HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use tavaborole topical solution safely and effectively. See full prescribing information for tavaborole topical solution.

Tavaborole topical solution

Initial U.S. Approval: 2014

-- INDICATIONS AND USAGE--Tavaborole topical solution is an oxaborole antifungal indicated for the topical treatment of onychomycosis of the toenails due to Trichophytonrubrum or Trichophytonmentagrophytes. (1)

- --DOSAGE AND ADMINISTRATION------ Apply tavaborole topical solution to affected toenails once daily for 48 weeks. (2)
- Tavaborole topical solution should be applied to the entire toenail surface and under the tip of each toenail being treated. (2)
- For topical use only. (2)

---DOSAGE FORMS AND STRENGTHS---Solution, 5% (3)

None. (4)

-CONTRADICTIONS-

--ADVERSE REACTIONS--Common adverse reactions occurring in ≥ 1% in subjects treated with tavaborole topical solution included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact

Encube Ethicals Private Limited at 1-833-285-4151 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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- DOSAGE FORMS AND STRENGTHS CONTRAINDICATIONS
- **ADVERSE REACTIONS** 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience
- **USE IN SPECIFIC POPULATIONS** 8.1 Pregnancy
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17 PATIENT COUNSELING INFORMATION *Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE Tavaborole topical solution, 5% is an oxaborole antifungal indicated for the treatment of onychomycosis of the toenails due to Trichophytonrubrum or Trichophytonmentagrophytes.

2 DOSAGE AND ADMINISTRATION Apply tavaborole topical solution to affected toenails once daily for 48 weeks.

Tavaborole topical solution should be applied to the entire toenail surface and under the tip of each toenail being

Tavaborole topical solution is for topical use only and not for

oral, ophthalmic, or intravaginal use. 3 DOSAGE FORMS AND STRENGTHS

Tavaborole topical solution, 5% is a clear, colorless alcoholbased solution. Each milliliter of solution contains 43.5 mg (5% w/w) of tavaborole.

4 CONTRAINDICATIONS

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two clinical trials, 791 subjects were treated with tavaborole topical solution. The most commonly reported adverse reactions are listed below (Table 1).

Table 1: Adverse Reactions Occurring in ≥1% of tavaborole topical solution, 5%-Treated Subjects and

| Preferred Term | Tavaborole topical solution N= 791 n(%) | Vehicle N= 395 n(%) |
|------------------------------|---|---------------------------|
| Application site exfoliation | 21 (2.7%) | 1 (0.3%) |
| Ingrown toenail | 20 (2.5%) | 1 (0.3%) |
| Application site erythema | 13 (1.6%) | 0 (0%) |
| Application site dermatitis | 10 (1.3%) | 0 (0%) |

6.2 Postmarketing Experience The following adverse reactions have been identified during postmarketing use of tavaborole topical solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate

their frequency or establish a causal relationship to drug

Hypersensitivity; contact allergy

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

product exposure:

Risk Summary There are no available data on tavaborole topical solution use in pregnant women to inform a drug associated risk for

major birth defects, miscarriage or adverse maternal or fetal outcomes. In oral animal reproductive studies, administration of tavaborole during the period of organogenesis resulted in embryofetal toxicity and malformations at 570 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons in rats and embryofetal toxicity at 155 times the MRHD based on AUC comparisons in rabbits. Embryofetal toxicity was noted following dermal administration in rabbits up to 36 times the MRHD based on AUC comparisons [seeData].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage 15% to 20% of clinically recognized pregnancies.

Oral Administration: In an oral embryofetal development study in rats, oral doses of 30, 100, and 300 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and drug-related skeletal malformations and

variations suggestive of delayed development (i.e., a delay in ossification) were noted in fetuses at 300 mg/kg/day tavaborole [570 times the MRHD based on AUC comparisons]. No developmentaltoxicity was noted in rats at 100 mg/kg/day tavaborole (26 times the MRHD based on AUC comparisons).

In an oral embryofetal development study in rabbits, oral doses of 15, 50, and 150 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 7-19) to pregnant female rabbits. In the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 150 mg/kg/day tavaborole. No drug related malformations were noted in rabbits at 150 mg/kg/day tavaborole (155 times the MRHD based on AUC comparisons). No embryofetal mortality was noted in rabbits at 50 mg/kg/day tavaborole (16 times the MRHD based on AUC comparisons).

