CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

CHEMISTRY REVIEW(S)

NDA 204096

Addendum #1 to Review #1

Astagraf XL
(tacrolimus extended-release capsules)

Astellas Pharma US, Inc.

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
and Biopharmaceutics Team

for the Division of Transplant and Ophthalmic Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 204096 [Original 1 –Kidney]
   NDA 204096 [Original 2 – Liver (Males)] *Indication withdrawn 07-FEB-2013*

   This New Drug Application was originally submitted as NDA 50-811 on 19-DEC-2005. NDA 50-811 was withdrawn on 29-JAN-2009 (see below for detailed application history).

2. REVIEW#: Addendum #1 to Review #1

3. REVIEW DATE: July 11, 2013

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 50-811 (original and amendments)	19-DEC-2005, etc.

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Original NDA (0000)	21-SEP-2012
Amendment (0007) (response to DMEPA packaging request)	10-JAN-2013
Amendment (0028) (regarding Kerry site 483)	18-APR-2013
Amendment (0030) (response to cmc / biopharmaceutics information request)	19-APR-2013
Amendment (0033) (proposed labeling covering alcohol dose dumping)	24-MAY-2013
Labeling (0034)	05-MAY-2013
Amendment (0036) (response to cmc / biopharmaceutics information request / preliminary draft PMC	07-JUN-2013
Amendment (0038) (Package Insert)	**28-JUN-2013**

Amendment (0040) (Labeling / Container-Carton)	**03-JUL-2013**
Amendment (0041) (withdrawal of [redacted] (b) (4)	**03-JUL-2013**
Amendment (0042) (PMC; other agreements)	**09-JUL-2013**

7. NAME & ADDRESS OF APPLICANT:

Name:	Astellas Pharma US, Inc. (formerly Fujisawa)
Address:	1 Astellas Way Northbrook, IL 60062
Representative:	Glen W. Spears, Ph.D. Associate Director, Regulatory Affairs
Telephone:	Tel: 224-205-5935 Fax: 224-205-5755

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Astagraf XL (formerly Advagraf)
b) Non-Proprietary Name (USAN): tacrolimus
c) Code Name/#: FK506; FK506E (MR4) Capsules
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSIN: 505(b)(1)

10. PHARMACOL. CATEGROY: Immunosuppressant

11. DOASAGE FORM: extended-release capsules

12. STRENGTH/POTENCY: 0.5, 1 and 5 mg [redacted] (b) (4)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

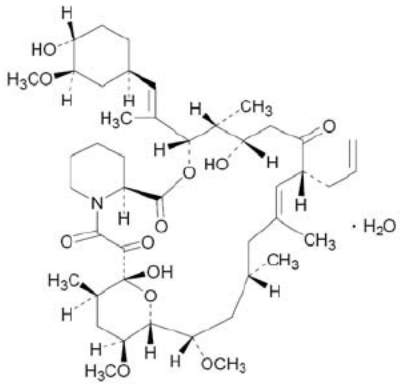
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

CAS: [3S-[3R*[E(1S*, 3S*, 4S*)], 4S*, 5R*, 8S*, 9E, 12R*, 14R*, 15S*, 16R*, 18S*, 19S*, 26aR*]]-5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 26, 26a-hexadecahydro-5,19-di-hydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14, 16-dimethoxy-4, 10, 12, 18-tetramethyl-8-(2-propenyl)-15, 19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclo-tricosine-1, 7, 20, 21 (4H,23H)-tetrone, monohydrate.

Empirical Formula: $C_{44}H_{69}NO_{12}.H_2O$
Formula Weight: 822.03



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16833	2	Astellas	Tacrolimus drug substance	7			Drug substance used in approved products*
(b) (4)	4		(b) (4)	4			
	4			4			

(b) (4)	3	(b) (4)	4			
	3		4			
	3		4			
	3		4			
	3		4			
	3		4			

e CMC originally submitted in NDA 50-708 and subsequent supplements Same information subsequently compiled in DMF 16833

[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
Original NDA	NDA 50-811 *	Prograf MR / Advagraf
Original IND and amendments	IND 64,148	Prograf MR
Original NDA and Supplements	NDA 50-708 #	Prograf Capsules
Original NDA and Supplements	NDA 50-709	Prograf Injection

* NDA 50-811, submitted 19-DEC-2005, was administratively split per indication on January 11, 2007:

NDA 50-811 Kidney Indication
NDA 50-815 Liver Indication
NDA 50-816 Heart Indication

Approvable letters for the kidney and liver indications were issued on 19-JAN-2007. NDA 50-816 was issued a not approvable letter on 19-JAN-2007. (b) (4)

NDA 50-708, Prograf (tacrolimus) Capsules, submitted 23-JUL-1993, was approved on 08-APR-1994.

