-life specifications after 12 months for commercial image and after 24 months for non-debossed tablets stored at 25º C/60% RH and 30º C/65% RH and after 6 months of storage at 40º C/75% RH. In addition, photostability data are provided for one supportive stability batch of XP13512 ER Tablets. The stability data for XP13512 ER tablets showed no significant change in assay, degradation products, and dissolution for any of the conditions tested. Results of accelerated and long-term stability studies demonstrated the chemical and physical stability of XP13512 ER tablets. Therefore no statistical analysis is provided. A shelf-life of 36 months is proposed by the applicant to the product when stored under the following conditions: Store at 25° C (77° F); excursions permitted to 15 to 30° C (59 to 86° F).

Drug substance

XP13512 is a small molecule with molecular formula $C_{16}H_{27}NO_6$ and molecular weight 329.39. There is a single chiral center (b) (4), the drug substance is a racemic mixture. The drug substance has (b) (4) According to Biopharmaceutics Classification System (BCS), gabapentin enacarbil is classified as a BCS Class 2 compound (low solubility, high permeability). Gabapentin enacarbil is a white to off-white powder. The bulk drug substance is a (b) (4)

(b) (4) . The applicant provided adequate information regarding structure elucidation and confirmation, method of manufacture, in-process controls, test methods, container closure system, and stability testing of gabapentin enacarbil drug substance. The specifications for drug substance included Description (Visual), Identification (IR), Assay (HPLC), Impurities (b) (4) impurities: HPLC and (b) (4): GC), (b) (4) and Residue on Ignition. Validated analytical methods were provided in the submission.

Gabapentin enacarbil does not have a USP monograph; therefore, its specifications were set by the manufacturer, (b) (4), on the basis of knowledge of the established manufacturing process (batch analysis data) and according to ICH guidelines related to drug substance. The manufacturing process involves (b) (4)

Release data of drug substance batches used in clinical trials, primary drug product stability studies, and manufacturing of registration batches is provided. No significant variations between the individual gabapentin enacarbil batches manufactured via the commercial process have been observed. Gabapentin enacarbil batches are consistent with respect to the analytical parameters tested. The content of gabapentin enacarbil (HPLC, (b) (4)%) is adequate. The specifications for the each specified impurities (b) (4) for the drug substance release specifications are included.

Initially, the drug substance stability data included twelve months of long-term stability data for three primary stability batches manufactured in (b) (4) using the proposed commercial process (b) (4) using the proposed commercial process with the minor process improvements (see section S.2.5). Thirty six months stability data is provided for one supportive batch. In amendment 0014 dated 29-MAY-09, the applicant provided updated 24 months stability data for the three primary stability batches batches and 12 months long-term data for fourth primary stability batch using the proposed commercial process with the minor process improvements (stored at at 5° C, 25° C/60% RH, and 30° C/65% RH and 6 months at 40° C/75% RH). No significant change in description, content, drug-related impurities, and (b) (4) was observed after storage at 5° C and 25° C/60% RH for 24 months and 30° C/65% RH for 12 months or 40° C/75% RH for 6 months. All results complied with the specification. The stability data demonstrated the chemical and physical stability of the drug substance. A (b) (4) retest period is proposed when stored up to 25º C (77º F) and it is granted. The applicant has proposed (b) (4)

applicant need to provide information about the acceptability of site by the FDA to support the proposed post approval site changes in a submission of a CBE-30 supplement. We will send our decision to the applicant of submitting this information in CBE-30 in the action letter. The fourth protocol provides for filing of a change in (b) (4) as a CBE-0 supplement. It is acceptable, since the applicant is committed to provide sufficient information as described above to support changes in manufacturing process post approval changes by (b) (4) in a CBE-0 supplement.