In an oral pre- and post-natal development study in rats, oral doses of 15, 60, and 100 mg/kg/day tavaborole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development AUC comparisons).

was noted at 5% and 10% tavaborole solution. A decrease in fetal bodyweight was noted at 10% tavaborole solution. No drug related malformations were noted in rabbits at 10% tavaborole solution (36 times the MRHD based on AUC comparisons). No embryofetal toxicity was noted in rabbits at 5% tavaborole solution (26 times the MRHD based on AUC comparisons).

8.2 Lactation

There is no information available on the presence effects on the breastfed child from tavaborole topical solution

8.4 Pediatric Use

established in patients 6 years of age and older. Use of tavaborole topical solution in these age groups is supported by evidence from adequate and well-controlled studies of tavaborole topical solution in adults with additional data from an open-label pharmacokinetics study of tavaborole in subjects 12 years to less than 17 years old [see Clinical Pharmacology (12.3)].

8.5 Geriatric Use

In clinical trials of 791 subjects who were exposed tavaborole topical solution, 19% were 65 years of age and over, while 4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

Tavaborole topical solution, 5% contains tavaborole, 5% (w/w) in a clear, colorless alcohol-based solution for topical use. The active ingredient, tavaborole, is an oxaborole antifungal with the chemical name of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. The chemical formula is C₇H₆BFO₂, the molecular weight is 151.93 and

Tavaborole is a white to off-white powder. It is slightly soluble in water and freely soluble in ethanol and propylene glycol.

Each mL of tavaborole topical solution contains 43.5 mg of tavaborole. Inactive ingredients include alcohol USP (87.43% v/v), propylene glycol USP, and edetate calcium

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Tavaborole topical solution is an oxaborole antifungal [see Clinical Pharmacology (12.4)].

12.2 Pharmacodynamics expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics Tavaborole undergoes extensive metabolism. Renal

PATIENT INFORMATION

Tavaborole (ta va bor ole) topical solution, 5%

Important information: tavaborole topical solution is for use on toenails only. Do not use tavaborole topical solutionin your mouth, eyes, or

What is tavaborole topical solution?

Tavaborole topical solution is a prescription medicine used to treat fungal infections of the

It is not known if tavaborole topical solution is safe and effective in children less than 6 years age. Before using tavaborole topical solution, tell

- your healthcare provider about all of your medical conditions, including if you: are pregnant or plan to become pregnant. It is not known if tavaborole topical solution can
- harm your unborn baby. are breastfeeding or plan to breastfeed. It is not known if tavaborole passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during your treatment with tavaborole topical solution.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use tavaborole topical

See the "Instructions for Use" at the end of this Patient Information for detailed information about the right way to use tavaborole topical

- Use tavaborole topical solution exactly as your healthcare provider tells you to
- Apply tavaborole topical solution to your affected toenails 1 time each day.
- Tavaborole topical solution is used for 48 weeeks.
- It is not known if the use of nail polish or other cosmetic nail products (such as gel nails or acrylic nails) will affect how tavaborole topical solution works.

What should I avoid while using tavaborole

Tavaborole topical solution is flammable. Avoid heat and flame while applying tavaborole topical solution to your toenail.

What are the possible side effects of tavaborole topical solution?

The most common side effects of tavaborole topical solution include: skin peeling, ingrown toenail, redness, itching, and swelling.

Tavaborole topical solution may cause irritation at or near the application site. Tell your healthcare provider if you develop irritation at the application site that does not go away. These are not all of the possible side effects of tavaborole topical solution.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-

How should I store tavaborole topical

- Store tavaborole topical solution at room temperature, between 68°F to 77°F (20°C
- Tavaborole topical solution is flammable.
- Keep away from heat and flame. Keep the bottle tightly closed.
- Safely throw away tavaborole topical solution after 3 months of inserting the

Keep tavaborole topical solution and all medicines out of the reach of children.

General information about the safe and effective use of tavaborole topical solution.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use tavaborole topical solution for a condition for which it was not prescribed. Do not give tavaborole topical solution to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about tavaborole topical solution that is written for health professionals.

