PRODUCT MONOGRAPH

^{Pr}JUBLIA™

Efinaconazole Topical Solution, 10% w/w

Topical Antifungal Agent

Valeant Canada LP
2150 St. Elzéar West
Laval, QC
H7L 4A8

Date of Preparation:
July 7, 2017

Submission Control No: 204442

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PrJUBLIA™

Efinaconazole Topical Solution 10% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Topical solution, 10% w/w	None *For a complete listing, see the Dosage Forms, Composition and Packaging sections of the product monograph.*

INDICATIONS AND CLINICAL USE

JUBLIA (Efinaconazole Topical Solution, 10% w/w), a triazole antifungal agent, is indicated for the topical treatment of mild to moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in immunocompetent adult patients.

Geriatrics (≥ 65 years of age):
Of the total number of subjects in clinical studies ofJUBLIA, 8.3% were 65 years of age and over while none were 75 years of age and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age):
Safety and effectiveness of JUBLIA in pediatric patients under the age of 18 have not been studied.

CONTRAINDICATIONS

JUBLIA (Efinaconazole Topical Solution, 10% w/w) is contraindicated in patients with a known hypersensitivity to efinaconazole or to any of the excipients of JUBLIA or component of the container (see DOSAGE FORMS, COMPOSITION and PACKAGING).

WARNINGS AND PRECAUTIONS

General

Safety and effectiveness of JUBLIA (Efinaconazole Topical Solution, 10% w/w) have not been studied in patients with a history and/or clinical signs of immunosuppression, with HIV infection, uncontrolled diabetes, pregnant and nursing women, other toenail infection (except *Candida*), toenail infection extended to matrix, patients with only lateral toenail disease, severe plantar (moccasin) tinea pedis.

Concomitant use of other antifungal therapy with JUBLIA has not been evaluated.

Safety and efficacy of daily use of JUBLIA for longer than 48 weeks have not been established.

Use Outside of Nail Area

JUBLIA (efinaconazole) is not for ophthalmic, oral, or intravaginal use. It is for topical use on toenails and immediately adjacent skin only.

Flammability

JUBLIA is flammable; keep away from heat or flame.

Site Irritation

If a reaction suggesting sensitivity or severe irritation should occur with the use of JUBLIA, treatment should be discontinued and appropriate therapy instituted, as recommended by the healthcare professional.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women with JUBLIA. JUBLIA should not be used during pregnancy unless the expected benefit to the mother outweighs any potential risk to the fetus (see TOXICOLOGY, Reproductive and Developmental Toxicity, and PHARMACOKINETICS).

Nursing Women:
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, JUBLIA should not be used in the treatment of nursing women unless the expected benefit outweighs the possibility of any potential risk to the infant.

Pediatrics (< 18 years of age):
Safety and effectiveness of JUBLIA in pediatric patients under the age of 18 have not been studied.

Geriatrics (≥ 65 years of age):
Of the total number of subjects in clinical studies of JUBLIA, 8.3% were 65 years of age and over while none were 75 years of age and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The data described below reflect exposure to JUBLIA (Efinaconazole Topical Solution, 10% w/w) applied topically to toenails once a day in 1189 patients in two identical Vehicle controlled Phase 3 clinical studies in which 1124 (94.5%) patients were exposed for 24 weeks and 757 (63.7%) patients were exposed for 48 weeks.

The total number of patients who reported a treatment-emergent adverse reaction (based on adverse events assessed by the Investigator to be at least possibly related to study medication) was 6.1% in the JUBLIA arm and 3.5% in the Vehicle treatment arm.

The most common treatment-emergent adverse reactions reported in patients treated with JUBLIA were application site dermatitis (2.0%) and application site vesicles (1.4%).
The majority of adverse events in the JUBLIA arm were mild to moderate in severity as assessed by the Investigator. Rate of study treatment discontinuation due to adverse events was 2.7% (32/1189) in the JUBLIA group compared to 0.2% (1/401) in the Vehicle group. The most common adverse event that led to study treatment discontinuation was application site dermatitis 1.1% (13/1189).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The treatment-emergent adverse events assessed by the Investigator as definitely, probably, or possibly drug related and reported in ≥ 1% of patients treated with JUBLIA compared with those reported in patients treated with the Vehicle are presented in Table 1.