B. Description of How the Drug Product is Intended to be Used

Solzira™ (gabapentin enacarbil) ER Tablets (600 mg strength) will be marketed into bottles only. Summary for all of the gabapentin enacarbil tablet stability studies performed by Patheon Pharmaceuticals, Inc., Cincinnati, Ohio is provided. Gabapentin enacarbil tablets are packed in bottles only. The recommended dose for the treatment of RLS is 1200 mg. The suitability of the container/closure system is demonstrated by the stability data under ICH conditions in stability section of this review. Letters of Authorization to refer DMFs for container closure is for use in packaging the tablets in bottles is provided. Adequate information about packaging components and manufacturer were provided. A shelf-life of 36 months is proposed by the applicant to the product when stored under the following conditions: Store at 25° C (77° F); excursions permitted to 15 to 30° C (59 to 86° F). (See USP Controlled Room Temperature) and it is granted after the review of the updated stability data (24 months of data on the commercial batches stored at 25° C/60% RH).

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC point of view NDA 22-399 for Solzira™ (gabapentin enacarbil) ER Tablets is recommended **APPROVABLE**. Consult was sent to Raanan Bloom, OPS/PARSGSK (03-AUG-09) by Mr, Don Henry (ONDQA PM) to evaluate the data submitted by the applicant for Environmental Assessment (EA) for gabapentin enacarbil. It is required to prepare an EA if the expected introduction concentration (EIC) to the aquatic environment is >1 ppb.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name:	Chhagan G. Tele, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	Beverly Conner, Pharm.D.

C. CC Block

See DFS.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22399	ORIG 1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA
NDA 22399	ORIG 1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA
NDA 22399	ORIG 1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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

/s/

CHHAGAN G TELE
08/31/2009

RAMESH K SOOD
08/31/2009

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products/
NDA:	22-399
Applicant:	GlaxoSmithKline (GSK)
Stamp Date:	15-Sep-2008
PDUFA Date:	15-Jul-2009
Trademark:	Solzira (proposed)
Established Name:	Gabapentin enacarbil
Dosage Form:	Extended release tablets
Route of Administration:	Oral
Indication:	Restless legs syndrome
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

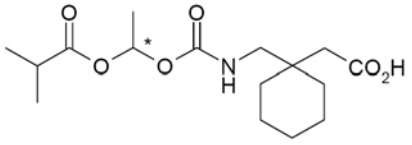
Summary

Gabapentin was initially developed by Parke-Davis (now Pfizer) as Neurontin® Capsules for treatment of epilepsy under NDA 20-345. It is currently marketed in three dosage forms, i.e., capsule, tablet, and oral solution, for treatment of epilepsy and post-herpetic neuralgia.

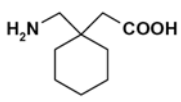
Gabapentin enacarbil (XP13512) is a non-ester, orally administered, prodrug for gabapentin developed by XenoPort for treatment of restless legs syndrome (RLS) under IND 71,352. In April 2008, XenoPort licensed the product to GSK. In the current NDA, GSK proposes marketing of gabapentin enacarbil as extended release tablets containing 600 mg of the active ingredient (equivalent to 312 mg gabapentin). The recommended dose is 1200 mg/day, to be taken at 5:00 pm with food.

Drug Substance

The active ingredient is gabapentin enacarbil (XP13512), a prodrug for gabapentin. The chemical name is 1-[[[[1-(2-methyl-1-oxopropoxy)ethoxy]carbonyl]amino]methyl]-cyclohexaneacetic acid.



Gabapentin Enacarbil



Gabapentin

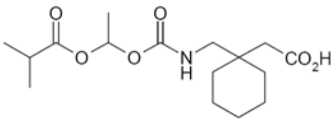
The oral bioavailability of gabapentin, the active moiety of XP13512, is not dose proportional; i.e., as the dose is increased from 300 mg tid to 1600 mg tid, bioavailability decreases from 60% to 27%. [Neurontin® package insert] The applicant indicates that the XP13512 prodrug was designed to overcome pharmacokinetic limitations of gabapentin. The prodrug was designed to be stable in gastrointestinal contents and to be actively absorbed by high capacity nutrient transporters present throughout intestinal tract, resulting in high bioavailability and dose proportional exposure.

XP13512 is a small molecule with molecular formula $C_{16}H_{27}NO_6$ and molecular weight 329.4. There is a single chiral center (b) (4), the drug substance is a racemic mixture. The drug substance has (b) (4) Based on solubility properties and data from human mass balance studies, the applicant classifies XP13512 as a BCS Class 2 compound. Other physical properties of XP13512 include (b) (4)

XP13512 is manufactured by (b) (4). The manufacturing process involves (b) (4) as starting materials was negotiated with the firm during End of Phase 2 and pre-NDA CMC meetings held on 24-Oct-2006 and 16-Apr-2008.