18. STATUS:

ODNQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		

EES	Overall recommendation of ACCEPTABLE	29-MAY-2013	Office of Compliance (see attached EES Summary Report)
Pharm/Tox	n/a		
ONDQA Biopharmaceutics	Acceptable with PMCs	Per this review	M. Seggel
LNC	n/a		
Methods Validation	n/a		
OSE / DMEPA	Proprietary name acceptable Other labeling issues resolved	31-MAY-2013 see DARRTS	J. Lee / K. Townsend J. Lee / J. Wilkins Parker
EA	Categorical exclusion acceptable	Review #1	M. Seggel
Product Quality Microbiology	Acceptable	07-DEC-2012	E. Pfeiler

19. GOAL DATES:

PDUFA: 21-JUL-2013

The Chemistry and Biopharmaceutics Review for NDA 204096

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Tacrolimus drug substance chemistry, manufacturing and controls is incorporated into this New Drug Application by reference to Astellas' approved NDA 50-708 (Prograf (tacrolimus) capsules), and to their associated Type II DMF 16833. There are no outstanding drug substance CMC issues.

In general, sufficient information to assure the identity, strength, purity, and quality and bioavailability of the drug product, Astagraf XL (tacrolimus extended-release capsules), is provided in this NDA. However, evolving concerns about the potential for (b) (4) of amorphous tacrolimus in the (b) (4) formulation and in the drug product, and interest in enhancing the utility of proposed regulatory dissolution test method and acceptance criteria necessitated the development of post-marketing commitments to address these issues. Agreement between FDA and Astellas regarding the post-marketing commitments and timelines is documented in an amendment dated 09-JUL-2013 (ectd 0042).

The Office of Compliance issued an overall recommendation of "Acceptable" on 29-MAY-2013 (see attached EES Report).

Revisions to the labeling (package insert, container and carton labels) were made at our request. The labeling as submitted in amendments dated 28-JUN-2013 and 03-JUL-2013, and as revised by DTOP on 11-JUL-2013, is now acceptable.

Therefore, from the CMC and Biopharmaceutics perspectives, this NDA is recommended for approval.

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

Agreement has been reached on Post-Marketing Commitments to (1) optimize the dissolution test method with respect to detection of (b) (4) of the amorphous drug in the drug product, (2) develop suitably discriminating dissolution test acceptance criteria, (3) evaluate the relationship between (b) (4) and dissolution, and (4) characterize the potential for (b) (4) of amorphous

tacrolimus in the (b) (4) See Review Attachment 4, Post-Marketing Commitments, for details.

II. Summary of Chemistry and Biopharmaceutics Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Astagraf XL (tacrolimus extended-release capsules) is a new solid oral dosage form of tacrolimus intended for once a day administration. Capsules contain the equivalent of 0.5-, 1- or 5-mg of anhydrous tacrolimus. Currently approved formulations of tacrolimus manufactured by Astellas include Prograf Capsules (also in 0.5-, 1- and 5-mg strengths), Prograf Injection and Protopic Ointment.

As with Prograf immediate-release capsules, (b) (4) of tacrolimus is prepared by (b) (4) (b) (4) (b) (4) (b) (4) The stability of the (b) (4) for up to (b) (4) months has been demonstrated. In the absence of data confirming that the solid state form of tacrolimus in the (b) (4) Astellas has agreed to limit the shelf-life of the material to (b) (4) months. Astellas also agreed to characterize the (b) (4) of tacrolimus in the (b) (4) (see PMC #4). In addition, data on drug product manufactured from stressed and aged (b) (4) should be obtained. Note that the manufacturer uses the date at which the (b) (4) as the date of manufacture of the drug product.

To achieve extended release of tacrolimus, (b) (4) The formulation is otherwise qualitatively the same as that of Prograf Capsules. In addition to tacrolimus and ethylcellulose, the (b) (4) contains (b) (4)

In the Astagraf XL formulation, the release of tacrolimus is (b) (4) Based on the previous experience with Prograf Capsules formulation development and because of the low aqueous solubility of tacrolimus (b) (4) hydroxypropyl methylcellulose (b) (4) (b) (4) Lactose is used to (b) (4) The proportions of inactive ingredients and tacrolimus are the same across all three product strengths, the only differences being the amount filled into each capsule and the capsule size.

