Onychomycosis Therapy: JUBLIA® (efinaconazole) topical solution, 10% and KERYDIN™ (tavaborole) topical solution, 5%

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Jublia (efinaconazole) topical solution is an azole (triazole class) antifungal agent indicated for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Kerydin (tavaborole) topical solution is an oxaborole antifungal agent indicated for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

Onychomycosis is a common dermatological condition. It is an infection of the nail apparatus caused by fungi that include dermatophytes, non-dermatophyte molds and yeasts (mostly Candida species). The toenails are affected in 80% of cases. Dermatophyte infection due to *Trichophyton rubrum* and/or *Trichophyton mentagrophytes* are the cause in over 90% of cases. Onychomycosis is characterized by thickening of the distal end of the nail associated with some loosening or separation of the nail plate from the nail bed (onycholysis), and buildup of debris in the space created by the onycholysis (subungual hyperkeratosis). The nail plate turns yellow and vertical
bundles appear at the distal end of the nails. These foot infections are not life-threatening but it may cause discomfort and pain.

Onychomycosis may be classified clinically as distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), candidal onychomycosis and total dystrophic onychomycosis. Any of these may eventually progress to total nail dystrophy where the nail plate is almost completely destroyed. DLSO accounts for the majority of cases and is almost always due to dermatophyte infection. SWO is also nearly always due to a dermatophyte infection, most commonly *Tricophyton mentagrophytes*. It is much less common than DLSO. Only about 50% of nail dystrophy cases are caused by fungi making it important to establish the cause to rule out other conditions with similar presentations such as psoriasis and nail trauma. Despite this most onychomycosis is treated based on clinical presentation alone.

Treatment should be initiated only with mycological confirmation of infection. Laboratory diagnosis consists of direct microscopy to visualize fungal elements in the nail sample and culture to identify the species. The relative efficacy of different antifungal agents against different fungi is not completely understood and is poorly described due to use of different doses and dose scheduling, differing endpoints in the clinical studies, length of treatment, and lack of active comparisons. A common surrogate measure of efficacy is mycologic cure rate defined as having negative potassium hydroxide (KOH) on microscopy and negative fungal culture. Another measure used to assess efficacy is complete cure which is defined as no clinical involvement of the target nail plus negative KOH and negative culture. Mycologic cure rates are numerically better than clinical cure rates and as a result may overemphasize efficacy of treatment.

Both topical and oral agents are available for the treatment of fungal nail infection. The goal of treatment is to eradicate the causative organism as demonstrated by microscopy and culture. There are several topical antifungal preparations available both as prescription only medicines and over-the-counter products. Topical therapy may be useful for the treatment of SWO and in very early cases of DLSO where the infection may be confined to the distal edge of the nail. Systemic therapy is more successful than topical treatment. Treatment of onychomycosis with these agents is for durations of usually months.

Agents used to treat onychomycosis include oral Terbinafine, oral Itraconazole, oral Fluconazole (for Candida species), topical Efinaconazole (Jublia), topical Tavaborole (Kerydin) and topical Ciclopirox nail lacquer. There are no clinical trials that compare oral antifungal agents to topical agents. However, oral agents appear to achieve higher mycological cures than those seen with topical agents. Oral Terbinafine is said to be the most effective agent and is considered first line treatment. When used continuously the mycologic cure rate is 76%; when used intermittently the mycologic cure rate is 59%. Oral Itraconazole is recommended when Terbinafine cannot be used. It has a mycologic cure rate of 63% with pulse dosing and 59% with continuous dosing. The absolute mycologic cure rate for Jublia is 36.5-38.4% (Jublia package insert). The absolute mycologic cure rate for Kerydin is 23.7-23.9 (Kerydin package insert). The absolute mycologic cure rate for topical Ciclopirox is 18-27% (package insert Penlac).

A meta-analysis of onychomycosis treatments found the risk of severe liver injury or asymptomatic elevations of serum transaminases with all agents to be less than 2%.
Onychomycosis Therapy: JUBLIA® (efinaconazole) topical solution, 10% and KERYDIN™ (tavaborole) topical solution, 5% (cont.)

Jublia (efinaconazole) inhibits fungal lanosterol 14-alpha demethylase that is involved in the biosynthesis of ergosterol, an integral component of fungal cell membrane. Safety and effectiveness in pediatric individuals has not been established.

Kerydin (tavaborole) inhibits fungal protein synthesis by inhibiting aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS). Safety and effectiveness in pediatric individuals has not been established.

Coverage is dependent on individual member plan benefit.

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline
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- **Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

- **Contraindication**
  Use of a drug that is not recommended by the manufacturer or FDA labelling
  
  Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

- **Non-adherence**
  Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

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**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

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**Criteria:**

See “Resources” section for FDA-approved dosage.

- Precertification for Jublia and Kerydin requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacy precert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Jublia and Kerydin is considered **medically necessary** with medical record documentation of **ALL** of the following:
  1. Individual is 18 years of age or older
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2. Medical record documentation of a diagnosis of onychomycosis of toenail(s)

3. Medical record confirmation the causative organism is EITHER:
   - *Trichophyton rubrum*
   - *Trichophyton mentagrophytes*

4. Individual cannot use both oral Terbinafine and Itraconazole due to ONE of the following:
   - Use of oral agents resulted in worsening of condition or no improvement
   - Experienced a significant adverse drug event while on oral agents
   - Has a documented contraindication to use of oral agent evidenced by:
     - For Terbinafine and Itraconazole: Pre-existing liver disease
     - For Itraconazole: Evidence of ventricular dysfunction such as heart failure or history of heart failure

- Jublia and Kerydin for all other indications not previously listed is considered experimental or investigational based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

**Resources:**


Onychomycosis Therapy: JUBLIA® (efinaconazole) topical solution, 10% and KERYDIN™ (tavaborole) topical solution, 5% (cont.)

FDA-approved indication and dosage:

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<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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| JUBLIA is an azole antifungal indicated for the topical treatment of onychomycosis of the toenails due to Trichophyton rubrum and Trichophyton mentagrophytes. | 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.  
For topical use only.  
Not for oral, ophthalmic, or intravaginal use. |
| KERYDIN is an oxaborole antifungal indicated for the topical treatment of onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes. | Apply KERYDIN to affected toenails once daily for 48 weeks.  
KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated.  
KERYDIN is for topical use only and not for oral, ophthalmic, or intravaginal use. |