What are the ingredients in tavaborole topical solution?

Active ingredient: tavaborole

Inactive ingredients: alcohol USP (87.43% v/v), propylene glycol USP, and edetate calcium

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For more information, call Encube Ethicals Private Limited at **1-833-285-4151** or FDA at **1-**800-FDA-1088

This Patient Information has been approved

by the U.S. Food and Drug Administration.

Revised 09/2020

Black

Instructions for Use

Tavaborole (ta va bor ole) topical solution, 5% Important information: tavaborole topical solution is for use on toenails only. Do not use tavaborole topical solution in your mouth, eyes,

or vagina. Read the Instructions for Use that comes with tavaborole topical solution before you start using it. Talk to your healthcare provider if you have any questions.

How to apply tavaborole topical solution:

Your toenails should be clean and dry before you apply tavaborole topical solution.

Step 1: Before you apply tavaborole topical solution to your affected toenail for the first time, remove the cap from the tavaborole topical solution bottle. (See Figure A) Throw away the

Step 2: Remove the wrapping from the dropper that comes with tavaborole topical solution. Insert the dropper into the tavaborole topical solution bottle. (See Figure B)

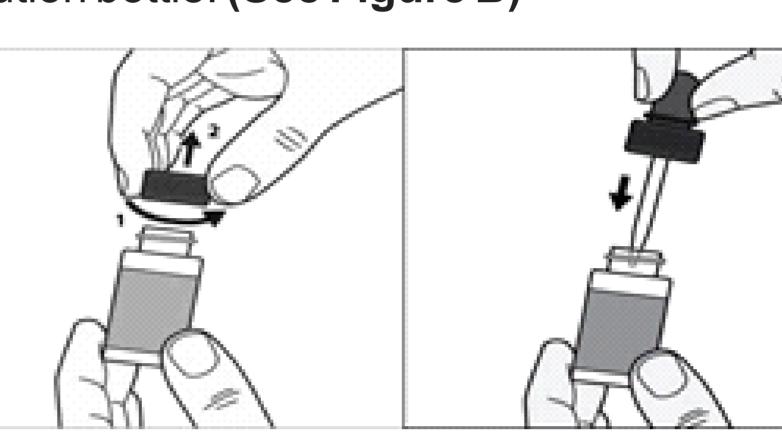


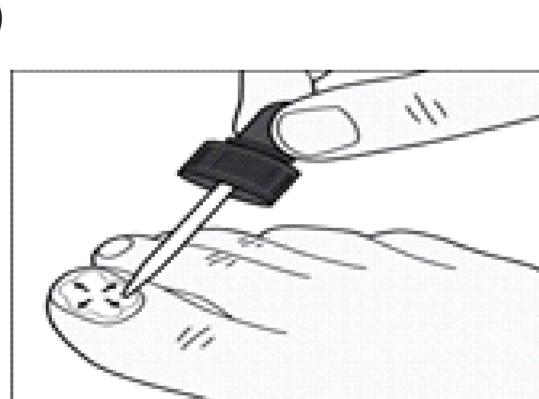
Figure A

other purpose.

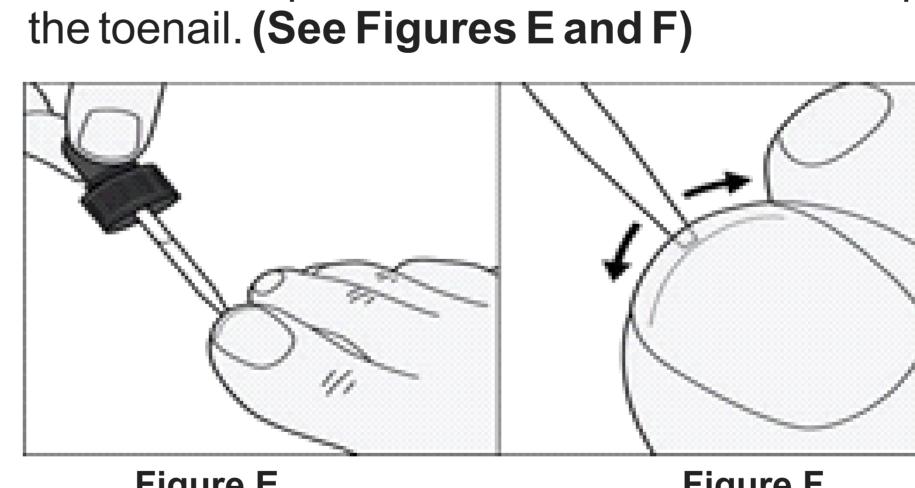
Step 3: With the dropper inserted into the tavaborole topical solution, squeeze the bulb and then release the bulb to draw tavaborole

