CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204141Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 10, 2013
From	Tatiana Oussova, MD, MPH
Subject	Deputy Director for Safety Summary Review
NDA/BLA #	204141
Applicant Name	Taro Pharmaceuticals USA, Inc.
Date of Submission	Letter date: June 11, 2012 CDER Stamp Date: June 12, 2012
PDUFA Goal Date	April 12, 2013
Proprietary Name / Established (USAN) Name	Topicort/desoximethasone
Dosage Forms / Strength	Topical Spray, 0.25%
Proposed Indication(s)	Treatment of (b) (4) plaque psoriasis in patients 18 years of age and older
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Melinda McCord, MD
Statistical Review	Carin Kim, Ph.D.
Pharmacology Toxicology Review	Renqin Duan, Ph.D.
CMC Review/OBP Review	Hamid Shafiei, Ph.D.
Clinical Pharmacology Review	An-Chi Lu, M.S., Pharm. D.
DSI	Roy Blat, Ph. D.
CDTL Review	Gordana Diglisic, MD
PMHS	Elizabeth Durmovicz, MD
DMEP	Ali Mohamadi, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff
DMEP=Division of Metabolic and Endocrine Products

1. Introduction

This application is an original NDA # 204141 for Topicort (desoximethasone) Topical Spray 0.25% in which the applicant is seeking an approval of this product for the treatment of [redacted] (b) (4) psoriasis in patients 18 years of age and above.
This is a new dosage form of currently marketed desoximethasone.
No pediatric studies were provided with this application.
There are no outstanding clinical or regulatory concerns. All discipline reviews have been completed and approval is recommended. This review will briefly summarize the review team conclusions and my concurrence with the approval recommendation.

2. Background

Desoximetasone is a synthetic corticosteroid which is currently marketed in the United States in various topical dosage forms (cream, ointment and gel) and 0.05% and 0.25% strengths.
NDA 17856 for Topicort Cream was first approved in 1977.
All currently marketed Topicort dosage forms are approved for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
Safety profile of these products is well –established and there are no new safety concerns with this dosage form.
The applicant submitted 2 pivotal clinical trials in support of efficacy and safety of this new dosage form.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

Two multi-center, randomized, double-blind, vehicle- controlled clinical trials were conducted in 239 subjects aged 18 years and older with moderate to severe plaque psoriasis of the body. In both trials, randomized subjects applied Topicort Topical Spray or vehicle spray to the affected areas twice daily for 4 weeks. At enrollment subjects had a minimum body surface area of involvement of 10%, and a Physician's Global Assessment score (PGA) of 3 (moderate) or 4 (severe).

Efficacy was assessed at Week 4 as the proportion of subjects who were considered a Clinical Success ("clear" (0) or "almost clear" (1) according to the PGA scale). Table below presents the efficacy results.

Number of Subjects (%) with Clinical Success (scored as clear or almost clear) at Week 4.

Parameter	**Trial 1**		**Trial 2**	
	Topicort® N=59	**Vehicle N=60**	**Topicort® N=60**	**Vehicle N=60**
Clinical Success	18 (30.5%)	3 (5.0%)	32 (53.3%)	11 (18.3%)

The applicant demonstrated superiority of the product over vehicle in both trials. The results of the trials were supportive of the proposed indication in the proposed population.

8. Safety

A total of 149 subjects with moderate to severe plaque psoriasis of the body were exposed to Topicort Topical Spray while applying it twice daily for 4 weeks during clinical trials. Safety was assessed at Day 7, 14 and 28. Vital signs were assessed at baseline and at the end of the treatment (Day 28). Laboratory assessments were not performed during these trials.

Adverse reactions that occurred in ≥ 1% of subjects treated with Topicort Topical Spray were application site dryness (2.7%), application site irritation (2.7%) and application site pruritus (2.0%).

Another less common adverse reaction (<1% but >0.1%) was folliculitis.

Evaluation of potential for HPA axis suppression was conducted. In a trial including 21 evaluable subjects (out of 24 subjects participating in this trial) 18 years of age or older with moderate to severe plaque psoriasis, adrenal suppression was identified in 1 out of 12 subjects having involvement of 10-15% of body surface area (BSA) and 2 out of 9 subjects having

involvement of >15% of BSA after treatment with Topicort Topical Spray twice daily for 28 days.

Clinical studies of Topicort® Topical Spray did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
Topicort Topical Spray is flammable. Warning to avoid heat, flame or smoking when using this product is included in the label.

9. Advisory Committee Meeting

No Advisory Committee was necessary for this product.

10. Pediatrics

This application is subject to the requirements of the Pediatric Research Equity Act (PREA).

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

Based on PeRC recommendations, the applicant revised its request and requested a waiver for ages 0-1 year 11 months and deferral for ages 2-16 years 11 months.

A partial waiver was granted per applicant request because of the concern regarding increased systemic absorption in this age group and higher risk of HPA axis suppression.
A deferral for the submission of studies in patients (b) (4) years was granted, as the adult studies are ready for approval and the pediatric study has not been completed.

The applicant will conduct a trial in approximately 100 evaluable subjects age 2-16 years 11 months with plaque psoriasis to evaluate the safety and effect of Topicort Topical Spray, 0.25% on HPA axis and the pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. The trial should be conducted in sequential cohorts (Cohort 1: age 12 years to 16 years 11 months; Cohort 2: age 6 years to 11 years and 11 month; Cohort 3: age 2 years to 5 years and 11 months). Safety assessments would also include: vital signs, physical examinations, local safety, and adverse events.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling discussions with the applicant have concluded, with submission of agreed upon physician's labeling, patient labeling, and carton/container labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - This application will be approved.

- Benefit-Risk Assessment – The benefits and risks of this product are consistent with the benefits and risk of many similar products currently approved for marketing. This product has provided sufficient evidence of safety and efficacy to support use as described in approved labeling.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None necessary.
- Recommendation for other Postmarketing Requirements and Commitments:

  This application is subject to PREA and will have a required pediatric assessment as described above under PEDIATRICS.
  In addition, non-clinical PMR would be required under FDAAA to address a theoretical concern regarding the product teratogenicity:

  A two year dermal rat carcinogenicity study will be conducted under the following timelines:
  Final Study Protocol: 04/30/15
  Study Completion: 05/31/17
  Final Study Report: 05/31/18

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/s/

TATIANA OUSSOVA
04/10/2013