Stage 1: Preparation of XP13512:

(b) (4)



(XP13512)
$C_{16}H_{27}NO_6$
(329.39)

Gabapentin used in the manufacture of XP13512 will comply with current USP requirements. As the USP monograph does not allow any impurity greater that 0.1% no significant carry-over of impurities would be expected.

(b) (4)

Figure 9 (b) (4)

(b) (4)

The proposed drug substance specification is reproduced below. In addition to (b) (4)

SPECIFICATION FOR XP13512

Test	Acceptance Criteria
Description	(b) (4)
Identification by IR	
XP13512 Content by HPLC (b) (4)	
Drug-related impurities content by HPLC (% w/w) (b) (4) Total impurities	
(b) (4)	
Residue on ignition (% w/w)	

The proposed analytical procedures for XP13512 are straight-forward. A single reverse phase, gradient HPLC method (C8 column, acetonitrile-aqueous phosphate, pH 2.5 mobile phase) is used for assay and determination of related substances.

The drug substance stability package includes twelve months of long-term stability data for three (b) (4) kg scale batches that are identified by the applicant as commercial process primary stability batches, and six months long-term data for one (b) (4) kg scale batch manufactured using *"the proposed commercial process with process improvements"*. Thirty six months stability data are presented for one supportive batch. All drug substance batches were manufactured by (b) (4) A (b) (4) retest period is proposed.

The applicant has proposed four comparability protocols that provide for post-approval changes to drug substance manufacture and control. The first three protocols are included in Module 3.2.S.2.1 and provide for submission of site changes for drug substance manufacture, release testing, and stability testing in the Annual Report. The fourth, which is submitted in Module 3.2.S.2.2, provides for filing of a change (b) (4) as a CBE-0 supplement. It is noted that submission of a CBE-30 supplement would normally be required for the manufacturing and testing site changes described. Similarly, the proposed process modification would normally require submission of a prior approval supplement.

Drug Product

The proposed dosage form for Solzira® (gabapentin enacarbil extended release tablets), is an extended release tablet containing 600 mg XP13512 in (b) (4). The tablets are white to almost white oval shaped tablets debossed on one side with "GS LFG". Occasional black/grey spots may be present and are considered acceptable by the applicant. The quantitative formulation is summarized in Table 1.

Table 1 Composition of XP13512 ER Tablets, 600 mg

Component	Quantity (mg/tablet)	Function	Reference to Standard
(b) (4)			

Note:
1. Assuming 100% conversion of XP13512 to gabapentin *in vivo*, 600 mg of XP13512 (MW 329.39) is equivalent to 312 mg of gabapentin (MW 171.24) on a molecular weight basis.
2. GlaxoSmithKline Internal Specification.
3. (b) (4)
4.

All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements. The proposed commercial tablet formulation is qualitatively identical to the tablets used for Phase 3 clinical trials and will be manufactured at the same site. Two changes to the commercial drug product have been made since the manufacture of pivotal clinical supplies. These are the addition of a debossed image and (b) (4) These changes are characterized by the applicant as minor.

(b) (4)

The drug product will be manufactured by Patheon Pharmaceuticals at the firm's Cincinnati, Ohio facility using (b) (4) The applicant indicates that development of the product followed a traditional approach, but that *"…the manufacturing process has been assessed to determine the most critical aspects, and additional work has been performed on these aspects to generate better process and product understanding."* The information provided in the Pharmaceutical Development Section appears to reflect a thorough investigation of product characteristics and

manufacturing process parameters. Evaluation of the applicant's level of process understanding, however, is deferred to the primary reviewer.