The same formulation was used for all clinical samples (single-dose biopharmaceutics studies, repeated-dose biopharmaceutics studies, phase 2 and phase 3 studies), primary stability batches and proposed commercial production batches.

Two new process impurities were identified in the tacrolimus extended-release formulation. Related substances (b) (4) are (b) (4) of (b) (4) and have only been observed in the (b) (4) extended-release formulation. Another (b) (4) is the (b) (4) of (b) (4) which was identified as an impurity in (b) (4) (b) (4) The (b) (4) The (b) (4) They are therefore considered inconsequential. Any potential impact on solid-state form is unknown. (b) (4) in the (b) (4) is limited to NMT (b) (4)%.

The product specification includes tests for identification, assay, related substances, content uniformity, (b) (4), microbial limits and dissolution (multi-point test: 0.5, 1.5, 7 and 24 hours). The analytical procedures are similar to those employed for Prograf Capsules, although 0.1% sodium lauryl sulfate (SLS) is included in the dissolution medium to facilitate dissolution. The dissolution test is capable of identifying manufacturing issues (b) (4) as exemplified by the OOS investigation resulting of a dissolution failure observed in one batch of 0.5 mg capsules; this is discussed in more detail in review section P.3). However, it is currently unclear if the regulatory dissolution method is sufficiently sensitive to detect levels of (b) (4) that may affect bioavailability. Further optimization of the method is necessary, as is enhancement of the acceptance criteria. This will be addressed in PMC #1 and PMC #2. The potential affect of (b) (4) on (b) (4) and dissolution will be evaluated under PMC #3. Note that an IVIVC has not developed for this formulation of tacrolimus.

Dose dumping in patients who have consumed alcohol near the time of dosage administration is a concern with extended-release products. To evaluate the potential for dose dumping from Astagraf XL, *in vitro* dissolution studies were conducted. While the presence of 20% ethanol in the dissolution medium resulted in a modest increase in the rate of dissolution, the increase (5%-20% higher levels) was not considered clinically significant. However, when additional studies were recently conducted, in vitro dose dumping was observed in pH 1.2 medium with 20 - 40% alcohol. The package insert was revised to include language warning alcohol consumption when taking Astagraf XL capsules.

The stability profile of Astagraf XL is comparable to that of the immediate-release product. No new degradation products, other than the (b) (4) were observed.

The drug product is packaged in (non-child resistant) blisters for in-hospital use and in 30-count HDPE bottles for outpatient dispensing.

Drug substance CMC is documented in NDA 50-708 (Prograf Capsules) and Type II DMF 16833. Tacrolimus (FK506) is a macrolide (macrolactam) antibiotic produced by the bacterium *Streptomyces tsukubaensis*. This bacterium was first isolated from a soil sample from Tsukuba City, Ibaraki Prefecture, Japan in 1984.

Tacrolimus is virtually insoluble in water [redacted] but is very soluble in methanol and chloroform. Tacrolimus, which is isolated as the [redacted] is not hygroscopic, nor is it [redacted]. Tacrolimus is also somewhat [redacted] However, in general, tacrolimus has excellent long-term stability. Tacrolimus has been characterized as a BCS II drug (G. Amidon).

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

Like Prograf (tacrolimus) capsules, Astagraf XL (tacrolimus extended-release capsules) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. Astagraf XL is intended for once-a-day dosing while Prograf immediate-release capsules are typically dosed twice daily. The recommended initial dose ranges from approximately 0.1 mg/kg to 0.2 mg/kg. The daily dosage may be adjusted based on clinical assessments of rejection and tolerability, and to maintain trough whole blood concentrations within certain ranges (therapeutic dose monitoring, TDM). Astagraf XL is to be taken in the morning. Currently, [redacted] is not recommended.

The product has a 36-month expiration dating period when stored in the original blister/blister pouch or bottle at 25°C (excursions to 15-30°C permitted) [see USP].

