CLINICAL INSIGHTS

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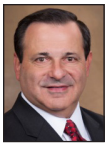
Julia® (efinaconazole) Topical Solution, 10%: An Option for Onychomycosis Therapy



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The management of toenail onychomycosis sometimes can be challenging. The condition—marked by discoloration, thickening, roughening, opacity, pitting, splitting, dyschromia, and nail plate destruction[1,2]—accounts for more than half of all nail disease. About one-fifth of US physician visits for dermatophytoses are for onychomycosis.[3]

Risk factors for onychomycosis include immunodeficiency, diabetes, and older age.[4] Nail trauma and concurrent fungal infections are also risk factors for developing onychomycosis. Onychomycosis may be more common in smokers and in men—although men and women appear to present for treatment in equal proportion.[3,5,6] While advanced age is a risk factor for onychomycosis, the majority of those seeking treatment appear to be 55 or younger.[3]

THE PROBLEM OF ONYCHOMYCOSIS

Mycotic nails should be treated. Untreated onychomycosis may lead to permanent damage of the nail plate and its attachments, and it may be associated with significant clinical issues. Mycotic nails can serve as a reservoir for fungal infections. As such, affected individuals can spread infection to others via public showers, pools, and other surfaces.[7]

Another reason that onychomycosis should be treated is because the disease can be progressive,[5] and the presence of fungal nail disease may complicate pre-existing medical conditions, such as diabetes.[8]

Certain lifestyle factors are also associated with increased risk for onychomycosis. Wearing occlusive shoes, using public sports and exercise facilities, and using public nail salons all increase one's risk for developing toenail onychomycosis. Poor foot hygiene is also a risk factor for toenail infection.[5,6]

TABLE 1. RATIONALE FOR TREATMENT OF ONYCHOMYCOSIS[4,5]

- Untreated onychomysosis may lead to permanent damage of the nail plate and its attachments
- Mycotic nails can serve as a reservoir for fungal infections
- Affected individuals can spread infection to others (public showers, pools, and other surfaces)
- May complicate pre-existing medical conditions

Many patients are not receiving adequate treatment for toenail onychomycosis. In one survey, patients presenting to doctors with onychomycosis had been living with the condition for a decade or more.[9] One in five respondents reported having onychomycosis for at least 20 years![9]

Surveys do not indicate why patients delay seeking treatment for onychomycosis from a physician. We do know that available oral medications, while effective, require monitoring that some patients prefer to avoid. Topical treatments generally have been considered to have little efficacy.

Julia (efinaconazole) Topical Solution, 10%, from Valeant is the first prescription azole antifungal indicated for the topical treatment of onychomycosis of the toenails caused by *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Julia is for topical use only and is not for oral, ophthalmic, or intravaginal use.

DATA FOR JULIA

The two Phase III pivotal trials that supported approval of Julia involved 1,640 evaluable patients treated once daily with Julia for 48 weeks.[10] The primary efficacy endpoint was the percent of participants who achieved complete cure at the 52-week endpoint. Complete cure is defined as both 0% clinical involvement of the target toenail and mycological cure, defined as both negative KOH and negative fungal culture.[10]

One of the secondary efficacy endpoints was complete or almost complete cure, which requires mycological cure—as demonstrated by negative KOH and negative fungal culture—and 5% or less of affected toenail remaining.[10]

Involvement of 5% or less of the toenail is a high hurdle for an onychomycosis drug.

In Study 1, 17.8% of subjects treated with Julia were completely cured at 52 weeks, compared to only 3.3% of subjects treated

TABLE 2. COMPLETE CURE RATES AT 52 WEEKS

	Jublia	Vehicle
Study 1	17.8%	3.3%
Study 2	15.2%	5.5%

TABLE 3. COMPLETE OR ALMOST COMPLETE CURE RATES AT 52 WEEKS

	Jublia	Vehicle
Study 1	26%	7%
Study 2	23%	8%

TABLE 4. MYCOLOGICAL CURE

	Jublia	Vehicle
Study 1	55%	17%
Study 2	53%	17%

with vehicle.[10] In Study 2, 15.2% of subjects treated with Jublia were completely cured at 52 weeks, compared to only 5.5% of subjects treated with vehicle (Table 2).[10]

In terms of complete or almost complete cure, about one-quarter of treated subjects (26% in Study 1; 23% in Study 2) achieved this endpoint at 52 weeks, compared to 7% and 8% of controls, respectively (Table 3).[10]

Roughly half of subjects treated with Jublia (55% and 53%, respectively) achieved mycological cure in Study 1 and Study 2. This compares to just 17% of controls in each study (Table 4).[10]

The most common adverse events were ingrown toenail, application site dermatitis, application site vesicles, and pain (Table 5). The incidence was low, as shown. Patients should be instructed to contact their healthcare professional if a reaction suggesting sensitivity or severe irritation occurs.[10]

TABLE 5. 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%)

ABOUT JUBLIA

Once-daily topical Jublia's high clearance rates may be related to the formulation. With multiple pathways to reach the nail bed, the azole formulation reaches the site of infection. It is applied to the toenail, the toenail folds and bed, the hyponychium, and the undersurface of the toenail plate. The low surface tension of the formulation allows it to go around the distal toenail edge and enter into the air gap. Patient instructions call for application to the distal nail edge, in addition to the top of the nail plate itself.

Jublia is a clear solution, applied daily to the nail with a novel bottle that has a built-in flow-through brush applicator and debridement is not required. When used as directed, there are minimal concerns for systemic side effects such as drug-drug interactions or acute liver injury, given the low systemic absorption, as described in the product labeling.[10]

However, since there are no well-controlled studies in pregnant or nursing women, Jublia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and caution should be exercised when Jublia is administered to a nursing mother. Safety and efficacy have not been established in pediatric patients.