The proposed regulatory specification for XP13512 ER Tablets is shown below. (b) (4)

1. SPECIFICATION FOR XP13512 ER TABLETS, 600 MG

Test	Acceptance Criteria
Description	(b) (4)
Identification of XP13512 by HPLC-RT[1]	
Identification of XP13512 by HPLC-UV[1]	
Assay (HPLC)	
Uniformity of Dosage Units by Weight Variation[1]	
Degradation Products (%w/w) (b) (4)	
Individual Unspecified Degradation Products[2] (% w/w)	
Total Degradation Products[3] (%w/w)	
Dissolution	Complies with USP <711>
	Time (hrs) / % Released
	0.5 / (b) (4)
	6
	24

Note:
1. Performed at release only.
2. Report all unspecified degradation products individually ≥0.05% w/w with the corresponding relative retention time. Includes only drug product related degradation products. Known drug substance (b) (4) impurities are not included.
3. Total degradation products is the sum of all degradation products above or equal to 0.05% w/w. Known drug substance (b) (4) impurities are not included.

The proposed analytical procedures are straight-forward. A single reverse phase, gradient HPLC method (C18 column, acetonitrile-aqueous phosphate, pH 2.5 mobile phase) is used for assay and determination of related substances. Tablet dissolution results are quantitated by HPLC using an isocratic aqueous phosphate-acetonitrile mobile phase.

XP13512 ER Tablets will be packaged in (b) (4) 30-, 60-, and 180-count, (b) (4) bottles with (b) (4). Each bottle configuration includes either (b) (4) desiccant (b) (4) desiccant (b) (4)

filled with (b) (4) . The 30-, 60-, and 180-count bottles are unit of use packages. The proposed container closure system was chosen to minimize degradation of the active ingredient. Use of alternate desiccants (b) (4) resulted in substantial degradation under accelerated storage conditions. Due to stability concerns the applicant proposes to include instructions to dispense the product in the original container in labeling.

The NDA stability package includes long-term data through twelve months for three pilot-scale batches of non-debossed XP13512 ER Tablets and six months of long-term data for three pilot-scale, commercial image, debossed tablets. A (b) (4) expiration dating period is proposed.

The applicant has proposed (b) (4) .

Critical issues for review

Drug Substance

By prior agreement, manufacture of the drug substance involves (b) (4) from the designated starting materials. Designation of (b) (4) starting material was allowed based on the applicant's controls strategy for this material. Therefore, it is recommended that the supporting documentation for (b) (4) be examined carefully to verify that the applicant has adequately demonstrated the adequacy of the controls for the starting material. In particular, the ability of the manufacturing process to (b) (4) should be evaluated to confirm that no additional controls are needed in the drug substance specification. Additionally, the sponsor's change control procedures for (b) (4) should be evaluated.

Drug Product

The drug product is (b) (4) The primary issues with respect to manufacture and control of the dosage form are related to the physicochemical properties of the drug substance itself. Therefore, it is recommended that the impact of manufacturing process parameters on the stability of active ingredient be evaluated closely.

Additional issues

Administrative: An environmental assessment for gabapentin enacarbil release tablets is included in Module 1 of the application. It is requested that the ONDQA Project Manager arrange for a consult review.

Establishment Evaluation: A full list of manufacturing sites and contract testing facilities is appended to the Form 356h. A copy is included in Attachment 1. All sites have been entered into EES, and were submitted for facility evaluation on 29-Sep-2008.

Labeling/Established Name: The active ingredient, gabapentin enacarbil, is (b) (4) form of the prodrug. There are no issues related to consistency between the established name "gabapentin enacarbil extended release tablets" and labeled potency. In this case, however, the active ingredient is a prodrug for an approved active moiety, gabapentin. Therefore, relationship between the labeled amount of the prodrug and the resulting dose should be considered in labeling. This may not be a critical consideration for the current NDA. Neurontin® (gabapentin) is not approved for treatment of restless legs syndrome; and the applicant does not propose to market XP13512 ER tablets for the same indications (i.e., epilepsy and post-herpetic neuralgia) for which Neurontin® (gabapentin) is approved.

Comments for 74-Day Letter

There are no comments for the 74-Day letter.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a relatively well-characterized small molecule and the dosage form is relatively simple. The proposed (b) (4) team for review. No novel manufacturing processes are involved and the submission does not appear to require a review by the Manufacturing Sciences Branch.

Martha R. Heimann, Ph.D. 06-Oct-2008
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. 06-Oct-2008
Branch Chief Date

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/s/

Martha Heimann
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CHEMIST

Ramesh Sood
10/7/2008 01:23:32 PM
CHEMIST