C. Basis for Approvability or Not-Approval Recommendation

The CMC information in NDA 204096 is essentially the same as provided in NDA 50-811. The current NDA has updated drug product stability data and describes the implementation of tighter [redacted] Preliminary information about the [redacted] of amorphous tacrolimus to the [redacted] is provided. Additional characterization of the potential for [redacted] of tacrolimus in the [redacted] and in the drug product is necessary. The [redacted] of tacrolimus in some generic versions of Prograf (tacrolimus) capsules has been observed by OPS/OTR. While there is currently no indication that the same is occurring in Astagraf XL or the [redacted] Astellas has agreed to evaluate analytical methods (dissolution and a direct test) that may be suitable for detecting [redacted] Based on limited data from capsules exposed to [redacted], it appears that [redacted] adversely affects dissolution. This may be due to [redacted]

(b) (4) of tacrolimus. A (b) (4) could lead to an (b) (4) of the amorphous form of tacrolimus to a (b) (4)

Astellas has agreed to conduct studies regarding (b) (4) under the post-marketing commitments.

Note that NDA 50-811 was recommended for approval from the chemistry, manufacturing and controls perspective on January 19, 2007 (see NDA 50-708 Chemistry Review #1) and OCP had agreed to the proposed dissolution test and acceptance criteria. However, upon re-review it was determined that additional in vitro alcohol dose dumping data was needed. Specifically, the in vitro dissolution of Astagraf XL capsules in acidic medium containing 40% alcohol had not previously been evaluated. This study was conducted as requested; in vitro dose dumping was observed under these conditions. The current regulatory dissolution method is based on the method established for immediate-release tacrolimus capsules. To achieve greater than (b) (4)% dissolved at the final, 24-hour time point, 0.1% sodium lauryl sulfate is included in the dissolution medium. The utility of the dissolution test method with respect to detection of (b) (4) may be adversely affected by the presence of SLS in the dissolution medium. Astellas has agreed to optimize the dissolution method for detection of (b) (4) content as part of the post-marketing commitments. The inclusion of 0.1% SLS in the dissolution medium consistently results in greater than (b) (4)% dissolved at 24 hours. Ideally, the final time point for an extended release product should occur at the time when not less than (b) (4)% dissolved is reached, and not necessarily at 24 hours. There is currently a paucity of data obtained at time points other than 0.5, 1.5, 7 and 24 hours. Under the post-marketing commitments, Astellas has agreed to further define the dissolution profile by sampling at multiple times. Until additional dissolution data are available and a justification for revisions can be made, the regulatory dissolution test will include sampling at 0.5, 1.5, 7 and 24 hours.

Drug substance CMC is adequately addressed in Astellas' NDA 50-708 and Type II DMF 16833.

The manufacture and control of Astagraf XL (tacrolimus extended-release capsules) parallel those of Prograf immediate-release capsules. All aspects of drug product CMC have been adequately documented. Evidence that the product can be consistently manufactured (except as discussed below) in such a manner as to provide assurance of its identity, strength, quality, purity, potency and bioavailability is provided. The drug product specification further ensures that the product will meet the established quality standard. The manufacturing facilities have acceptable cGMP status.

In 2010, a batch of 0.5 mg capsules marketed in Europe was recalled following a dissolution failure on stability (70% released at 1.5 hours, upper limit NMT 68%). The dissolution failure was ultimately attributed to (b) (4) (b) (4)

(b) (4)

With regard to labeling, Astellas originally proposed naming the product 'Prograf MR (tacrolimus modified release capsules)'. Under NDA 50-811, the trademark 'Advagraf' was found acceptable. However, in the current review cycle, 'Advagraf' was deemed unacceptably promotional. The proprietary name, 'Astagraf XL' was found acceptable.

The different strength Prograf Capsules are distinguished, in part, by the use of bottles with different color caps. Astellas proposed using the (b) (4) to distinguish the different strengths of the extended-release product. However, given that the bottle (b) (4) are so prominent, this could potentially result in a dispensing error. Astellas has developed a distinct bottle shape and distinct bottle cap colors for the Astagraf XL products. Nevertheless, the potential for confusion and inadvertent medication errors, including those related to capsule shell colors, were carefully considered by the OND review team. In addition, the (b) (4) was withdrawn from the NDA after the FDA notified the applicant of concerns about potential medication errors – (b) (4) while the 5 mg capsule bottle has an orange closure (cap) and orange trade dress.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Mark R. Seggel, Chemistry and Biopharmaceutics Reviewer

B. Endorsement Block

{see electronic signature page}
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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/s/

MARK R SEGGEL
07/12/2013

ANGELICA DORANTES
07/12/2013

RAPTI D MADURAWE
07/12/2013

NDA 204096

Astagraf XL
(tacrolimus extended-release capsules)

Astellas Pharma US, Inc.

