Medical Officer's Review of NDA 22-408
Efficacy Supplement/S-05

Supporting Doc #: 156
Doc type: Efficacy supplement/S-05 Standard Review
Correspondence date: March 4, 2014
CDER Stamp date: March 4, 2014
Sponsor: Para PRO Pharmaceuticals, LLC
Drug: Natroba (spinosad) topical suspension, 0.9%
Route of Administration: topical
Dosage Form: Topical suspension
Active Ingredient: spinosad
Pharmacologic Category: lice product

Current Indication: topical treatment of head lice infestation in patients four years of age and older
Proposed Indication: topical treatment of head lice infestation in patients six months of age and older
Review start date: Sept 3, 2014
Review completion date: Oct. 8, 2014
PDUFA Goal Date: Jan. 4, 2015
Medical Officer: Patricia Brown
Team Leader: Gordana Diglisic
Project Manager: Dawn Williams

Clinical Pharmacology Reviewer (review date 9/18/2014): Doanh Tran, Ph.D.

Regulatory Background:
NDA 22-408, Natroba (spinosad) Topical Suspension, 0.9% was approved January 18, 2011 for (from approved product labeling) the "…topical treatment of head lice infestations in patients four years (4) of age and older."

The applicant originally proposed that the indication include patients as young as 6 months. Although the applicant's maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of Natroba (spinosad) Topical Suspension, 0.9%, only 8 healthy subjects without lice infestation under the age of 4 years were evaluated.

To support a claim for use of Natroba in subjects under the age of 4 years, the applicant was asked to provide safety and pharmacokinetic data for spinosad, as well as benzyl alcohol, in lice-infested pediatric subjects aged 6 – 24 months. Benzyl alcohol is present at (b) (4) as an excipient in the Natroba drug product.

The deferred pediatric trial under PREA was as follows (see approval letter 1/18/2011):

> A pharmacokinetic and safety study in pediatric patients ages 6 months to 4 years of age with active head lice infestation. This study should be conducted under maximum use conditions and include a minimum of 24 evaluable patients who will undergo pharmacokinetic sampling and assessments of local and systemic safety at appropriate time points.

Current Submission:
On March 4, 2014 the applicant submitted the final trial report as part of a supplement (S-005, supporting document # 156) to the FDA along with a request for a labeling modification to extend the approved age range down to 6-month old infants. The final trial report submitted was the same as that submitted March 12, 2013 in supporting document # 88.

Because the trial included changes to the indication supported by clinical data, in addition to PK assessments, it was determined that a user fee would be required to review the data in order to support the requested labeling changes. Since the applicant did not submit a user fee, the Division issued a 'No User Fee Received' letter stating that the application was not acceptable for filing.

Upon further review of NDA 22408 Supplement-5, it was determined that this COR-SNDAACK-12 (No User Fee Received) letter was issued in error and no user fee was required for this supplement. Under section 736(a)(1)(c) of the Federal Food, Drug, and Cosmetic Act, Exception for Previously Filed Application or Supplement, the user fee requirement for this indication was previously met with the original filing of the application. Therefore the application was considered acceptable for filing and has been reviewed.

Review:
The clinical study report for the PMR trial (SPN-109-11) was previously reviewed by this clinical reviewer under supporting document # 88 in a review dated June 5, 2013. It was also previously reviewed by the clinical pharmacology reviewer (Doanh Tran, PhD), review dated March 25, 2013.

Summary of Previous Review:
Trial SPN-109-11:
Objective:
The objective of this study was to determine the topical absorption and safety of Natroba (spinosad) Topical Suspension, 0.9% product for a single, 10 minute treatment in subjects 6 months to 4 years of age for spinosad (Spinosyn A and Spinosyn D) and benzyl alcohol.

Subject Population:
Male and female subjects, ages 6 months to 4 years with active head lice infestations, 26 analyzed

Demographics:
The mean age of the subjects was 27.3 months, and a little over half of the subjects (57.7%; 15/26) were male. The majority of subjects (73.1%; 19/26) were Hispanic/Latino, and most subjects (88.5%; 23/26) were White. The distribution between age groups was: 6 months < 2 years of age (12 subjects) and 2 years to 4 years of age (14 subjects).

Exposure:
The mean application time (from the start of application to the end of application) was 11.14 minutes (ranged from 9.8 minutes to 18 minutes). A bottle of Natroba contained approximately 60 grams. The mean weight of Natroba applied was 22.13 grams (ranged from 4.0 grams to 51.4 grams).

Pharmacokinetics:
PK samplings were obtained at 0 (pretreatment) and at 0.5, 1, 3, 6, and 12 hours after the application of Natroba to the hair. For PK results, see clinical pharmacology reviewer Mid-cycle notes.

