DESCRIPTION:

Tetrabenazine (Xenazine) acts as an inhibitor of vesicular monoamine transporter 2 (VMAT2), leading to depletion of dopamine and other monoamines (norepinephrine and serotonin) in the central nervous system. Ultimately its actions as a monoamine depleting agent and dopamine receptor blocker translate to improvement in symptoms associated with Huntington’s disease (HD). Tetrabenazine was granted orphan drug status by the US Food and Drug Administration (FDA) for the treatment of chorea in people with Huntington’s disease in 1997; in 2008 tetrabenazine received FDA-approval in this setting.

HD is characterized by a triad of movement disorder, cognitive decline, and behavioral changes. Although chorea is the prototypical movement disorder in HD and is usually present with middle-age or elderly onset, the full spectrum of motor impairment in HD includes eye movement abnormalities, parkinsonian features and dystonia, myoclonus, tics, ataxia, dysarthria and dysphagia, spasticity with hyperreflexia, and extensor plantar responses. Symptomatic treatment of chorea is needed if it causes functional disability or social embarrassment. With the exception of tetrabenazine, a variety of available agents (e.g., amantadine, neuroleptics, atypical antipsychotics) have been used, with inconsistent or little benefit. The safety and efficacy of tetrabenazine in the management of chorea associated with HD is based principally on results from a randomized, double-blind, placebo controlled study (n=84). Subjects were randomized to tetrabenazine (titrated over 7 weeks followed by a 5-week maintenance phase) or placebo (titrated over 7 weeks followed by a 5-week maintenance phase). The primary efficacy endpoint was the improvement in the Unified Huntington’s Disease Rating Scale (UHDRS) total chorea score. The total chorea score during the maintenance period was reduced from baseline by an estimated 5 units in the tetrabenazine group compared with an estimated 1.5 units in the placebo group; these results corresponded to a treatment-related reduction in the total chorea score of 23.5% (3.5 units), which was considered to be both statistically and clinically significant. An open-label extension of this study
demonstrated continued efficacy of tetrabenazine in suppressing chorea due to Huntington’s disease for up to 80 weeks.

Tetrabenazine has been evaluated for the treatment of other involuntary movement disorders, including tardive dyskinesia (TDk). TDk is a persistent drug-induced hyperkinetic movement disorder that is most commonly associated with use of central dopamine receptor-blocking agents (e.g., metoclopramide, neuroleptic agents, haloperidol). The management of TDk is challenging; although there are several interventions available, no single agent has been identified as a definitive therapy for TDk. The proposed efficacy of tetrabenazine in the management of symptoms associated with TDk is primarily supported by retrospective studies that included small numbers of subjects. Additionally, the majority of studies do not include a control group and do not report statistical values. The largest prospective study was a single-blind, open-label study conducted by Ondo et al and evaluated subjects who did not respond to conventional anti-TDk treatment. Subjects were included if they had discontinued the offending medication(s) and any other treatment for TDk at least 30 days prior to entering the study. The primary endpoint was the mean change in the modified Abnormal Involuntary Movement Scale (AIMS) motor subset score pre-treatment to post-treatment. The scores were calculated based on the subjects’ motor functioning as assessed via a videotape recording. The mean tetrabenazine dose was 57.9 mg per day and the mean score on the AIMS motor subset improved 54.2% from 17.9 (SD=4.4) to 8.2 (SD=5.3) (p<0.001). This study has several limitations; it is subject to the usual limitations of any open-label trial and it did not include a control arm.

Deutetrabenazine is a VMAT2 inhibitor that was FDA approved in April 2017. It is structurally similar to tetrabenazine but contains a deuterium atom that alters the pharmacokinetics to prolong half-life and decrease peak concentrations of the active metabolite. This results in less frequent daily dosing and the potential for less adverse reactions.

Deutetrabenazine was evaluated in 90 patients with Huntington’s disease in a randomized, double-blind, placebo-controlled trial. All patients enrolled had a UHDRS total maximal chorea score of 8 or higher (range 0-28) at baseline. The patients received therapy titrated over 8 weeks followed by 4 weeks of maintenance therapy and one week washout. The primary endpoint was the change in the total maximal chorea score from baseline (week 0) to maintenance therapy (week 9 and week 12). Deutetrabenazine significantly improved the total maximal chorea score compared to placebo (-4.4 vs. -1.9, difference -2.5; p<0.001). Following a one-week wash out, chorea scores returned to baseline in both treatment groups. Significant improvements were also noted in the following secondary endpoints: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and 36-Item Short Form Health Survey (SF-36). The minimal clinically important differences have not been defined for these endpoints. All of the safety measures were similar between treatment groups with the exception of swallowing disturbance in which deutetrabenazine resulted in improvement. The most common adverse reactions with deutetrabenazine were diarrhea, dry mouth, and somnolence.

The Food and Drug Administration (FDA) approved deutetrabenazine in August 2017 for the treatment of adults with tardive dyskinesia. In 2 separate randomized, double-blind, placebo-controlled trials, deutetrabenazine was evaluated in patients with moderate to severe tardive dyskinesia. Patients enrolled had an underlying psychiatric condition such as schizophrenia, schizoaffective disorder or a mood disorder. Patients were permitted to continue medications for the management of psychiatric conditions if on a stable treatment regimen for at least 30 to 45 days. Patients with a history of suicidal ideation, untreated depression or undertreated psychiatric disease were excluded. The mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score (items 1 through 7) at week 12 was the primary efficacy endpoint. In trial 1, deutetrabenazine at a fixed dose of 24 mg and 36 mg per day significantly decreased dopamine receptor blocker-induced tardive dyskinesia severity.
compared with placebo at week 12, as measured by least-square mean difference from baseline on AIMS Dyskinesia Total score (-3.2 and -3.3 vs -1.4 (p<0.005). In trial 2, deutetabenazine at a mean titrated dose of 38 (8 SD) mg per day also significantly decreased tardive dyskinesia severity compared with placebo at week 12 (-3 vs -1.6, p = 0.019). The most common adverse reactions were insomnia and nasopharyngitis.

