Measure Title: HEPATIC ENZYME MONITORING FOR PERSONS USING ANTIMYCOTIC PHARMACOTHERAPY (TERBINAFINE AND ITRACONAZOLE)

Disease State: Liver Disease

Indicator Classification¹: Medication Monitoring

Strength of Recommendation²: A

Clinical Intent: To ensure that all eligible members who have a new prescription for certain antimycotic pharmacotherapy receive the necessary pre-treatment evaluation.

Physician Specialties: Refer to PQSR 2007 Specialty Matrix

Clinical Rationale

Disease Burden
- The product monograph for terbinafine states that “Rare cases of liver failure, some leading to death or liver transplantation, have occurred with the use of terbinafine hydrochloride tablets for the treatment of onychomycosis in individual with and without pre-existing liver disease.”[1]
- The FDA issued a public health advisory about terbinafine and intraconazole citing the association between congestive heart failure and hepatic adverse events with the administration of these therapies.[2]
- The crude incidence rate of acute liver injury associated with itraconazole use is approximately 1:10,000.[3]

Reason for Indicated Intervention or Treatment
- Terbinafine’s hepatotoxic effects are acknowledged in the drug’s product monographs [4], and have been reported multiple times in the literature.[5-18]
- Itraconazole-induced hepatotoxicity is also well-documented in the literature.[3, 19-23]

Evidence supporting Intervention or Treatment
- There are at least 16 case reports in the English literature describing the development of necro-inflammatory and cholestatic hepatotoxicity with terbinafine use [5-17], and at least 5 case reports from non-English literature. [18, 24-27]
- Similarly, multiple case reports have described hepatotoxicity associated with itraconazole use.[19-22]
- A cohort study of 19,488 patients showed that patients taking itraconazole had a relative risk of 17.7 (95% confidence interval 2.6, 72.6) of developing acute liver injury when compared to the risk among nonusers.[3]
- A review of five randomized controlled trials and nonrandomized cohort studies of 442 patients taking itraconazole showed that 1.6% of patients stopped the medication due to hepatotoxicity (95% confidence interval, 1.0-4.2).[28]

Clinical Recommendations

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• The 2005 Physicians' Desk Reference (PDR) recommends pre-treatment serum transaminase (AST and ALT) tests for all patients before starting terbinafine pills, and for patients on the medication with symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper quadrant abdominal pain or jaundice, dark urine or pale stools.[28]

• The PDR strongly discourages the use of itraconazole in patients with elevated or abnormal liver enzymes or active liver disease. As a result, pretreatment serum transaminase (AST and ALT) tests are advised. Liver function monitoring should be done in patients with pre-existing liver function abnormalities and those who have experienced liver toxicity with other medications. Those developing signs and symptoms suggestive of liver dysfunction should also get testing.[28]

• For continuous treatment, the American Academy of Family Physicians recommends checking baseline liver enzyme levels before starting terbinafine or itraconazole, and then testing every four to six weeks during treatment. No testing is suggested for pulse therapy.[29]

Source
Adapted for HMSA from Health Benchmarks, Inc. Standard Algorithm

Denominator
Continuously enrolled members who received a prescription for oral treatment with Lamisil (Terbinafine) or Sporanox (Itraconazole) during the first 358 days of the measurement year.

Exclusion
Members who received a prescription for oral treatment with Lamisil (Terbinafine) or Sporanox (Itraconazole) during the 365 days prior to the index date.

Numerator
Members who received one hepatic enzyme (AST or ALT) test between 3 months prior through 7 days after the index date.

Relevant Billings Codes:
CPT-4 codes: 80053, 80076, 84450, 84460

Interpretation of Score
High score implies better performance

Physician Attribution
Score only the physicians who prescribed the member Lamisil (Terbinafine) or Sporanox (Itraconazole) as qualified in the denominator.
References

1. Novartis, lamisil. 2005, Novartis Pharmaceuticals Corporation: East Hanover, NJ.


23. Somchit, N., et al., Hepatotoxicity induced by antifungal drugs


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1 Indicator Classification (Adapted from Health Plan Employer Data Information Set (HEDIS®) technical specifications)

**Diagnosis**

Measures applicable to patients receiving diagnostic workups for a symptom or condition that delineate appropriate laboratory or radiological testing to be performed (e.g. evaluation of thyroid nodule; pregnancy test in patients with vaginal bleeding or abdominal pain)

**Effectiveness of Care**

**Prevention**

Measures applicable to asymptomatic individuals that are designed to prevent the onset of the targeted condition (e.g. immunizations).

**Screening**

Measures applicable to asymptomatic patients who have risk factors or pre-clinical disease, but in whom the condition has not become clinically apparent (e.g. pap smears; screening for elevated blood pressure).

**Disease Management**

Measures applicable to individuals diagnosed with a condition that are part of the treatment or management of the condition (e.g. cholesterol reduction in patients with diabetes; radiation therapy following breast conserving surgery; appropriate follow-up after acute event).

**Medication Monitoring**

Measures applicable to patients taking medications with narrow therapeutic windows and/or potential preventable significant side effects or adverse reactions (e.g. thyroid stimulating hormone (TSH) testing after levothyroxine dose change; hepatic enzyme monitoring for patients using antimycotic pharmacotherapy)

**Medication Adherence**

Measures applicable to patients taking medications for chronic conditions that are designed to assess patient adherence to medication (e.g. adherence to lipid lowering medication).

**Utilization**

Measures applicable to patients receiving treatment for a symptom or condition that advocate appropriate utilization of laboratory and pharmaceutical resources (e.g. conservative use of imaging for low back pain; inappropriate use of antibiotics for viral upper respiratory infection).
2 Strength of Recommendation

Strength of Recommendation Based on a Body of Evidence

Is this a key recommendation for clinicians regarding diagnosis or treatment that merits a label?  
Yes

Is the recommendation based on patient-oriented evidence (i.e., an improvement in morbidity, mortality, symptoms, quality of life, or cost)?  
Yes

Is the recommendation based on opinion, bench research, a consensus guideline, usual practice, clinical experience, or a case series study?  
No

Is the recommendation based on one of the following?  
• Cochrane Review with a clear recommendation  
• USPSTF: Grade A recommendation  
• Clinical Evidence rating of Beneficial  
• Consistent findings from at least two good-quality randomized controlled trials or a systematic review/meta-analysis of same  
• Validated clinical decision rule in a relevant population  
• Consistent findings from at least two good-quality diagnostic cohort studies or systematic review/meta-analysis of same  
Yes

No

Strength of Recommendation not needed

Strength of Recommendation = C

Strength of Recommendation = A

Strength of Recommendation = B

FIGURE 2. Algorithm for determining the strength of a recommendation based on a body of evidence (applies to clinical recommendations regarding diagnosis, treatment, prevention, or screening). While this algorithm provides a general guideline, authors and editors may adjust the strength of recommendation based on the benefits, harms, and costs of the intervention being recommended. (USPSTF = U.S. Preventive Services Task Force)