Table 1 - Drug Related Treatment-Emergent Adverse Events Reported by ≥ 1% of Patients Treated with JUBLIA for up to 48 Weeks

Adverse Event **System Organ Class**/Preferred Term	**JUBLIA** **N = 1189** **n (%)**	**Vehicle** **N = 401** **n (%)**
General disorders and administration site conditions		
Application site dermatitis	24 (2.0%)	1 (0.2%)
Application site vesicles	17 (1.4%)	0 (0.0%)

Less Common Clinical Trial Adverse Drug Reactions (> 0.1% to <1%)

Cardiac Disorders: Ventricular extrasystole (0.1%)

Eye Disorders: Blepharitis (0.1%), eye pruritus (0.1%), and vision blurred (0.1%).

General Disorders and Administration Site Conditions: Application site reactions: discolouration (0.3%), eczema (0.2%), erythema (0.8%), exfoliation (0.6%), irritation (0.3%), pain (0.4%), paraesthesia (0.3%), pruritus (0.4%), and swelling (0.5%).

Infections and Infestations: Nasopharyngitis (0.2%)

Nervous System Disorders: Headache (0.2%).

Skin and Subcutaneous Tissue Disorders: Onychomadesis (0.3%)

DRUG INTERACTIONS

Drug-Drug Interactions
Topical administration of JUBLIA (Efinaconazole Topical Solution, 10% w/w) has very low systemic exposure, therefore potential interactions between JUBLIA and other drugs have not been evaluated (see ACTION AND CLINICAL PHARMACOLOGY, Absorption and DETAILED PHARMACOLOGY).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
No debridement is necessary when treating onychomycosis with JUBLIA (Efinaconazole Topical Solution, 10% w/w). Removal of previously applied JUBLIA is not required as there is no buildup from daily application. Patients should clip their toenail(s) every four weeks and clippings should be discarded. The unaffected toenail(s) should be clipped before the affected ones.

Recommended Dose and Dosage Adjustment
JUBLIA (efinaconazole) should be topically applied once daily (preferably at bedtime). One drop of JUBLIA should be applied onto the affected toenail(s). A second drop should be applied onto the affected big toenail(s).

A complete cure may be seen some months after mycological cure is achieved. This is related to time required for outgrowth of healthy nail.

Missed Dose
Physicians should use clinical judgement based on the severity of the infection.

Administration

JUBLIA (efinaconazole) should be topically applied once daily (preferably at bedtime) to the affected toenails, with the built-in flow-through brush applicator provided. JUBLIA should completely cover the toenail, the nail folds, nail bed, hyponychium and the undersurface of the nailplate.

JUBLIA should be applied to clean dry nails. Once applied, JUBLIA should be allowed to dry thoroughly before touching the treated areas with bed sheets, socks or other clothing (see PART III CONSUMER INFORMATION).

OVERDOSAGE

Penetration of JUBLIA (Efinaconazole Topical Solution, 10% w/w) by the topical route leads to low systemic concentration levels. There are no data available on human oral bioavailability however, oral bioavailability in rats (0.4%) is very low.

No reports of overdose were observed in clinical trials either through topical use or by ingestion, however, overdose is unlikely to occur with topical application due to low systemic concentration levels. No specific antidote is known.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Efinaconazole is a triazole antifungal agent. Efinaconazole inhibits fungal lanosterol 14α-demethylase involved in ergosterol biosynthesis. The accumulation of 14α-methyl sterols and subsequent loss of ergosterol in the fungi cell wall may be responsible for the fungistatic and fungicidal activity of efinaconazole. Efinaconazole is shown *in vitro* to be substantially adsorbed to keratin but keratin binding is weak. Efinaconazole's low keratin affinity is expected to result in increased availability of free drug to the nail infection site.

Pharmacokinetics

Absorption:

Administration of JUBLIA by the topical route leads to low systemic efinaconazole concentrations. Systemic absorption of efinaconazole in 18 patients with severe onychomycosis was determined after application of JUBLIA once daily for 28 days to patients' 10 toenails and 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 plasma C_{max} on Day 28 was 0.67 ng/mL. The mean plasma concentration versus time profile was generally flat over the course of treatment. In onychomycosis patients, the steady state plasma concentration range was 0.1-1.5 ng/mL for efinaconazole and 0.2-7.5 ng/mL for H3 metabolite. In a separate study of healthy volunteers, the plasma half-life of JUBLIA at day 10 following repeat treatment applications repeated to all 10 toenails was 29.9 hours.

