CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the**

Date of This Review:	May 18, 2018
Application Type and Number:	NDA 210115
Product Name and Strength:	Prograf Granules (tacrolimus for oral suspension), 0.2 mg and 1 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
Panorama #:	2018-22794717
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Prograf Granules, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Prograf (tacrolimus) capsules and injection were approved on April 8, 1994, under NDA 050708 and NDA 050709, respectively, and are indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney, liver, and heart transplants. On July 13, 2013, Astagraf XL (tacrolimus extended-release capsules) (NDA 204096) was approved for the prophylaxis of organ rejection in patients receiving a kidney transplant in combination with other immunosuppressants. At the time of approval of NDA 204096 (Astagraf XL), Astellas committed to a Post Marketing Requirement under the Pediatric Research Equity Act (PREA), to develop an age-appropriate formulation to allow for dosing of tacrolimus in patients ages 1 to less than 5 years.[a] On July 26, 2017, the Applicant submitted NDA 210115, which proposes the use of *immediate-release* tacrolimus for oral suspension for the prevention of rejection in pediatric heart, kidney, or liver transplant recipients.

The Applicant previously submitted the proposed proprietary name, "Prograf***", for review under NDA 210115, which DMEPA evaluated and found conditionally acceptable in OSE review #2017-17604504[b], dated December 13, 2017. However, following a May 1, 2018 teleconference with the FDA, the Applicant withdrew the proposed proprietary name Prograf*** for NDA 210115, and submitted the name, Prograf Granules, for review on May 2, 2018.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on May 2, 2018 and the proposed Prescribing Information submitted on May 14, 2018.

- Intended Pronunciation: PRO-graf GRAN-ules
- Active Ingredient: tacrolimus for oral suspension
- Indication of Use: prevention of rejection in pediatric heart, kidney, or liver transplant recipients
- Route of Administration: oral

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[a] Germain J. Annual Status Report Review Form: Postmarketing Requirements and Commitments Summary for Astagraf XL (tacrolimus extended release) NDA 204096 on 17 SEP 2014. Silver Spring (MD): FDA, CDER, OND, DTOP (US); 2014 SEP 24.

[b] Patel, M. Proprietary Name Review for Prograf (tacrolimus) for oral suspension (NDA 210115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 13. Panorama No.: 2017-17604504.

- Dosage Form: for oral suspension
- Strength: 0.2 mg and 1 mg
- Dose and Frequency:

Patient Population	Initial Oral Dosage	Observed Whole Blood Trough Concentrations
Pediatric liver transplant	0.2 mg/kg/day oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL

- How Supplied: Carton containing 50 unit-dose packets
- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Transplant and Ophthalmology Products (DTOP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[c].

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Prograf Granules, in their submission. This proprietary name is comprised of the root name, Prograf, and a modifier, Granules. The modifier, Granules, describes the product that is dispensed to the patient prior to being mixed into an oral suspension, which is the intended dosage form for administration. Therefore, we evaluate the modifier in Section 2.2.5.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, May 9, 2018, e-mail, the Division of Transplant and Ophthalmology Products (DTOP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

[c] USAN stem search conducted on May 2, 2018.

2.2.4 FDA Name Simulation Studies

Forty (n=40) practitioners participated in DMEPA's prescription studies. The responses did overlap with the root name of the proposed product 'Prograf.' Four (outpatient n= 1, inpatient n=3) participants in the prescription study only listed 'Prograf', without the modifier 'Granules'. We discuss the omission of the modifier in Section 2.2.5. Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Safety assessment of the modifier

Under NDA 210115, the Applicant proposes a new oral dosage form of tacrolimus for oral suspension, in strengths of 0.2 mg and 1 mg, to be marketed under the same root name as the currently approved product, Prograf, with a modifier, Granules.

