Prior Authorization Guidelines
Antidepressants with Cytochrome P450 Mediated Drug Interactions

TCA with fluoxetine (strong 2D6 inhibitor)
TCA with paroxetine (strong 2D6 inhibitor)
TCA with bupropion (moderate 2D6 inhibitor)
TCA with duloxetine (moderate 2D6 inhibitor)
TCA with sertraline (moderate-weak 2D6 inhibitor)
Clomipramine with fluvoxamine (strong 1A2 inhibitor)

Background:
Tricyclic antidepressants (TCAs) continue to be utilized as a treatment option for depression. The pharmacokinetics of TCAs are characterized by substantial presystemic first-pass metabolism, a large volume of distribution, extensive protein binding, and an elimination half-life averaging about 1-3 days. Metabolic clearance of tricyclics is dependent primarily on hepatic Cytochrome P450 (CYP) oxidative enzymes. The activities of some P450 isoenzymes may be influenced by the concomitant use of other medications. Patient variables, such as gender, ethnicity and age, also affect TCA metabolism. Metabolism of TCAs, especially their hydroxylation, results in the formation of active metabolites, which contribute to both the therapeutic and the adverse effects of these compounds.

SSRIs vary in their ability to cause clinically significant drug interactions based upon the inhibition of the liver Cytochrome P450 (CYP) isoenzymes. When a drug, that is a potent inhibitor of one or more of the CYP isoenzymes, is combined with a narrow therapeutic index medication, toxicity may result. As stated above, tricyclic antidepressants (TCAs) are dependent upon CYP2D6 for metabolism; clomipramine is dependent upon CYP1A2. Serious, life threatening side effects may occur very rapidly when TCAs are combined with potent inhibitors of these enzymes. It is of the utmost importance that Providers are knowledgeable of the interaction potential. The monitoring requirements for these drugs are critical to safe prescribing. For these reasons, Providers must submit a Prior Authorization Request for drugs prescribed in the combinations that are listed above.

Approved Behavioral Health Indications:
Treatment Resistant Depression
Obsessive Compulsive Disorder (clomipramine with fluvoxamine)

Guidelines for Approval:
1. Approval will be granted when a member is transitioning from one medication to another.
2. Evidence of adequate trials of at least three (3) individual formulary antidepressants, from at least two (2) different therapeutic classes, for 4-6 weeks at maximum tolerated doses. Failure is due to:
   a. Break through symptoms or an inadequate response at maximum tolerated doses, or
   b. Adverse reaction(s)

And
3. Documentation confirming that trials of at least two (2) evidenced based augmentation strategies have been tried for an adequate trial and failed, resulted in significant side effects, or are contraindicated. Examples of augmentation strategies include lithium, thyroid hormone, bupropion, mirtazapine, quetiapine, or aripiprazole. Failure is due to:
   a. Inadequate response at maximum tolerated doses,

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4. Initial TCA treatment should be initiated at the lowest possible dosage.
5. Supporting clinical documentation must be provided with the initial prior authorization request.
   These parameters include the following:
   a. Assessment showing there is no evidence of cardiovascular conduction delays,
   b. Heart rate,
   c. Blood pressure, and
   d. TCA levels.

Additional Requirements:
1. Provider must provide supporting documentation that:
   a. Adherence to the treatment regimen is not a contributing factor to the inadequate
      response to the medication trials,

Coverage is Not Authorized for:
1. Members with known hypersensitivity to the requested medication(s).
2. Prior Authorization Requests that do not meet the above stated criteria.
3. Members currently taking an MAOI medication.

References:
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2. American Psychiatric Association Practice Guideline for the Treatment of patients with Major
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3. Preskorn, Sheldon H. The Potential for Clinically Significant Drug-Drug Interactions involving the
   CYP 2D6 system: Effects with Fluoxetine and Paroxetine versus Sertraline. Journal of Psychiatric
4. Spina E; Trifiro G; Caraci F. Clinically Significant Drug Interactions with Newer Antidepressants.
5. Indiana University Division of Clinical Pharmacology P450 Drug Interaction Table.
   \url{http://medicine.iupui.edu/clinpharm/ddis/table.aspx} Accessed 7/2/13
   Pharmacokinet. 1995;29 Suppl 1:26-31; discussion 31-2
7. Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Study
8. Rush AJ; Trivedi MH; Stewart JW; et al. Combining Medications to Enhance Depression Outcomes
   (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. Am J