Distribution:

Efinaconazole *in vitro* binding to human plasma proteins is high, 95.8% - 96.5%. Because of low systemic levels, efinaconazole plasma protein binding is not expected to be clinically relevant. Plasma protein binding was not concentration-dependent over a range 50– 2500 ng/mL. Efinaconazole *in vitro* bound to human serum albumin (95.2%), α1-acid glycoprotein (85.5%) and to γ-globulin (4.4%). As albumin concentration is high in plasma relative to other proteins, efinaconazole is expected to be mainly bound to human serum albumin *in vivo.*

Efinaconazole penetrates through nails *in vitro* after JUBLIA administration, suggesting drug penetrations to the site of fungal infection in the nail and the nail bed, though clinical relevance is unknown. The penetration of JUBLIA was evaluated in an *in vitro* investigation after daily application of radiolabelled efinaconazole (10%) to human nails for 28 days at 55.1 µL/cm^2. After 28 days, the cumulative radioactivity in the receptor fluid and in the nail plate, on a percent basis of total administered radioactivity, was 0.03% and 0.16% (3.11 mg eq/g), respectively. The flux rate was relatively constant from Days 18 to 28, mean 1.40 µg eq/cm^2/day, suggesting steady state attainment.

Metabolism and Excretion:
JUBLIA (efinaconazole) is extensively metabolized through oxidative/reductive processes, with the potential of additional metabolite glucuronidation.
Analysis of human plasma confirmed that H3 is the only major efinaconazole metabolite.

JUBLIA is considered a non inhibitor and non inducer of the CYP450 enzyme family.
In *in-vitro* studies using human liver microsomes, efinaconazole inhibited CYP2C8, CYP2C9, CYP2C19 and CYP3A4 enzyme activities at concentrations higher than clinical systemic exposure levels. In addition, *in vitro* studies in human primary hepatocytes showed that efinaconazole did not induce CYP1A2 or CYP3A4 activities. Therefore, efinaconazole is unlikely to affect the pharmacokinetics of substrates of the major CYP450 isoenzymes through inhibition or induction mechanisms (see DETAILED PHARMACOLOGY).

Efinaconazole metabolites are excreted in urine and bile/feces.

STORAGE AND STABILITY
Store at controlled room temperature (15-30°C). Keep bottle tightly closed and store in an upright position.

SPECIAL HANDLING INSTRUCTIONS
Keep out of the reach and sight of children. Solution is flammable; keep away from heat or flame.

DOSAGE FORMS, COMPOSITION AND PACKAGING
JUBLIA contains efinaconazole 10% w/w in a clear, low surface tension solution for topical application.

JUBLIA (efinaconazole) Solution 10% w/w is supplied in a white plastic squeeze-bottle with built-in flow-through brush applicator. Each bottle contains 8 mL of solution.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

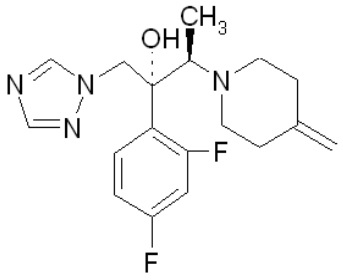
Proper name: Efinaconazole

Chemical name: ((2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol)

Molecular formula: $C_{18}H_{22}F_2N_4O$

Molecular weight: 348.39

Structural formula:



Physicochemical properties:
- white to pale yellow crystals or crystalline powder
- melting point: 86 to 89 °C
- pH of a saturated solution is between 5.5 and 7.5
- practically insoluble or insoluble in water

CLINICAL TRIALS

The safety and efficacy of once daily use of JUBLIA (Efinaconazole Topical Solution, 10% w/w) for the treatment of onychomycosis of the toenail were assessed in two identical Phase III clinical trials which included patients with 20% to 50% clinical involvement of the area of the target great toenail, without dermatophytomas or lunula (matrix) involvement. Patients had positive dermatophyte culture and positive potassium hydroxide (KOH) examination from the target toenail. Patients were not excluded for concomitant *Candida* infection.

Table 2 provides the design and demographics of the 2 pivotal Phase III clinical trials.