CONCLUSION

Toenail onychomycosis is a common medical concern with potentially significant clinical issues associated with it; The condition requires treatment.[11] Mycotic nails may serve as a reservoir for other fungal infections. Patients with untreated toenail onychmycosis may infect themselves and others.[4,5]

Immunodeficiency, diabetes, and older age—all risk factors for onychomycosis—are also conditions associated with multi-drug therapy, thus making topical therapy a good option for many of these patients.[2]

An effective topical treatment option with low systemic exposure may be a desirable option for patient care. Once-daily Jublia Topical Solution, 10% has demonstrated efficacy and tolerability.

In summary, complete cure rates for Jublia were 17.8% and 15.2%, in Studies 1 and 2, respectively. And at the end of the treatment period, more than half of subjects treated with Jublia had no dermatophytes present in the treated nails. The treatment has no expected drug interactions and requires no liver function tests. It has a favorable tolerability profile, with the most commonly reported adverse events being ingrown toenail and application site reactions (all reported in less than 3% of patients).[10]

Applied once-daily for 48 weeks, Jublia Topical Solution, 10% offers a topical treatment option for the millions of patients living with toenail onychomycosis.

Given the prevalence of onychomycosis, its potential clinical implications, and the data that you've seen for Jublia Topical Solution, 10%, it may be a suitable topical formulation option for your patients. ■ DM/JUB/14/0234

See Prescribing Information on adjacent pages.

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4. Gazes MI, Zeichner J. Onychomycosis in close quarter living review of the literature. Mycoses. 2013;56(6):610-3.
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8. Matricciani L, Talbot K, Jones S. Safety and efficacy of tinea pedis and onychomycosis treatment in people with diabetes: a systematic review. J Foot Ankle Res. 2011 Dec 4;4:26.
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10. Jublia PI
11. Pariser D, Scher RK, Elewski B, Rich P. Promoting and maintaining or restoring healthy nails: practical recommendations for clinicians and patients. Semin Cutan Med Surg. 2013;32(2 Suppl 1):S13-4.

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: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

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

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with JUBLIA in pregnant women. JUBLIA should be used during pregnancy only if the 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 prenatal pup mortality, reduced live litter sizes and increased postnatal 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 postnatal 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

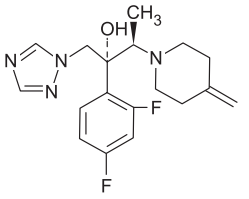
Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

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 subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

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 CYP450 enzyme family. In in vitro studies using human liver microsomes, efinaconazole did not inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2PE1 and CYP3A4 enzyme activities at expected clinical systemic concentrations. In vitro studies in human primary 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 membranes.

Activity In Vitro and In Vivo
Efinaconazole has been shown to be active against isolates of the following microorganisms, both in vitro and in clinical infections. Efinaconazole exhibits in vitro minimum inhibitory concentrations (MICs) of 0.06 µg/mL 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 administration 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 skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons).
Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration 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 efinaconzole (279 times 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).

14 CLINICAL STUDIES
The safety and efficacy of once daily use of JUBLIA for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multi-center, randomized, double-blind clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement. The trials compared 48-weeks of treatment with JUBLIA to the vehicle solution. The Complete Cure rate was assessed at Week 52 (4-weeks after completion of therapy). Complete cure was defined as 0% involvement of the target toenail (no clinical evidence of onychomycosis of the target toenail) in addition to Mycologic Cure, defined as both negative fungal culture and negative KOH. Table 2 lists

Table 2: Efficacy Endpoints

	Trial 1		Trial 2	
	JUBLIA	**Vehicle**	**JUBLIA**	**Vehicle**
	N = 656	**N = 214**	**N = 580**	**N = 201**
Complete Cure[a]	117 17.8%	7 3.3%	88 15.2%	11 5.5%
Complete or Almost Complete Cure[b]	173 26.4%	15 7.0%	136 23.4%	15 7.5%
Mycologic Cure[c]	362 55.2%	36 16.8%	310 53.4%	34 16.9%

[a] Complete cure defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture.
[b] Complete or almost complete cure defined as ≤5% affected target toenail area involved and negative KOH and culture.
[c] Mycologic cure defined as negative KOH and negative culture.

16 HOW SUPPLIED/STORAGE AND HANDLING
JUBLIA (efinaconazole) topical solution, 10% is a clear, colorless to pale yellow solution supplied in a white plastic bottle with an integrated flow-through brush applicator as follows:
- 4 mL (NDC 0187-5400-04)
- 8 mL (NDC 0187-5400-08)

Storage and Handling Conditions:
Store at 20°C - 25°C (68°F - 77°F); excursions permitted to
15°C - 30°C (59°F - 86°F) [*see USP Controlled Room Temperature*].
- Solution is flammable; keep away from heat or flame
- Protect from freezing
- Keep out of the reach of children
- Keep bottle tightly closed
- Store in upright position

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information)
- JUBLIA is for external use only and is not for ophthalmic, oral, or intravaginal use. It is for use on toenails and immediately adjacent skin only.
- Apply JUBLIA once daily to clean dry toenails. Wait for at least 10 minutes after showering, bathing, or washing before applying.
- Use JUBLIA only on the affected toenails, as directed by your healthcare provider.
- Inform a health care professional if the area of application shows signs of persistent irritation (for example, redness, itching, swelling).
- Avoid pedicures, the use of nail polish, and cosmetic nail products while using JUBLIA.
- Flammable, avoid use near heat or open flame.

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

Manufactured by:
Kaken Pharmaceutical Co. Ltd
Shizuoka, Japan

Product of Japan

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