Table 1. Product Characteristics of Prograf Granules and Prograf

<table>
<tr><th>Product</th><th>Prograf Granules (NDA 210115)</th><th>Prograf (NDA 050708 and NDA 050709)</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td><td>April 8, 1994</td></tr>
<tr><td>Active Ingredient</td><td>tacrolimus for oral suspension</td><td>tacrolimus</td></tr>
<tr><td>Indication</td><td colspan="2">prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants</td></tr>
<tr><td>Route of Administration</td><td>Oral</td><td>Oral (NDA 050708)
Intravenous (NDA 050709)</td></tr>
<tr><td>Dosage Form:</td><td>for oral suspension</td><td>capsules (NDA 050708)
injection (NDA 050709)</td></tr>
<tr><td>Strength:</td><td>0.2 mg, 1 mg</td><td>0.5 mg, 1 mg, and 5 mg (NDA 050708)
5 mg/mL (NDA 050709)</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>Patient Population</th><th>Initial Oral Dosage (formulation)</th><th>Observed Whole Blood Trough Concentration</th></tr>
<tr><td>Pediatric Liver transplant</td><td>0.2 mg/kg/day oral suspension, divided in two doses, every 12 hours</td><td>month 1-12: 5-20 ng/mL</td></tr>
</table>
</td><td>Oral Capsules-
<table>
<tr><th>Patient Population</th><th>Initial Oral Dosage (formulation)</th><th>Observed Whole Blood Trough Concentration</th></tr>
<tr><td colspan="3">ADULT</td></tr>
<tr><td colspan="3">Kidney Transplant</td></tr>
<tr><td>With azathioprine</td><td>0.2 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>month 1-3: 7-20 ng/mL
month 4-12: 5-15 ng/mL</td></tr>
<tr><td>With MMF/IL-2 receptor antagonist</td><td>0.1 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>month 1-12: 4-11 ng/mL</td></tr>
<tr><td colspan="3">Liver Transplant</td></tr>
<tr><td>With corticosteroids</td><td>0.1-0.15 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td colspan="3">Heart Transplant</td></tr>
<tr><td>With azathioprine or MMF</td><td>0.075 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>month 1-3: 10-20 ng/mL
month ≥ 4: 5-15 ng/mL</td></tr>
<tr><td colspan="3">PEDIATRIC</td></tr>
<tr><td colspan="3">Kidney Transplant</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td colspan="3">Liver Transplant</td></tr>
<tr><td></td><td>0.15-0.2 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td colspan="3">Heart Transplant</td></tr>
<tr><td></td><td>0.1-0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours</td><td>month 1-12: 5-20 ng/mL</td></tr>
</table>
Injection-
• The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous intravenous infusion. Adult patients should receive doses at the lower end of the dosing range.
</td></tr>
<tr><td>Preparation/ Administration:</td><td>Mixed with water and administered via a glass cup or non-PVC oral syringe.</td><td>Capsules (NDA 050708)
• Swallowed whole orally
Injection (NDA 050708)
• Dilute with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Then is given via intravenous infusion</td></tr>
<tr><td>How Supplied:</td><td>Carton containing 50 unit-dose packets</td><td>Capsules (NDA 050708)
• Bottle – 100 count
• 10 blister cards of 10 capsules
Injection (NDA 050708)
• Sterile solution in a 1 mL ampule, in boxes of 10 ampules</td></tr>
<tr><td>Storage:</td><td>Store at 25ºC (77ºF); excursions permitted from 15°C to 30ºC (59°F to 86ºF).</td><td>Capsules (NDA 050708)
• Store at 25ºC (77ºF); excursions permitted from 15°C to 30ºC (59°F to 86ºF)
Injection (NDA 050708)
• Store between 5°C and 25°C (41°F and 77°F).</td></tr>
</table>

Tacrolimus is currently available in capsules and injection formulations and shares the same active ingredient and indication as the proposed product. The addition of a modifier to Prograf will differentiate the proposed product from the currently marketed oral capsules and injection. It is not uncommon for modifiers to be used to denote a specific formulation or packaging configuration as part of a product line extension. However, we also note that omission and

oversight of a modifier is cited in literature[d] as a common cause of medication error. Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. Both oral dosage forms are available in a 1 mg strength and we note there is a possibility of wrong dosage form errors if the modifier is omitted. According the Prescribing Information and the DTOP Clinical team, although the total daily granules dose should be equal to the total daily capsule dose, healthcare providers must perform therapeutic drug monitoring following conversion to any alternative formulation of tacrolimus, and dose adjustments must be made to ensure that systemic exposure to tacrolimus is maintained. The DTOP clinical team also notes that the patients and caregivers receive extensive training prior to discharge from the hospital post transplantation and that switching of formulations should be monitored carefully.

The Office of Policy for Pharmaceutical Quality (OPPQ) expressed concerns with use of the modifier 'Granules' for the proposed product and stated that use of 'Granules' for this product would be inconsistent with the current nomenclature framework of reserving 'Granules' for instances when the drug product is administered as granules (see USP Nomenclature Guidelines[e]).