Study Design and Demographics

Table 2- Summary of study design and patient demographics for pivotal Phase III clinical trials in onychomycosis

Study #	**Trial Design**	**Dosage, Route of Administration and Duration of Therapy**	**Number of Patients N**	**Mean Age in Years (Range)**	**Gender % M/F**
Study DPSI-IDP-108-P3-01	Phase 3, Multicenter, Randomized (3:1), Double-Blind Study evaluating the safety and efficacy of IDP-108 topical solution versus Vehicle in subjects with mild to moderate onychomycosis of the toenails	JUBLIA Vehicle Topical: Once daily Duration of Therapy: 48 weeks	618 202	52.3 (20-71) 52.0 (18-70)	74/25 74/25
Study DPSI-IDP-108-P3-02	Phase 3, Multicenter, Randomized (3:1), Double-Blind Study evaluating the safety and efficacy of IDP-108 topical solution versus Vehicle in subjects with mild to moderate onychomycosis of the toenails	JUBLIA Vehicle Topical: Once daily Duration of Therapy: 48 weeks	580 201	50.6 (18-71) 50.7 (18-70)	80/20 81/18

Table 3 below displays the primary efficacy results obtained from Study DPSI-IDP-108-P3-01 and Study DPSI-IDP-108-P3-02.

Table 3: Primary Efficacy Results (Complete Cure) at week 52 in the ITT[1] population

Study #	**Primary efficacy endpoint**	**JUBLIA % (n/N)**	**Vehicle % (n/N)**	***p*-value[3]**
DPSI-IDP-108-P3-01	Complete Cure[2] at Week 52	18.8% (116/618)	3.5% (7/202)	<0.001
DPSI-IDP-108-P3-02	Complete Cure at Week 52	15.2% (88/580)	5.5% (11/201)	<0.001

[1]ITT=Intent to treat
[2]Complete Cure at Week 52 (4-weeks after completion of therapy) defined as 0% clinical involvement of the target toenail (toenail is totally clear) in addition to Mycologic Cure, defined as a negative fungal culture and a negative potassium hydroxide (KOH) examination of the target toenail sample.
[3]*p*-value from a Cochran-Mantel-Haenszel test, stratified by analysis center

Study DPSI-IDP-108-P3-01

It was observed that the percentage of subjects who achieved a Complete Cure was greater in the active group than in the Vehicle group by Week 24 and that the percentage of successful subjects in the active group continued to increase over time through the four week post-treatment follow-up visit (Week 52).

Study DPSI-IDP-108-P3-02

It was observed that the percentage of subjects who achieved a Complete Cure was greater in the active group than in the Vehicle group by Week 36 and that the percentage of successful subjects in the active group continued to increase over time through the four-week post treatment follow-up visit (Week 52).

Table 4 below displays the secondary efficacy results obtained from Study DPSI-IDP-108-P3-01 and Study DPSI-IDP-108-P3-02.

Table 4: **Secondary Efficacy Results at week 52 in the ITT[1] Population**

Study #	**Secondary efficacy endpoints**	**JUBLIA % (n/N)**	**Vehicle % (n/N)**	***p*-value**
DPSI-IDP-108-P3-01	Clinical Efficacy[2] at Week 52	46% (281/618)	18% (36/202)	<0.001
	Mycologic Cure[3] rate at Week 52	55.3% (342/618)	16.8% (34/202)	<0.001
	Unaffected New Nail[4] Growth at Week 52 LS Mean[5] (mm)	5.0	1.5	<0.001
DPSI-IDP-108-P3-02	Clinical Efficacy at Week 52	31% (180/580)	11.9% (24/201)	<0.001
	Mycologic Cure rate at Week 52	53.4% (310/580)	16.9% (34/201)	<0.001
	Unaffected New Nail Growth at Week 52 LS Mean (mm)	3.8	0.9	<0.001

[1]ITT=Intent to treat
[2]Clinical Efficacy is defined as an affected target toenail area of less than 10%.
[3]Mycologic Cure is defined as a negative fungal culture and a negative potassium hydroxide (KOH) examination of the target toenail sample.
[4]Unaffected New Nail Growth is defined as the change from baseline in the healthy [unaffected] target toenail measurement for the target toenail.
[5]LS Mean: Least Square Mean

Table 5: Mycological Cure[1] Rate at Treatment Period Intervals in the ITT[2] Population

Treatment Period (week)	Study DPSI-108-P3-01		Study DPSI-108-P3-02	
	JUBLIA N=618 n (%)	Vehicle N=202 n (%)	JUBLIA N=580 n (%)	Vehicle N=201 n (%)
12	149 (24)	29 (14)	128 (22)	25 (12)
24	298 (48)	50 (25)	264 (46)	39 (19)
36	339 (55)	41 (20)	301 (52)	38 (19)
48	347 (56)	52 (26)	316 (55)	40 (20)
52	342 (55)	34 (17)	310 (53)	34 (17)

[1]Mycologic Cure is defined as a negative fungal culture and a negative potassium hydroxide (KOH) examination of the target toenail sample.
[2]ITT=Intent to treat

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

In a guinea pig maximization test, efinaconazole was a mild skin sensitizer. In a Buehler guinea pig test, treatment with a prototype efinaconazole formulation and its vehicle were positive for skin sensitization. However, there was no strong evidence of skin sensitization to JUBLIA in a human repeat insult patch test.