Step 4: Remove the dropper from the bottle and hold the dropper tip over your affected toenail. Slowly squeeze the bulb to apply tavaborole topical solution to your toenail. Apply enough solution to completely cover your toenail. You may need to use more than one

Figure D)



apply tavaborole topical solution under the tip of the toenail. Use the dropper tip to gently spread tavaborole topical solution under the entire tip of the toenail. (See Figures E and F)



Step 9: Let the tavaborole topical solution dry completely. This may take a couple of minutes. Avoid getting tavaborole topical solution on skin that is not surrounding the treated toenail(s).If tavaborole topical solution comes in contact with surrounding skin, use a tissue to wipe any excess solution from the surrounding skin. **Do** not wipe tavaborole topical solution off of

Step 10: After applying tavaborole topical solution to your toenails, insert the dropper back

Step 11: Wash your hands with soap and water

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excretion is the major route of elimination of the metabolites

metabolites were shown to be excreted primarily in the urine.

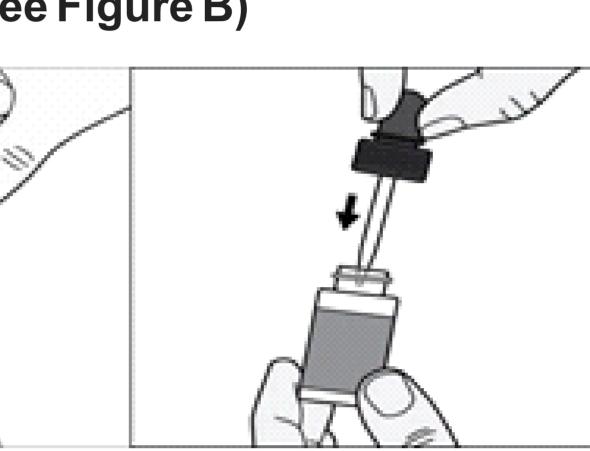


Figure B

Only apply tavaborole topical solution using the provided dropper. Do not use the dropper for any

topical solution into the dropper.

drop. (See Figure C)

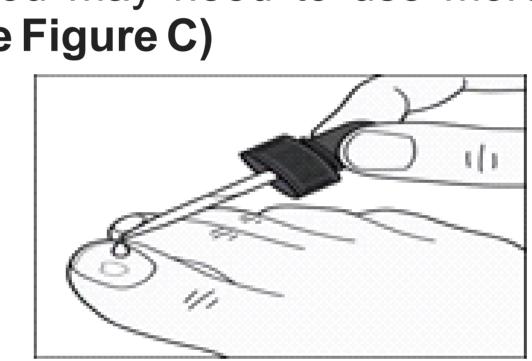


Figure C **Step 6:** Use the dropper tip to gently spread tavaborole topical solution to cover the entire toenail up to the edges of the toenail. (See