We note that the modifier 'Granules' is associated with sprinkling the product directly on the tongue or food, as based on currently marketed products. However, it is unclear whether this modifier for this product will be misinterpreted as such by patients and caregivers. Additionally, DTOP stated the following for their rationale for including 'Granules' in the proprietary name:

- to differentiate this dosage form from capsules because of the 1 mg strength overlap between the capsules and the for oral suspension.
- to mitigate any confusion for the patient/caregiver since they would receive the product in its native form (i.e., granules) and not in an oral suspension.

To address DMEPA and OPPQ's concerns, during the May 1, 2018 teleconference, we requested the Applicant to propose labeling that may help mitigate this risk. In revised labels and labeling submitted on May 9, 2018, the Applicant proposes to add a statement on the carton labeling to indicate that the product must be mixed with water prior to administration.

We agree that the use of a modifier to distinguish this product from the capsule formulation is appropriate. Although the use of the modifier 'Granules' is inconsistent with USP nomenclature guidelines and there are some medication error concerns, such concerns can be managed through labels and labeling[f]. Thus, in this instance, we find the use of the modifier 'Granules' acceptable.

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[d] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

[e] Available from USP website (http://www.usp.org/health-quality-safety/compendial-nomenclature); USP Nomenclature Guidelines, referenced in USP General Chapter <1121> *Nomenclature*, Revised March 24, 2016, p. 36.

[f] Pending label and labeling review (RCM No.: 2017-1524-1)

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Transplant and Ophthalmology Products (DTOP) via e-mail on May 17, 2018. At that time, we also requested additional information or concerns that could inform our review. DTOP did not state additional concerns with the proposed proprietary name, Prograf Granules.

3 CONCLUSION

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Danyal Chaudhry, OSE project manager, at 301-796-3813.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Prograf Granules, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on May 2, 2018, are altered prior to approval of the marketing application, the name must be resubmitted for review.

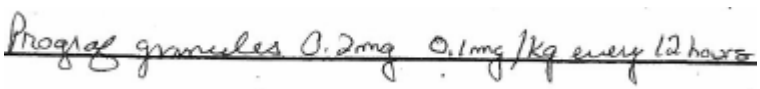
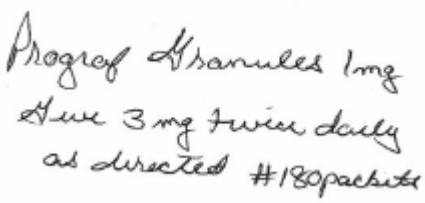
4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

Appendix A: Prescription Simulation Samples and Results

Figure 1. Prograf Granules Study (Conducted on May 4, 2018)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  Outpatient Prescription: 	Prograf Granules 1 mg Give 3 mg twice daily as directed Dispense 180 packets.

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

310 People Received Study
40 People Responded

Study Name: Prograf Granules

Total	16	9	15	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
PROFRAF GRANULES	1	0	0	1
PROGRA GRANULES	1	0	0	1
PROGRAF	1	0	3	4
PROGRAF GRANULES	12	9	12	33
PROGROF GRANULES	1	0	0	1

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

/s/

MADHURI R PATEL
05/18/2018

SARAH K VEE
05/18/2018

MISHALE P MISTRY
05/18/2018

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 13, 2017
Application Type and Number:	NDA 210115
Product Name and Strength:	Prograf (tacrolimus for oral suspension) 0.2 mg and 1 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
Panorama #:	2017- 17604504
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Prograf, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Prograf (tacrolimus) capsules and injection were approved on April 8, 1994, under NDA 050708 and NDA 050709, respectively, and are indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney, liver, and heart transplants. On July 13, 2013, Astagraf XL (tacrolimus extended-release capsules) (NDA 204096) was approved for the prophylaxis of organ rejection in patients receiving a kidney transplant in combination with other immunosuppressants. At the time of approval of NDA 204096 (Astagraf XL), Astellas committed to a Post Marketing Requirement under the Pediatric Research Equity Act (PREA), to develop an age-appropriate formulation to allow for dosing of tacrolimus in patients ages 1 to less than 5 years.[a] On July 26, 2017, the Applicant submitted NDA 210115, which proposes the use of *immediate-release* tacrolimus for oral suspension for the prevention of rejection in pediatric heart, kidney, or liver transplant recipients. Therefore, the Applicant submitted the name, Prograf, for oral suspension, under NDA 210115, on September 15, 2017.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 15, 2017 proprietary name submission and proposed Prescribing Information submitted on July 26, 2017.