Safety Pharmacology

The safety pharmacology of efinaconazole was characterized after acute exposure in CNS, cardiovascular, respiratory, gastrointestinal and renal preparations and/or animals. Efinaconazole was without effects on core physiological systems or effects were only noted at high doses.

Efinaconazole and the major human plasma metabolite, H3, have negligible or no potential to increase QT interval based on *in vitro* hERG inhibition. This hERG inhibition model used electrophysiological assessment of I_{Kr} potassium current in human cells transfected with human hERG cDNA. The H3 metabolite was inactive on hERG-mediated current at 100 μM (22500 ng/mL) and lower concentrations while efinaconazole produced slight inhibition, 17%, at the maximal soluble concentration of 10 μM (3480 ng/mL).

Efinaconazole has limited potential for any adverse secondary or off target pharmacological effects because only high parenteral doses produced test article effects. Furthermore, systemic efinaconazole and H3 metabolite exposure in the parenteral animal and ex vivo studies is expected to be far above the low ng/mL plasma levels in clinical topical nail therapy.

Pharmacokinetics

The nonclinical pharmacokinetics of efinaconazole was characterized in rats and dogs and included dermal, oral, subcutaneous and intravenous routes of administration.
Efinaconazole is absorbed systemically after topical application to the skin of laboratory animals but the percent of applied dose absorbed is low. It ranged from 6 to 16% of applied drug levels in all nonclinical species and with different formulations examined. The bioavailability of efinaconazole was low following oral administration which may be due to first pass hepatic metabolism. Efinaconazole was well absorbed following subcutaneous administration and the bioavailability was 75% as compared to intravenous administration. Studies conducted with repeated subcutaneous administration in rats indicates that steady state is reached in four days. After either subcutaneous injection or dermal application in rats, efinaconazole is widely distributed in tissues, with moderate accumulation in liver, adrenal glands, fat and Harderian glands. However, there is no persistence in any tissue and tissue elimination kinetics is similar to plasma. In pregnant rats, efinaconazole and/or metabolites accumulated in several fetal tissues, including liver, heart, kidney and GI tract. The elimination rates were comparable to maternal tissues with no apparent long-term tissue retention.

Dermal distribution kinetics of efinaconazole in guinea pigs indicates that the highest radioactivity concentration was found on the skin surface, and gradually decreased as depth increased. The radioactivity elimination rate from skin was slow. Efinaconazole was detected within the depth of 300 um from the skin surface including the corneal layer. Efinaconazole is highly plasma protein bound (>97%) in all species including human, and binding is not covalent nor concentration dependent. *In vivo* protein binding is less than values determined *in vitro* suggesting that the plasma metabolites have less binding. Albumin is the major plasma protein that binds efinaconazole. Drug interactions due to plasma protein binding are not expected based on the very low plasma levels observed in the clinical maximal use PK study in diseased toenails.

Efinaconazole is extensively metabolized. It is oxidatively metabolized, cleaved and conjugated to glucuronic acid. The studies have identified 5 metabolites (H1, H2, H3, H4 and H5) of efinaconazole. In rats and minipigs, H3 was the major efinaconazole plasma metabolite, and its levels usually equaled or exceeded those of parent drug. The *in vitro* and *in vivo* metabolite profiles in nonclinical species were similar to human with no unique human metabolite(s).

Efinaconazole metabolites, but not parent drug, were excreted in the bile and urine of rats and dogs which suggests complete metabolism of efinaconazole prior to excretion. Most of the absorbed radioactivity was eliminated during the first 72 hours after dermal and SC dosing in urine and feces. The excretion was roughly same between bile and urine. Efinaconazole and or its metabolites were excreted in milk from lactating rats. The radioactivity concentration in milk was higher than that in plasma concentration for 24 hours after the administration of 14C-efinaconazole to lactating rats. However, the elimination half-life of the milk radioactivity was about one half of that of the plasma radioactivity, suggesting that efinaconazole or its metabolites was not retained in milk.