Mark R. Seggel
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Division of New Drug Quality Assessment II
and Biopharmaceutics Team

for the Division of Transplant and Ophthalmic Products

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   NDA 204096 [Original 2 – Liver (Males)] *Indication withdrawn 07-FEB-2013*

   This New Drug Application was originally submitted as NDA 50-811 on 19-DEC-2005. NDA 50-811 was withdrawn 29-JAN-2009 (see below for detailed application history).

2. REVIEW#: 1

3. REVIEW DATE: June 14, 2013

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 50-811 (original and amendments)	19-DEC-2005, etc.

6. SUBMISSIONS BEING REVIEWED:

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Amendment (0036) (response to cmc / biopharmaceutics information request / preliminary draft PMC	07-JUN-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Astellas Pharma US, Inc. (formerly Fujisawa)
Address:	1 Astellas Way Northbrook, IL 60062
Representative:	Glen W. Spears, Ph.D. Associate Director, Regulatory Affairs
Telephone:	Tel: 224-205-5935 Fax: 224-205-5755

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Astagraf XL (formerly Advagraf)
b) Non-Proprietary Name (USAN): tacrolimus
c) Code Name/#: FK506; FK506E (MR4) Capsules
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSIN: 505(b)(1)

10. PHARMACOL. CATEGROY: Immunosuppressant

11. DOASAGE FORM: extended-release capsules

12. STRENGTH/POTENCY: 0.5, 1 and 5 mg [redacted] (b) (4)

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14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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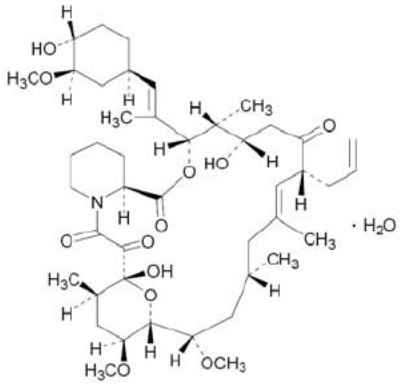

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A. DMFs:

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*Drug substance CMC original — information subsequently compiled in DMF 16833

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NDA 50-815 Liver Indication
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Approvable letters for the kidney and liver indications were issued on 19-JAN-2007. NDA 50-816 was issued a not approvable letter on 19-JAN-2007. (b) (4)

NDA 50-708, Prograf (tacrolimus) Capsules, submitted 23-JUL-1993, was approved 08-APR-1994.

18. STATUS:

ODNQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Overall recommendation of ACCEPTABLE	29-MAY-2013	Office of Compliance (see attached EES Summary Report)
Pharm/Tox	n/a		
ONDQA Biopharmaceutics	*PMC under negotiation*	per this review	M. Seggel
LNC	n/a		
Methods Validation	n/a		
OSE / DMEPA	Proprietary name acceptable *Other labeling issues pending*	31-MAY-2013 *pending*	J. Lee / K. Townsend J. Lee / J. Wilkins Parker

	resolution		
EA	Categorical exclusion acceptable	per this review	M. Seggel
Product Quality Microbiology	Acceptable	07-DEC-2012	E. Pfeiler

19. GOAL DATES:

GRMP: 16-JUN-2013
Labeling/PMC Discussion: 01-JUL-2013
PDUFA: 21-JUL-2013

The Chemistry and Biopharmaceutics Review for NDA 204096

The Executive Summary

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A. Recommendation and Conclusion on Approvability

Tacrolimus drug substance chemistry, manufacturing and controls is incorporated into this New Drug Application by reference to Astellas' approved NDA 50-708 (Prograf (tacrolimus) capsules), and to their associated Type II DMF 16833. There are no outstanding drug substance CMC issues.

In general, sufficient information to assure the identity, strength, purity, and quality and bioavailability of the drug product, Astagraf XL (tacrolimus extended-release capsules), is provided in this NDA. However, evolving concerns about the potential for (b) (4) of amorphous tacrolimus in the (b) (4) formulation and in the drug product, and interest in enhancing the utility of proposed regulatory dissolution test method and acceptance criteria have necessitated the development of post-marketing commitments to address these issues. As of the date of this review, the post-marketing commitments are not finalized.

An overall recommendation of "Acceptable" was issued by the Office of Compliance (see attached EES Report).