Table 1. Relevant Product Information for Prograf

Product	**Prograf (NDA 210115)**	**Prograf (NDA 050708 and NDA 050709)**
Initial Approval Date	N/A	April 8, 1994
Active Ingredient	tacrolimus	
Indication	Prograf is a calcineurin-inhibitor immunosuppressant indicated for: • Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants	
Route of Administration	Oral	Oral (NDA 050708) Intravenous (NDA 050709)
Dosage Form:	for oral suspension	Capsules (NDA 050708) Injection (NDA 050709)
Strength:	0.2 mg, 1 mg	0.5 mg, 1 mg, and 5 mg (NDA 050708)

[a] Germain J. Annual Status Report Review Form: Postmarketing Requirements and Commitments Summary for Astagraf XL (tacrolimus extended release) NDA 204096 on 17 SEP 2014. Silver Spring (MD): FDA, CDER, OND, DTOP (US); 2014 SEP 24.

<table>
<tr><td></td><td></td><td>5 mg/mL (NDA 050709)</td></tr>
<tr><td>Dose and Frequency</td><td colspan="2">Oral capsules/for oral suspension-
<table>
<tr><th>Patient Population</th><th>Recommended Initial Oral Dosage (two divided doses every 12 hours)</th><th>Observed Whole Blood Trough Concentrations</th></tr>
<tr><td>Adult Kidney transplant
In combination with azathioprine</td><td>0.2 mg/kg/day
(capsules)</td><td>month 1-3: 7-20 ng/mL
month 4-12: 5-15 ng/mL</td></tr>
<tr><td>In combination with MMF/IL-2 receptor antagonist</td><td>0.1 mg/kg/day
(capsules)</td><td>month 1-12: 4-11 ng/mL</td></tr>
<tr><td>Adult Liver transplant</td><td>0.10-0.15 mg/kg/day
(capsules)</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td>Pediatric Liver transplant</td><td>0.15-0.20 mg/kg/day
(capsule or granules)</td><td>month 1-12: 5-20 ng/mL</td></tr>
<tr><td>Adult Heart transplant</td><td>0.075 mg/kg/day
(capsules)</td><td>month 1-3: 10-20 ng/mL
month ≥ 4: 5-15 ng/mL</td></tr>
</table>
Injection-
The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range.</td></tr>
<tr><td>How Supplied:</td><td>Carton containing 50 packets</td><td>Capsules (NDA 050708)
Bottle – 100 count
10 blister cards of 10 capsules
Injection (NDA 050708)
Sterile solution in a 1 mL ampule, in boxes of 10 ampules</td></tr>
<tr><td>Storage:</td><td>Store at 25ºC (77ºF); excursions permitted from 15°C to 30ºC (59°F to 86ºF).</td><td>Capsules (NDA 050708)
Store at 25ºC (77ºF); excursions permitted from 15°C to 30ºC (59°F to 86ºF)
Injection (NDA 050708)
Store between 5°C and 25°C (41°F and 77°F).</td></tr>
</table>

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Transplant and Ophthalmology Products (DTOP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[b].

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Prograf in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, October 2, 2017 e-mail, the Division of Transplant and Ophthalmology Products (DTOP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving ***Prograf*** that would be relevant for this review.

Table 2. FAERS Search Strategy

Search Date	October 4, 2017
Drug Name	Prograf [product name] [product verbatim]

[b] USAN stem search conducted on November 1, 2017.

Table 2. FAERS Search Strategy	
Event (MedDRA Terms)	**DMEPA Official PNR Name Confusion Search Terms Event List:** Preferred Terms: CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR DRUG ADMINISTRATION ERROR DRUG DISPENSING ERROR DRUG PRESCRIBING ERROR INTERCEPTED DRUG DISPENSING ERROR INTERCEPTED DRUG PRESCRIBING ERROR INTERCEPTED MEDICATION ERROR MEDICATION ERROR PRODUCT NAME CONFUSION TRANSCRIPTION MEDICATION ERROR Lower Level Terms: INTERCEPTED PRODUCT SELECTION ERROR INTERCEPTED WRONG DRUG PRODUCT SELECTED INTERCEPTED WRONG DRUG SELECTED PRODUCT SELECTION ERROR WRONG DEVICE DISPENSED WRONG DRUG ADMINISTERED WRONG DRUG DISPENSED WRONG DRUG PRESCRIBED WRONG DRUG PRODUCT SELECTED WRONG DRUG SELECTED WRONG PRODUCT SELECTED
Date Limits	April 8, 1994 to October 1, 2017

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 93 reports were not included in the final analysis for the following reasons: 27 cases reported to the USP mentioned Advagraf- this product is not available in the United States. The other 66 cases were not related to name confusion errors [wrong strength (n=14), no error or insufficient information provided to determine if a medication error occurred (n=13), errors associated with a product other than Prograf (n=7), wrong dose error (n=8), wrong technique/compounding errors (n=7), wrong drug error not related to name confusion (n=6), dose omissions (n=3), deteriorated drug error (n=2), monitoring error (n=2), accidental exposure (n=1), manufacturing product quality issues (n=1), incorrect storage (n=1), and wrong route of administration (n=1)].