Efinaconazole inhibits several CYP450 isoforms, CYP2C8, CYP2C9, CYP2C19 and CYP3A4, but is less inhibitory than other therapeutic antifungals based on *in vitro* testing. The most sensitive isoform, CYP2C9, has a K_i that was at least 10-fold higher than peak efinaconazole plasma level in onychomycotic subjects and hence, no drug interactions are expected. There were some signs of possible enzyme induction, i.e. increased liver weight, centrilobular hypertrophy, and decreased plasma drug levels after repeated dosing, in some of the toxicology studies. However, efinaconazole did not induce CYP1A2 or CYP3A4 enzymatic activity in human hepatocyte preparations and no drug interactions due to CYP induction are expected in clinical use.

Microbiology

Activity *In Vitro* and *In Vivo*

Efinaconazole has been shown to be active both *in vitro* and in clinical studies for the treatment of toenail infections involving the following microorganisms:

Trichophyton mentagrophytes
Trichophyton rubrum

Efinaconazole is active *in vitro* against strains of the following organisms; however, the safety and effectiveness of efinaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials:

Candida albicans
Trichophyton tonsurans
Trichophyton verrucosum
Trichophyton schoenleinii
Epidermophyton floccosum
Scopulariopsis brevicaulis
Acremonium spp.
Fusarium spp.
Candida parapsilosis
Candida krusei
Candida tropicalis
Microsporum canis

Activity in Animal Models

In a guinea pig model of onychomycosis with *T. rubrum* infection, JUBLIA reduced nail mycological burden by reducing the number of fungi and preventing nail destruction.

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 suggested low resistance development potential. The clinical significance of these *in vitro* results is unknown.

TOXICOLOGY

Acute Toxicity

Assessments of efinaconazole acute toxicity were conducted in rat via dermal and subcutaneous (SC) administration, in mice via intraperitoneal administration, and in dog via dermal administration. Efinaconazole was well tolerated in both genders of all 3 species, with all LD_{50} values higher than 0.5 to 2 grams/kg.

Long Term Toxicity

The long term toxicity of efinaconazole was evaluated in minipig and mouse via dermal administration and in rats via subcutaneous administration.

Efinaconazole was generally well tolerated in rats with repeated daily doses of up to 30 (males) and 40 (females) mg/kg. The high doses were the maximum tolerated doses, based on increased frequency of severe injection site reactions and a 17% average lower body weight in males compared to controls. No target organs of toxicity were identified at any dose level. Administration of the propylene glycol Vehicle at 2 mL/kg over 6 months was not well tolerated and resulted in mortalities in all groups; Vehicle-related effects included severe dermal clinical signs, and gross and microscopic pathology findings at the injection sites. Early death in several efinaconazole-treated rats was attributed to spinal cord necrosis and urinary tract disease; these lesions also were noted in control rats and were attributed to the spread of injection site reactions (necrosis, abscessation). The NOAEL was determined to be 10 mg/kg/day in both male and female rats which had an exposure of 70 folds or more for efinaconazole and metabolite H3 as compared to human exposure levels.

In dermal toxicity studies, efinaconazole was well tolerated in minipigs at doses up to 150-200 mg /kg/day. Slight to moderate skin reactions were noted macroscopically and microscopically in all test article groups and Vehicle control and consisted of hyperkeratosis, acanthosis and localized inflammation. These skin effects were attributed to the Vehicle and were not considered adverse due to the mild severity of changes. Microscopic skin changes were resolved by the end of the drug-free recovery period. No target organs were identified at the high dose, which was the maximum feasible dose based on test article solubility and application rate. The NOAEL, established by the 30% strength, was determined to be >150 mg/kg/day which had an exposure of 208 folds for efinaconazole as compared to human exposure levels.

In 13 week dermal toxicity in mice, the systemic exposure to efinaconazole was much higher as compared to minipig. In this study an increase in liver weight and minimal to mild panlobular hepatocellular hypertrophy was observed 30% IDP-108, the local application of IDP-108 and/or the vehicle alone resulted in higher incidences of hyperkeratosis, epidermal hyperplasia, and mononuclear infiltrates in the treated skin. Higher concentration of the test article of 10% and 30% IDP-108 were associated with higher severity of these cutaneous changes compared to controls, and a low incidence of the formation of erosion/ulcers at the treated site. The NOAEL, established by the 30% strength which had an exposure of 700 folds or more for efinaconazole as

compared to human exposure levels.

