JUBLIA®
(efinaconazole)
topical solution, 10%
9462902 Rev. 05/2016

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JUBLIA safely and effectively. See full prescribing information for JUBLIA.

JUBLIA® (efinaconazole) topical solution, 10%
For topical use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

JUBLIA is an azole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.* (1)

------ DOSAGE AND ADMINISTRATION------

- Apply JUBLIA to affected toenails once daily for 48 weeks using the integrated flow-through brush applicator. (2)
- When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered. (2)
- For topical use only. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

-----DOSAGE FORMS AND STRENGTHS ----

Solution: 10%. (3)

----------CONTRAINDICATIONS ----------

None. (4)

---------- ADVERSE REACTIONS----------

The most common adverse reactions (incidence >1%) were ingrown toenails, application site dermatitis, application site vesicles, and application site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 05/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JUBLIA (efinaconazole) topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

2 DOSAGE AND ADMINISTRATION

Apply JUBLIA to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.
JUBLIA is for topical use only and not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

JUBLIA (efinaconazole) topical solution, 10% contains 100 mg of efinaconazole in each gram of clear, colorless to pale yellow solution.

4 CONTRAINDICATIONS

None.

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, 1227 subjects were treated with JUBLIA, 1161 for at least 24 weeks and 780 for 48 weeks. Adverse reactions reported within 48 weeks of treatment and in at least 1% of subjects treated with JUBLIA and those reported in subjects treated with the vehicle are presented in **Table 1**.

Table 1: Adverse Reactions Reported by at Least 1% of Subjects Treated for up to 48 Weeks

Adverse Event, n (%)	JUBLIA N = 1227	Vehicle N = 413
Ingrown toenail	28 (2.3%)	3 (0.7%)
Application site dermatitis	27 (2.2%)	1 (0.2%)
Application site vesicles	20 (1.6%)	0 (0.0%)
Application site pain	13 (1.1%)	1 (0.2%)

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

potential benefit justifies the potential risk to the fetus.
Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).
Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).
In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased pre-natal pup mortality, reduced live litter sizes and increased post-natal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on post-natal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

8.3 Nursing Mothers

It is not known whether efinaconazole is excreted in human milk. After repeated subcutaneous administration, efinaconazole was detected in milk of nursing rats. Because many drugs are excreted in human milk, caution should be exercised when JUBLIA is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical trials of JUBLIA, 11.3% were 65 and over, while none were 75 and over. No overall differences in safety and effectiveness were observed between these

What are the ingredients in JUBLIA?
Active ingredients: efinaconazole
Inactive ingredients: alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

by:
Valeant Pharmaceuticals International Inc.
Laval, Quebec H7L 4A8, Canada

For more information, call 1-800-321-4576.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Instructions for Use
JUBLIA® (joo-blee-uh)
(efinaconazole) topical solution, 10%

Important information: JUBLIA is for use on toenails and surrounding skin only.
Do not use JUBLIA in your mouth, eyes or vagina.

Read the Instructions for Use that comes with JUBLIA before you start using it. Talk to your healthcare provider if you have any questions.

How to apply JUBLIA:

Your toenails should be clean and dry before you apply JUBLIA.

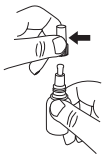
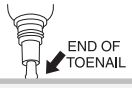


Figure A

Step 1: Before you apply JUBLIA to your affected toenail, remove the cap from the JUBLIA bottle **(See Figure A)**.


Figure B

Step 2: Hold the bottle upside down directly over the affected toenail and allow the product to moisten the brush. By turning the bottle upside down, the entire brush will become wet with the drug solution. Apply one drop of JUBLIA onto the toenail. **Do not squeeze** the bottle or press/rub the brush firmly against the toenail while applying JUBLIA **(See Figure B)**.



Step 3: For the big toenail, also apply a second drop to the end of the toenail by touching the tip


Figure D

Step 4: Use the brush attached to the bottle to **gently** apply JUBLIA. The goal is to make sure that the entire toenail including the cuticle, folds of the skin next to the sides of the toenail, and underneath the nail are covered with the drug solution. **(See Figure D)**. **Pressing or rubbing firmly against the toenail while applying JUBLIA could cause brush deformation and over application of the drug solution.**

Step 5: Repeat Steps 2 to 4 to apply JUBLIA to each affected toenail.

Step 6: Let JUBLIA dry completely.

Step 7: After applying JUBLIA to your affected toenails, place the cap on the bottle and screw it on tightly.

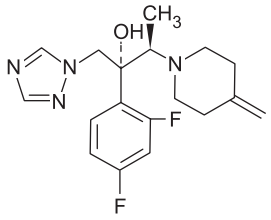
Step 8: Wash your hands with soap and water after applying JUBLIA.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Valeant Pharmaceuticals North America LLC,
Bridgewater, NJ 08807 USA

11 DESCRIPTION

JUBLIA (efinaconazole) topical solution, 10% is a clear colorless to pale yellow solution for topical use. Each gram of JUBLIA contains 100 mg of efinaconazole. Efinaconazole is an azole antifungal with a chemical name of ((2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol). The structural formula for efinaconazole is represented below:



Molecular Formula: $C_{18}H_{22}F_2N_4O$
Molecular Weight: 348.39

JUBLIA contains the following inactive ingredients: alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JUBLIA topical solution is an azole antifungal *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

The pharmacodynamics of JUBLIA is unknown.

12.3 Pharmacokinetics

Systemic absorption of efinaconazole in 18 adult subjects with severe onychomycosis was determined after application of JUBLIA once daily for 28 days to patients' 10 toenails and 0.5 cm adjacent skin. The concentration of efinaconazole in plasma was determined at multiple time points over the course of 24-hour periods on days 1, 14, and 28. Efinaconazole mean ± SD plasma C_{max} on Day 28 was 0.67 ± 0.37 ng/mL and the mean ± SD AUC was 12.15 ± 6.91 ng*h/mL. The plasma concentration versus time profile at steady state was generally flat over a 24-hour dosing interval. In a separate study of healthy volunteers, the plasma half-life of efinaconazole following daily applications when applied to all 10 toenails for 7 days was 29.9 hours.

Drug Interactions

JUBLIA is considered a non-inhibitor of the concentrations. *In vitro* studies in human prima hepatocytes showed that efinaconazole did not induce CYP1A2 or CYP3A4 activities.

12.4 Microbiology

Mechanism of Action

Efinaconazole is an azole antifungal. Efinaconazole inhibits fungal lanosterol 14α-demethylase involved in the biosynthesis of ergosterol, a constituent of fungal cell membran

Activity *In Vitro* and *In Vivo*

Efinaconazole has been shown to be active against isolates of the following microorganism both *in vitro* and in clinical infections. Efinaconazole exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.06 mcg/ or less against most (≥90%) isolates of the following microorganisms:

Trichophyton rubrum
Trichophyton mentagrophytes

Mechanism of Resistance

Efinaconazole drug resistance development was studied *in vitro* against *T. mentagrophytes, T. rubrum* and *C. albicans*. Serial passage of fungal cultures in the presence of sub-growth inhibitory concentrations of efinaconazole increased the MIC by up to 4-fold. The clinical significance of these *in vitro* results is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year dermal carcinogenicity study in mice was conducted with daily topical administratio of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded the interpretation of sk effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were not at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons) Efinaconazole revealed no evidence of mutagen or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberrat assay) and one *in vivo* genotoxicity test (mouse peripheral reticulocyte micronucleus assay). No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 tim the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).