Following exclusions, the search yielded four relevant cases.

Of the four cases, two cases (n=2) described name confusion involving Prograf and Flomax (tamsulosin), one case (n=1) described name confusion involving Prograf and Prozac, and one case (n=1) described name confusion involving Prograf and thiamine.

Prograf vs. Flomax (n=2)

One case (FAERS Case No. 7919696) described a drug dispensing error in which Flomax (tamsulosin) was dispensed instead of Prograf. Another case (FAERS Case No. 8433257) describes a drug dispensing error in which Prograf 1 mg was dispensed instead of Flomax 0.4 mg. The reports do not provide information on root causes and contributing factors.

We considered confusion with the name pair Prograf and Flomax. Prograf and Flomax may be located next to one another in the pharmacy if stored alphabetically by established name. However, we find that the two proprietary names have sufficient orthographic and phonetic differences and do not pose risk of error of confusion. Therefore, we find this name pair acceptable.

No new cases of drug name confusion involving Prograf and Flomax have been reported to FAERS since 2012.

Prograf vs. Prozac (n=1)

One case (FAERS Case No. 6296884) described a drug dispensing error in which Prozac 10 mg was dispensed instead of Prograf 10 mg. The report does not provide root causes or contributing factors. However, we note that Prograf and Prozac may be located next to one another in the pharmacy if stored alphabetically by brand name. The proprietary name, Prozac is available as a capsule (10 mg, 20 mg, 40 mg, and 60 mg) whereas Prograf is available as a capsule (0.5 mg, 1 mg, and 5 mg) and injection (5 mg/mL). We note that there may be overlap in product characteristics in terms of dose, dosage form, route of administration, and numerical similarity in strength (1 mg vs. 10 mg). However, given that Prozac has been on the market for almost 30 years and we have received one post-marketing medication error with Prograf in 2007 with no additional reports to date, we find this name pair acceptable.

Prograf vs. thiamine (n=1)

One case (FAERS Case No. 6718333) described a drug dispensing error in which the patient was admitted to the hospital and treated with maintenance fluid for possible ethanol withdrawal, but received 400 mg of Prograf via an unspecified route instead of thiamine 2.1 mg/kg/day. The report does not provide root causes or contributing factors.

We considered confusion with the name pair Prograf and thiamine. We find that the two products have sufficient orthographic and phonetic differences and do not pose risk of error of confusion. Additionally, we have not identified any new cases of drug name confusion involving Prograf and thiamine since 2008. Therefore, we find the name pair acceptable.

2.2.5 Multiple Dosage Forms Under a Single Proprietary Name

Under NDA 210115, the Applicant proposes a new oral dosage form of tacrolimus for oral suspension, in strengths of 0.2 mg and 1 mg, to be marketed under the same name as the currently approved product, Prograf.

Prograf is currently available in capsules and injection formulations and shares the same active ingredient and indication as the proposed product. We note there is an overlap in the 1 mg

strength between the proposed tacrolimus for oral suspension and the currently approved capsules. However, the dosing in pediatric patients can be achieved using either dosage form and the addition of the proposed dosage form of for oral suspension provides an option for pediatric patients who are unable to swallow oral capsules. The Division and the proposed Prescribing Information (PI) states that for conversion of pediatric patients (b) (4) (b) (4)

It is a common and accepted practice to have a product line with multiple dosage forms managed under one proprietary name within a single package insert. In this case, the residual risk of confusion between the tacrolimus for oral suspension and capsule and injection formulations of the product may be mitigated through labels and labeling intervention. Therefore, given the precedence for using this naming convention, we find the Applicant's proposal to market the proposed product with the proprietary name Prograf acceptable.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Transplant and Ophthalmology Products (DTOP) via e-mail on December 11, 2017. At that time, we also requested additional information or concerns that could inform our review. DTOP did not state additional concerns with the proposed proprietary name, Prograf.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Abiola Olagundoye-Alawode, OSE project manager, at 301-796-3982.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Prograf, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your September 15, 2017 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [c]

[c] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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/s/

MADHURI R PATEL
12/13/2017

SARAH K VEE
12/13/2017

MISHALE P MISTRY
12/13/2017