Genotoxicity

Efinaconazole was not mutagenic in a bacterial reverse mutation assay and was not clastogenic in mouse micronucleus and CHL cell chromosomal aberration tests.

Carcinongenicity

In a 2-year dermal carcinogenicity study in mice, efinaconazole showed no evidence of carcinogenicity at doses of up to 140 mg/kg/day (equivalent to approximately 16 and 248 times the clinical maximum use dose based on mg/m^2 and AUC, respectively).

Reproductive and Developmental Toxicity

In a fertility and early embryonic development study, subcutaneous efinaconazole administration to rats at doses up to 25 mg/kg/day had no effect on fertility in males or females. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but did not have effects at 5 mg/kg/day (equivalent to 58 times the clinical maximal use dose based on AUC).

Efinaconazole was tested for developmental toxicity in pregnant rats and rabbits via subcutaneous administration. At maternally toxic doses, efinaconazole was embryofetal and neonatal lethal in rats but not teratogenic at ≥89 times the AUC at the clinical maximal use dose. The maximal use dose in onychomycosis patients assumes ~42 mg/day efinaconazole (~420 mg/day JUBLIA to all 10 toenails). At lower maternally toxic doses, efinaconazole produced rat placental changes (increased weight and size, and decidua cell vacuolation) and the no observed adverse effect level (NOAEL) was 2 mg/kg/day (equivalent to 10 times the AUC in onychomycosis patients). The rat pre/postnatal NOAEL was 22 times the AUC in onychomycosis patients. In rabbits, efinaconazole was maternally toxic but did not affect embryofetal development at the high dose of 10 mg/kg/day (equivalent to 154 times the AUC in onychomycosis patients).

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PART III: CONSUMER INFORMATION

^{Pr}JUBLIA™
Efinaconazole Topical Solution, 10% w/w

This leaflet is part III of a three-part "Product Monograph" published when JUBLIA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JUBLIA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
JUBLIA is used on the toenail (topical) to treat a fungal infection (onychomycosis) caused by certain fungi (*Trichophyton species*). It is not known if JUBLIA is safe and effective in children.

What it does:
JUBLIA blocks the production of ergosterol, an important part of the fungal membrane leading to loss of proper function, fungal death and reduction of the infection.

When it should not be used:
Do not use JUBLIA if you are allergic to efinaconazole or any of the ingredients in JUBLIA (see What the nonmedicinal ingredients are).

What the medicinal ingredient is:
Efinaconazole

What the nonmedicinal ingredients are:
Alcohol, butylated hydroxytoluene, C12-15 alkyl lactate, citric acid, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

What dosage forms it comes in:
JUBLIA contains efinaconazole 10% w/w in a clear solution for topical application.

WARNINGS AND PRECAUTIONS

JUBLIA is not for eyes, mouth, nose, lips or intravaginal use. Avoid contact of JUBLIA with your eyes, mouth, nose, lips, or open wounds. It is for external use on toenails and immediately adjacent skin only. **In case of accidental contact rinse thoroughly with water. Consult with your healthcare provider if symptoms persist.**

Flammable:
JUBLIA is flammable; keep away from heat or flame.

Avoid the use of toenail polish, cosmetic toenail products, or having non-healthcare professional provided pedicures while using JUBLIA.

BEFORE you use JUBLIA talk to your doctor or pharmacist if you:

- are allergic to efinaconazole or any of the ingredients in JUBLIA.
- have any other skin or nail infection.
- are pregnant or plan to become pregnant. It is not known if JUBLIA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if JUBLIA passes into your breast milk.
- have any HIV infections, uncontrolled diabetes, other infections or a history or signs of immunosuppression (e.g. you can get infections easily).

INTERACTIONS WITH THIS MEDICATION

Drug interaction studies have not been done for JUBLIA.