Recommendations regarding the labeling (package insert, container and carton labels) have been made. Negotiations of all aspects of the labeling are underway at this time.

Therefore, from the CMC and Biopharmaceutics perspectives, this NDA is not recommended for approval. Final agreement must be reached on the post-marketing commitments and the labeling issues must be resolved before a recommendation for approval can be made.

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

Post-Marketing Commitments to (1) further characterize the potential for (b) (4) of amorphous tacrolimus in the (b) (4) and in the finished capsules, (2) optimize the dissolution test method with respect to detection of (b) (4) of the amorphous drug in the drug product, to (3) develop suitably discriminating dissolution test acceptance criteria are currently under negotiation.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Astagraf XL (tacrolimus extended-release capsules) is a new solid oral dosage form of tacrolimus intended for once a day administration. Capsules contain the equivalent of 0.5-, 1- or 5-mg of anhydrous tacrolimus. Currently approved formulations of tacrolimus manufactured by Astellas include Prograf Capsules (also in 0.5-, 1- and 5-mg strengths), Prograf Injection and Protopic Ointment.

As with Prograf immediate-release capsules, an (b) (4) of tacrolimus is prepared by a (b) (4) (b) (4) (b) (4) The stability of the (b) (4) for up to (b) (4) months has been demonstrated. However, data on product manufactured from stressed and aged (b) (4) should be obtained. In addition, data on (b) (4) content will be provided (as part of the PMC). Note that the manufacturer uses the date at which the (b) (4) as the date of manufacture of the drug product.

To achieve extended release of tacrolimus, (b) (4) The formulation is otherwise qualitatively the same as that of Prograf Capsules. In addition to tacrolimus and ethylcellulose, the (b) (4) contains (b) (4) . (b) (4) .

In the Astagraf XL formulation, the release of tacrolimus is (b) (4) Based on the previous experience with Prograf Capsules formulation development and because of the low aqueous solubility of tacrolimus (b) (4) hydroxypropyl methylcellulose (b) (4) Lactose is used to (b) (4) The proportions of inactive ingredients and tacrolimus are the same across all three product strengths, the only differences being the amount filled into each capsule and the capsule size.

The same formulation was used for all clinical samples (single-dose biopharmaceutics studies, repeated-dose biopharmaceutics studies, phase 2 and phase 3 studies), primary stability batches and proposed commercial production batches.

Two new process impurities were identified in the tacrolimus extended-release formulation. Related substances [redacted] are [redacted] of tacrolimus, and have only been observed in the [redacted] extended-release formulation. Another [redacted] which was identified as an impurity in [redacted] The [redacted] The [redacted] They are therefore considered inconsequential. Any potential impact on solid-state form is unknown. [redacted] in the [redacted] is limited to NMT [redacted]%.

The product specification includes tests for identification, assay, related substances, content uniformity, [redacted] (acceptance criterion to be added), microbial limits and dissolution (three-point test: 0.5, 1.5 and 24 hours). The analytical procedures are similar to those employed for Prograf Capsules, although 0.1% sodium lauryl sulfate (SLS) is included in the dissolution medium to facilitate dissolution. The dissolution test is capable of identifying manufacturing issues [redacted] as exemplified by the OOS investigation resulting of a dissolution failure observed in one batch of 0.5 mg capsules; this is discussed in more detail in review section P.3). However, it is currently unclear if the proposed regulatory dissolution method is sufficiently sensitive to detect levels of [redacted] that may impact bioavailability. Further optimization of the method is warranted, as is enhancement of the acceptance criteria. Note that an IVIVC has not developed for this formulation of tacrolimus.

Dose dumping in patients who have consumed alcohol near the time of dosage administration is a concern with extended-release products. To evaluate the potential for dose dumping from Astagraf XL, *in vitro* dissolution studies were conducted. While the presence of 20% ethanol in the dissolution medium resulted in a modest increase in the rate of dissolution, the increase (5%-20% higher levels) was not considered clinically significant. However, when additional studies were recently conducted, in vitro dose dumping was observed in pH 1.2 medium with 20 - 40% alcohol. The potential for in vivo dose dumping will be addressed by the clinical review team.

The stability profile of Astagraf XL is comparable to that of the immediate-release product. No new degradation products, other than the [redacted], were observed.

The drug product is packaged in (non-child resistant) blisters for in-hospital use and in 30-count HDPE bottles for outpatient dispensing.