Principal safety assessments: Adverse events, local safety assessment, vital signs, laboratory evaluation

Adverse Events**:**
No deaths, no serious adverse events, and adverse events leading to subject discontinuation were reported during the study.

Common adverse events:
A total of 13 adverse events were reported by 9 subjects (9/26 or 34.6%).
The most frequently reported AEs was pyrexia (26.9%, 7/26 subjects). Other AEs included; application site pruritus (11.5%, 3/26), pruritus (7.7%, 2/26), and erythema (3.8%, 1/26). Application site irritation is included in current Natroba labeling.

Pruritus:
The presence of pruritus (yes, no) also was evaluated at the screening visit and on Day 1 at Hours 0 (pre-treatment), 0.5, 1, 3, 6, and 12 hours post-treatment.

Regarding pruritus, of the 6 subjects who had pruritus post-treatment, 4 had pruritus pre-treatment, Day 1, and the other two had pruritus at screening. Clinically significant safety signals were not identified.

Skin, Scalp, Eye Irritation:
Assessment of the skin, scalp and eyes for any sign of irritation was performed using the Draize scale method of grading responses. Examinations occurred at the screening visit and on Day l at Hour 0 (pretreatment), and at 0.5, 1.0, 3.0, 6.0 and 12 hour post-treatment. Clinically significant safety signals were not identified.

Laboratory Evaluations, Vital Signs:
Clinically significant safety signals for laboratory evaluations, heart rate, and blood pressure were not identified. Although an AE of pyrexia was noted in 7/26 subjects, in the opinion of this reviewer, this AE does not represent a clinically significant safety signal. The temperature changes reported for individual subjects generally fall within variations due to circadian rhythms.

Conclusion:
This clinical reviewer has reviewed trial SPN-109-11 and finds no new clinically significant safety signals. This clinical reviewer concurs with the Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 in finding the results of trial SPN-109-11 acceptable to fulfill the PREA postmarketing requirement stated in the approval letter dated 1/18/2011.

Labeling:
Labeling changes follow:

Agency additions are in underline, Agency deletions are in ~~strikethrough~~.
Applicant additions are in underline, Applicant deletions are in ~~strikethrough~~.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Natroba (spinosad) topical suspension, 0.9%, for topical use
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) xx/2014

----------INDICATIONS AND USAGE----------
NATROBA Topical Suspension is a pediculicide indicated for the topical treatment of head lice infestations in patients six (6) months ~~four (4) years~~ of age and older. (1.1)

----------DOSAGE AND ADMINISTRATION----------
- For topical use only. Not for oral, ophthalmic, or intravaginal use.(2)
- Shake bottle well. (2)
- Apply product to dry scalp and hair using only the amount needed to cover the scalp and hair. (2)
- Rinse off with warm water after 10 minutes. (2)

Repeat treatment only if live lice are seen 7 days after first treatment. (2)
(Note: 'only' is also underlined.)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension: 9 mg of spinosad per gram of NATROBA Topical Suspension in 120 mL bottles (3)

(b) (4)

(b) (4)

Reviewer comment:
This section is deleted to conform to current labeling practices.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

NATROBA (spinosad) Topical Suspension is indicated for the topical treatment of head lice infestation in patients six (6) months ~~four (4) years~~ of age and older.

2 DOSAGE AND ADMINISTRATION

Applicant proposed:
Shake bottle well. Apply sufficient NATROBA Topical Suspension to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, then thoroughly rinse off NATROBA Topical Suspension with warm water. (b) (4) ,~~I~~if live lice are seen 7 days after the first treatment, a second treatment should be applied. Avoid contact with eyes.

Agency proposed:
Shake bottle well. Apply sufficient NATROBA Topical Suspension to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, then thoroughly rinse off NATROBA Topical Suspension with warm water. (b) (4) ,~~I~~If live lice are seen 7 days after the first treatment, a second treatment should be applied. Avoid contact with eyes.
Reviewer comment:
The applicant proposed change is not accepted because it does not add new information.

3 DOSAGE FORMS AND STRENGTHS

0.9%, viscous, slightly opaque, light orange-colored suspension in 120 mL bottles

6 ADVERSE REACTIONS

Systemic safety was not assessed in pediatric subjects under six months ~~four years~~ of age as laboratory parameters were not monitored in these controlled studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with NATROBA Topical Suspension in pregnant women. (b) (4)

[redacted] Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.4 Pediatric Use

The safety and effectiveness of NATROBA Topical Suspension have been established in pediatric patients six months ~~four years~~ of age and older with active head lice infestation *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Safety in pediatric patients below the age of six months ~~four years~~ has not been established.

NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death in neonates and low birth-weight infants. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants when administered intravenously.

Reviewer comment:
Referring to benzyl alcohol, the term 'intravenous administration,' is present in approved labeling for Ulesfia.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Applicant proposed:

An open-label, single-center [redacted] was conducted over a period of seven days to determine the pharmacokinetic profile of spinosad 1.8% in pediatric subjects with head lice infestation. Fourteen (14) subjects, 4 – 15 years of age, with head lice were enrolled into the [redacted]. All subjects applied a single topical (scalp) treatment of spinosad 1.8% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling. [redacted]. Results demonstrated that spinosad was below the limit of quantitation (3ng/mL) in all samples.

[redacted]

An open-label, two-center [redacted] was conducted over a period of 23 days to determine the pharmacokinetic profile of spinosad 0.9% and the ingredient benzyl alcohol in pediatric subjects with a head lice infestation. Twenty-six (26) subjects between 6 months to 4 years of age were enrolled into the study per protocol. All subjects applied a single topical (scalp) treatment of spinosad 0.9% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling over a 12 hour period. [redacted]

Agency proposed:

An open-label, single-center trial was conducted over a period of seven days to determine the pharmacokinetic profile of spinosad 1.8% in pediatric subjects with head lice infestation. Fourteen (14) subjects, 4 – 15 years of age, with head lice were enrolled into the trial. All subjects applied a single topical (scalp) treatment of spinosad 1.8% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling. Results demonstrated that spinosad was below the limit of quantitation (3ng/mL) in all samples. Plasma concentration of benzyl alcohol was not determined in these subjects.

An open-label, two-center trial was conducted over a period of 23 days to determine the pharmacokinetic profile of spinosad 0.9% and the ingredient benzyl alcohol in pediatric subjects with a head lice infestation. Twenty-six (26) subjects between 6 months to 4 years of age were enrolled into the study per protocol. All subjects applied a single topical (scalp) treatment of spinosad 0.9% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling over a 12 hour period. Plasma spinosad concentrations were below the limit of quantitation (3 ng/mL) in all samples.

Benzyl alcohol was quantifiable (above 1 µg/mL) in a total of 8 plasma samples in 6 out of 26 subjects (25%): four out of 12 subjects in the 6 months to <2 years age group and two out of 14 subjects in the 2 to 4 years age group. The highest observed concentration was 2.37 µg/mL. Benzyl alcohol concentrations at 12 hours post-treatment were below limit of quantification (1 µg/mL) for all subjects.

Reviewer comment:

Concur with labeling recommendation from clinical pharmacology reviewer Doanh Tran, PhD, review dated 9/18/2104.

17 PATIENT COUNSELING/INFORMATION

[See FDA-approved patient labeling (Patient Information)]

The patient should be instructed as follows:

- Shake bottle well immediately prior to use

- Do not swallow.
- Use NATROBA Topical Suspension only on dry scalp and dry scalp hair.
- (b) (4)
- Repeat treatment only if live lice are seen seven days after first treatment.
- Avoid contact with eyes. If NATROBA Topical Suspension gets in or near the eyes, rinse thoroughly with water.
- Wash hands after applying NATROBA Topical Suspension
- Use NATROBA Topical Suspension on children only under direct supervision of an adult.
- (b) (4)

Patient Information

It is not known if NATROBA Topical Suspension is safe for children under six months ~~4 years~~ of age or in people over age 65.

How should I use NATROBA Topical Suspension?

Applicant proposed:

- (b) (4)

Agency proposed:

- Use NATROBA Topical Suspension in one or two treatments that are one week apart. If live lice are seen one week (7 days) after you first used NATROBA Topical Suspension you will need to use NATROBA Topical Suspension again.

Reviewer comment:

The Agency proposal changes labeling back to the form in which it was originally approved and, in the opinion of this reviewer, is clearer than the applicant proposed version above.

Labeling Communication:

The sponsor accepted Agency proposed labeling changes on 9/30/2014.

Regulatory Conclusion:

This clinical reviewer concurs with the Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 in finding the results of trial SPN-109-11 acceptable to fulfill the PREA postmarketing requirement stated in the approval letter dated 1/18/2011.

It is recommended that this supplement (NDA 22408/S-05) be approved with labeling revisions as described above and attached below. A copy of sponsor agreed upon labeling follows the end of this review.

Status of PMR/PMCs for NDA 22-408:

Apart from the PMR addressed in this review, there are no other open PMR/PMCs for NDA 22-408.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA C BROWN
10/08/2014

GORDANA DIGLISIC
10/09/2014