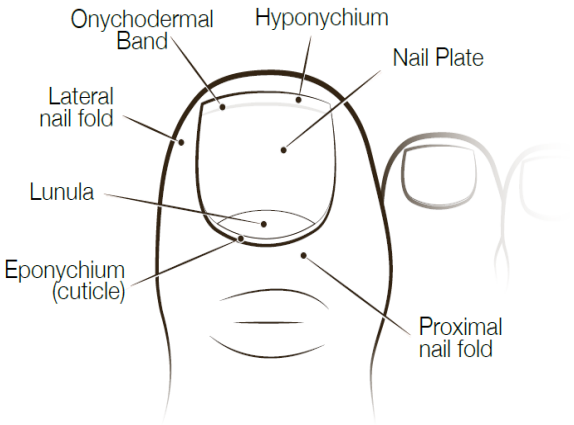
Tell your healthcare provider about all the medicines and skin products you use, including prescription and nonprescription medicines, vitamins, and herbal supplements. Use of other onychomycosis therapies with JUBLIA has not been assessed.

PROPER USE OF THIS MEDICATION

To help clear up your infection completely, it is important that you keep taking JUBLIA for the prescribed treatment period determined by your doctor, even if your symptoms begin to clear up. Stopping JUBLIA too soon may cause the infection to restart.

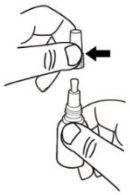
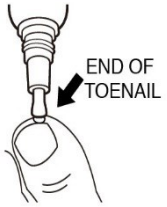
Usual adult dose:
Apply JUBLIA once daily to clean dry toenails. Wait for at least 10 minutes after showering, bathing, or washing before applying. Use JUBLIA only on the affected toenails, as directed by your healthcare provider. No removal of dead, damaged, or infected tissue is needed.

TOENAIL



Clip your toenails every four weeks and always discard the clippings. Be sure to clip unaffected toenails before clipping affected toenails. To avoid the possibility of spreading the infection, do not share toenail clippers with others. Be sure to clean the toenail clippers after each use. Daily clipping of the toenails is not needed.

Apply JUBLIA as follows:

Step 1: Remove the cap from the JUBLIA bottle.	
Step 2: For FIRST APPLICATION on DAY 1: Hold the bottle upside down directly over the affected toenail and **gently squeeze** the bottle to wet the brush. The entire brush will become moistened with the solution.	
Step 3: For all subsequent applications: Hold the bottle upside down and apply one drop of JUBLIA onto the toenail. The bottle may be gently squeezed to re-wet the brush if needed.	
Step 4: For the big toenail, also apply a second drop to the end of the toenail using the tip of the brush.	
Step 5: Using the applicator brush attached to the bottle **gently** spread the solution around the cuticle, folds of the skin next to the sides of the toenail, and underneath the toenail, if possible. **Do not squeeze** the bottle while spreading the solution. **Do not press or rub** the brush firmly against the toenail.	
Step 6: Repeat Steps 3 to 5 for all affected toenails. The affected toenails, other than the big toenails, require one drop of JUBLIA.	
Step 7: After applying JUBLIA, the entire toenail and surrounding skin should briefly glisten with a layer of the solution. Let the treated area dry before covering it with bedding, socks or other clothing.	
Step 8: Replace the cap tightly on the bottle when finished and store upright.	
Step 9: Wash your hands with soap and water after applying JUBLIA.	

JUBLIA is for external use only.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Try not to miss any doses. If you miss a dose of JUBLIA, apply it as soon as possible. However if it is almost time for your next dose, skip the missed dose and resume the normal dosing schedule of once a day. Do not double the doses and never make up for the missed dose. Take as prescribed by your healthcare provider.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, JUBLIA can cause side effects, although not everybody gets them.

Possible side effects of JUBLIA include: skin irritation around the toenail such as redness, itching, burning, or stinging in the surrounding skin. Stop use of JUBLIA and call your healthcare provider if you develop a severe skin rash or the skin becomes very red, itchy, swollen, blistered, or crusted.

Tell your healthcare provider if you have any side effects that bother you or that do not go away**.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Skin reactions (skin irritation around the toenail such as redness, itching, burning, or stinging in the surrounding skin)	✓		
Uncommon	Serious skin reactions (skin develops a rash, becomes very red, itchy, swollen, blistered or crusted)			✓

This is not a complete list of side effects. For any unexpected effects while taking JUBLIA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep JUBLIA and all medicines out of the reach and sight of children.

Store at controlled room temperature (15-30°C).
Store in an upright position.
Keep away from heat or open flame.
Keep the bottle tightly closed when not in use.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor:

Valeant Canada LP
2150 St. Elzéar Blvd., West
Laval, QC, H7L 4A8
1-800-361-4261

Or online at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html

This leaflet was prepared by Valeant Canada LP.

For more information on how to use Jublia, please consult www.jublia.ca

Last revised: July 7, 2017