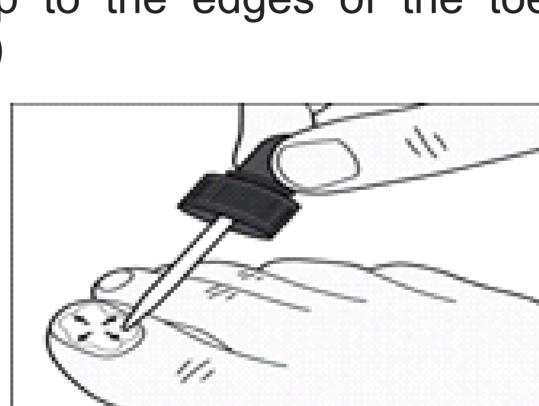


Figure D

Step 7: In addition to the top of the toenail, also

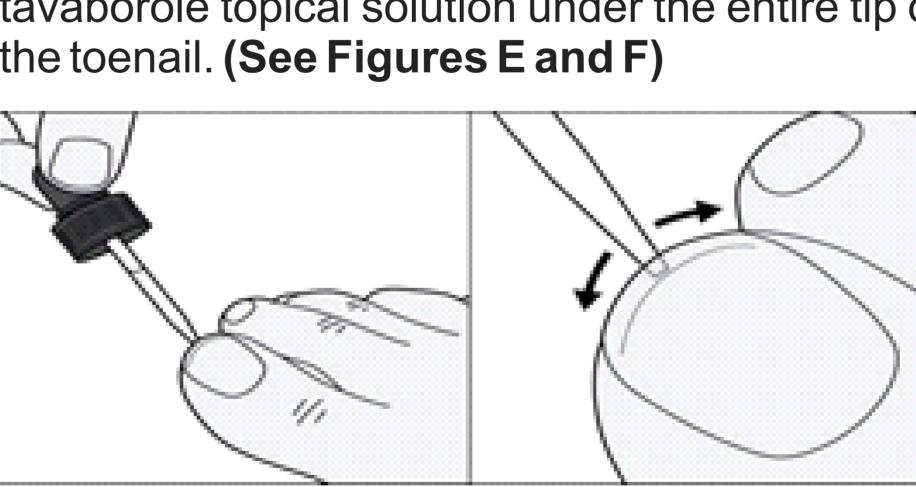


Figure F Figure E **Step 8:** Repeat Steps 3 to 7 to apply tavaborole topical solution to each affected toenail.

your toenails. into the bottle and screw it on tightly.

after applying tavaborole topical solution. This Patient Information and Instructions for Use

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In a clinical pharmacology trial of six healthy adult male volunteers who received a single topical application of 5% ¹C-tavaborole solution, tavaborole conjugates

The pharmacokinetics (PK) of tavaborole was investigated in 24 adult subjects with distal subungualonychomycosis involving at least 4 toenails (including at least 1 great toenail) following a single dose and a 2-week daily topical application of 200 µL of a 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail. Steady state was achieved after 14 days of dosing. After a single dose, the mean (\pm standard deviation) peak concentration (C_{max}) of tavaborole was 3.5 ± 2.3 ng/mL (n=21 with measurable concentrations, range 0.618-10.2 ng/mL, LLOQ=0.5 ng/mL),

 \pm SD was 75.8 \pm 44.5 ng*hr/mL. In another study PK of tavaborole was investigated in 22 subjects aged 12 years to less than 17 years with distal subungualonychomycosis involving at least 4 toenails (including at least 1 great toenail with at least 20% involvement) following once daily application of 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail for 29 days. On Day 29, the mean ± SD C_{max} was 5.9 ± 4.9 ng/mL (n=21 with measurable concentrations, range 1.0 -16.4 ng/mL, LLOQ=0.5 ng/mL), and the mean ± $SDAUC_{0-24}$ was 76.0 ± 62.5 ng*hr/mL.

Drug Interaction Studies

In Vitro Studies

In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

protein synthesis. Tavaborole inhibits protein synthesis by

Mechanism of Action The mechanism of action of tavaborole is inhibition of fungal

12.4 Microbiology

inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS). Activity in vitro and in clinical infections Tavaborole has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical

infections [see Indications and Usage (1)]:

Trichophytonmentagrophytes **Mechanism of Resistance**

Trichophytonrubrum

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 12.5, 25, and 50 mg/kg/day tavaborole were administered to rats once daily for 104 weeks. No drug related neoplastic findings were noted at oral doses up to 50

Trichophytonmentagrophytes and Trichophytonrubrum

strains from isolates collected in the clinical trials have not

demonstrated resistance following repeated exposure to

In a dermal carcinogenicity study in CD-1 mice, topical doses of 5%, 10%, and 15% tavaborole solution were administered to mice once daily for 104 weeks. No drug related neoplastic findings were noted at topical doses up to 15% tavaborole

mg/kg/day tavaborole (14 times the MRHD based on AUC

genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay). No effects on fertility were observed in male and female rats

that were administered oral doses up to 300 mg/kg/day

tavaborole (107 times the MRHD based on AUC

vehicle was applied once daily for 48 weeks in subjects with

20% to 60% clinical involvement of the target toenail, without

solution (89 times the MRHD based on AUC comparisons).