Drug substance CMC is documented in NDA 50-708 (Prograf Capsules) and Type II DMF 16833. Tacrolimus (FK506) is a macrolide (macrolactam) antibiotic produced by the bacterium *Streptomyces tsukubaensis*. This bacterium was first isolated from a soil

sample from Tsukuba City, Ibaraki Prefecture, Japan in 1984.

Tacrolimus is virtually insoluble in water [redacted] but is very soluble in methanol and chloroform. Tacrolimus, which is isolated as the [redacted] is not hygroscopic, nor is it [redacted] Tacrolimus is also somewhat [redacted] However, in general, tacrolimus has excellent long-term stability. Tacrolimus has been characterized as a BCS II drug (G. Amidon).

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

Like Prograf (tacrolimus) capsules, Astagraf XL (tacrolimus extended-release capsules) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. Astagraf XL is intended for once-a-day dosing while Prograf immediate-release capsules are typically dosed twice daily. The recommended initial dose ranges from approximately 0.1 mg/kg to 0.2 mg/kg. The daily dosage may be adjusted based on clinical assessments of rejection and tolerability, and to maintain trough whole blood concentrations within certain ranges (therapeutic dose monitoring, TDM). Astagraf XL is to be taken in the morning. Currently, [redacted] is not recommended.

The product has a 36-month expiration dating period when stored in the original blister/blister pouch or bottle at 25°C (excursions to 15-30°C permitted) [see USP].

C. Basis for Approvability or Not-Approval Recommendation

The CMC information in NDA 204096 is essentially the same as provided in NDA 50-811. The current NDA has updated drug product stability data and describes the implementation of tighter [redacted] Preliminary information about the [redacted] of amorphous tacrolimus to the [redacted] is provided. From the biopharmaceutics perspective, additional in vitro alcohol dose dumping data are available. Note that NDA 50-811 was recommended for approval from the chemistry, manufacturing and controls perspective on January 19, 2007 (see NDA 50-708 Chemistry Review #1) and OCP had agreed to the proposed dissolution test and acceptance criteria.

Drug substance CMC is adequately addressed in Astellas' NDA 50-708 and Type II DMF 16833.

The manufacture and control of Astagraf XL (tacrolimus extended-release capsules) parallel those of Prograf immediate-release capsules. All aspects of drug product CMC have been adequately documented. Evidence that the product can be consistently manufactured (except as discussed below) in such a manner as to provide assurance of

its identity, strength, quality, purity, potency and bioavailability is provided. The drug product specification further ensures that the product will meet the established quality standard. The manufacturing facilities have acceptable cGMP status.

In 2010, a batch of 0.5 mg capsules marketed in Europe was recalled following a dissolution failure on stability (70% released at 1.5 hours, upper limit NMT 68%). The dissolution failure was ultimately attributed to (b) (4)

With regard to labeling, Astellas originally proposed naming the product 'Prograf MR (tacrolimus modified release capsules)'. Under NDA 50-811, the trademark 'Advagraf' was found acceptable. However, in the current review cycle, 'Advagraf' was deemed unacceptably promotional. The proprietary name, 'Astagraf XL was recently found acceptable.

The different strength Prograf Capsules are distinguished, in part, by the use of bottles with different color caps. Astellas proposed using the (b) (4) to distinguish the different strengths of the extended-release product. However, given that the bottle (b) (4) are so prominent, this could potentially result in a dispensing error. Astellas has developed a distinct bottle shape and distinct bottle cap colors for the Astagraf XL products. Nevertheless, the potential for confusion and inadvertent medication errors, including those related to capsule shell colors, are under consideration by the OND review team at this time.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Mark R. Seggel, Chemist

B. Endorsement Block

{see electronic signature page}
Tapash Ghosh, Ph.D., Acting Biopharmaceutics Team Leader

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see darrts}

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/s/

MARK R SEGGEL
06/14/2013

TAPASH K GHOSH
06/14/2013

RAPTI D MADURAWE
06/14/2013

Smith, Jacquelyn

From: ees_admin@fda.gov
Sent: Wednesday, May 29, 2013 6:46 PM
To: Cuff, Althea; Olagbaju, Bose*; Shanmugam, Balajee; Godwin, Francis; Smith, Jacquelyn; Salganik, Maria*; Seggel, Mark R; Spain, Nancy *; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 204096/000 Decision: ACCEPTABLE, Decision Date: 05/29/2013, Re-evaluation Date: 02/10/2015

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