Tavaborole revealed no evidence of mutagenic or

clastogenic potential based on the results of two in vitro

comparisons) prior to and during early pregnancy. 14 CLINICAL STUDIES The efficacy and safety of tavaborole topical solution was evaluated in two multicenter, double-blind, randomized, vehicle-controlled trials. Tavaborole topical solutionor

dermatophytomas or lunula (matrix) involvement.

A total of 1194 subjects (795 Tavaborole topical solution, 399 Vehicle) 18 to 88 years of age, 82% male, 84% white, participated in these two trials. Efficacy assessments were made at 52 weeks following a 48-week treatment period. The Complete Cure efficacy endpoint included negative mycology (negative KOH wet mount and negative fungal culture) and Completely Clear Nail (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis). Efficacy

results from the two trials are summarized in Table 2. **Table 2: Efficacy Outcomes**

andculture.

presentations:

| | | Trial 1 | | Trial 2 | |
|--|--|--|---------------------------|---|---------------------------|
| | Efficacy Variable | Tavaborole topical solution N=399 n(%) | Vehicle N= 194 n(%) | Tavaborole topical solution N= 396 n(%) | Vehicle N= 205 n(%) |
| | Complete Cure [*] | 26 (6.5%) | 1 (0.5%) | 36 (9.1%) | 3 (1.5%) |
| | Complete or Almost Complete Cure [†] | 61 (15.3%) | 3 (1.5%) | 71 (17.9%) | 8 (3.9%) |

Mycologic Cure[‡] 124 (31.1%) 14 (7.2%) 142 (35.9%) 25 (12.2%) * Complete cure defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture. † Complete or almost complete cure defined as ≤ 10% affected target toenail area involved and negative KOH

‡ Mycologic cure defined as negative KOH and negative

16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Tavaborole topical solution, 5% is a clear, colorless solution supplied in an amber glass bottle with a screw cap. At initial

with one glass pointed-tip dropper.

use, the screw cap is replaced with the dropper assembly.

NDC 21922-020-12: One bottle containing 10 mL of solution The Packaging of This Product Contains Dry Natural

Tavaborole topical solution, 5% is supplied in the following

16.2 Storage and Handling Store at 20–25°C (68–77°F); excursions permitted to

15-30°C (59-86°F) [see USP Controlled Room

CAUTION: Flammable. Keep away from heat and flame. Discard product within 3 months after insertion of the

Keep bottle tightly closed. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Patient Information and

The patient should be told the following: The impact of nail polish or other cosmetic nail products on the efficacy of tavaborole topical solution

Product is flammable. Avoid use near heat or open

and the mean AUC_{last} \pm SD was 44.4 \pm 25.5 ng*hr/mL (n=21). has not been evaluated. After 2 weeks of daily dosing, the mean C_{max}±SD was 5.2 ± Inform a health care professional if the area of 3.5 ng/mL (n=24, range 1.5-12.8 ng/mL), and the mean AUCτ application shows signs of persistent irritation (for example, redness, itching, swelling).

Instructions for Use)

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were noted at 100 mg/kg/day (29 times the MRHD based on Topical administration: In a dermal embryofetal development study in rabbits, topical doses of 1%, 5%, and 10% tavaborole solution were administered during the period of organogenesis (gestational days 6-28) to pregnant female rabbits. A dose dependent increase in dermal irritation at the treatment site

Risk Summary tavaborole in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production after topical application of tavaborole topical solution to women who are breastfeeding. Tavaborole topical solution is systemically absorbed. The lack of clinical data during lactation precludes a clear determination of the risk of tavaborole topical solution to a breastfed infant. Therefore, the developmental and health benefits of breast feeding should be considered along with the mother's clinical need for tavaborole topical solution and any potential adverse

or from the underlying maternal condition. The safety and efficacy of tavaborole topical solution were

the structural formula is:

At therapeutic doses, tavaborole topical solution is not