**POSITION STATEMENT:**

**Comparative Effectiveness**

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

1. **Tetrabenazine (Xenazine) meets the definition of medical necessity** when used to treat the indications in Table 1, **ALL** of the indication-specific criteria are met and the member meets **ALL** criteria for requested formulation:

   1. Tetrabenazine tablet (generic)
      a. Dosage does not exceed 100 mg daily using the fewest number of tablets per day to permit three times per day dosing
   2. Xenazine®
      a. Member has tried and had intolerable adverse effects to generic tetrabenazine and **ALL** of the following must be submitted:
         i. The specific intolerance(s) to generic tetrabenazine and rationale for use of brand Xenazine must be provided
      b. Dosage does not exceed 100 mg daily using the fewest number of tablets per day to permit three times per day dosing

**Table 1**

<table>
<thead>
<tr>
<th>Indications and Specific Criteria</th>
<th>\textbf{ALL} of the following:</th>
</tr>
</thead>
</table>
| **Chorea associated with Huntington’s disease** | \textbf{A}. Member does not have hepatic dysfunction  
\textbf{B}. Member is not receiving concomitant monoamine oxidase inhibitor (MAOI) therapy (e.g., selegiline [Carbex], rasagiline [Azilect]), reserpine (Serpalan), or an additional |
VMAT2 inhibitor (e.g., deutetrabenazine, valbenazine).

C. Member is not actively suicidal or diagnosed with depression that is untreated or inadequately treated

<table>
<thead>
<tr>
<th>Tardive Dyskinesia</th>
<th>All of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. Member’s tardive dyskinesia has persisted for more than 3 months</td>
</tr>
<tr>
<td></td>
<td>B. ONE of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Member had an inadequate response to alternative approaches to alleviate symptoms (e.g., dose adjustment of the offending agent, discontinuation of the offending agent, switching to an alternative therapy)</td>
</tr>
<tr>
<td></td>
<td>2. Antipsychotic therapy is unable to be adjusted to alleviate symptoms of tardive dyskinesia due to risk of destabilizing the member’s psychiatric condition</td>
</tr>
<tr>
<td></td>
<td>C. Member is not actively suicidal or diagnosed with depression that is untreated or inadequately treated</td>
</tr>
<tr>
<td></td>
<td>D. Member does not have hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>E. Member is not receiving concomitant monoamine oxidase inhibitor (MAOI) therapy (e.g., selegiline [Carbex], rasagiline [Azilect], reserpine [Serpalan], or an additional VMAT2 inhibitor (e.g., deutetrabenazine, valbenazine).</td>
</tr>
</tbody>
</table>

Approval duration: 1 year

II. Continuation of tetrabenazine **meets the definition of medical necessity** for the indications in Table 1 when ALL of the following criteria are met:

A. The member has a beneficial response to tetrabenazine

B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage

C. The member meets the following based on the requested dosage form:

a. Tetrabenazine tablet (generic)

   1. Dosage does not exceed 100 mg daily using the fewest number of tablets per day to permit three times per day dosing

b. Xenazine®

   1. Member has tried and had intolerable adverse effects to generic tetrabenazine and ALL of the following must be submitted:

      i. The specific intolerance(s) to generic tetrabenazine and rationale for use of brand Xenazine must be provided


2. Dosage does not exceed 100 mg daily using the fewest number of tablets per day to permit three times per day dosing

Approval duration: 1 year

III. Initiation of deutetabenazine (Austedo) **meets the definition of medical necessity** when used to treat the indications in Table 2 and **ALL** of the indication-specific criteria are met:

**Table 2**

<table>
<thead>
<tr>
<th>Indications and Specific Criteria</th>
<th>ALL of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chorea associated with Huntington’s disease</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. Member has tried and had an inadequate response or intolerable adverse effects to tetrabenazine - the specific intolerance(s) and rationale for using Austedo must be provided</td>
</tr>
<tr>
<td></td>
<td>B. Member does not have hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>C. Member is not receiving concomitant monoamine oxidase inhibitor (MAOI) therapy (e.g., selegiline [Carbex], rasagiline [Azilect]), reserpine (Serpalan), or an additional VMAT2 inhibitor (e.g., tetrabenazine, valbenazine).</td>
</tr>
<tr>
<td></td>
<td>D. Member is not actively suicidal or diagnosed with depression that is untreated or inadequately treated</td>
</tr>
<tr>
<td></td>
<td>E. The dose does not exceed 48 mg daily using the fewest number of tablets per day to permit twice daily dosing</td>
</tr>
<tr>
<td><strong>Tardive Dyskinesia</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. Member’s tardive dyskinesia has persisted for more than 3 months – documentation must be provided</td>
</tr>
<tr>
<td></td>
<td>B. Member’s tardive dyskinesia is moderate to severe (i.e., score of 3 or 4 on item 8 of the Abnormal Involuntary Movement Scale (AIMS)) – documentation must be provided</td>
</tr>
<tr>
<td></td>
<td>C. <strong>ONE</strong> of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Member had an inadequate response to alternative approaches to alleviate symptoms (e.g., dose adjustment of the offending agent, discontinuation of the offending agent, switching to an alternative therapy) – documentation must be provided</td>
</tr>
<tr>
<td></td>
<td>2. Antipsychotic therapy is unable to be adjusted to alleviate symptoms of tardive dyskinesia due to risk of destabilizing the member’s psychiatric condition –</td>
</tr>
</tbody>
</table>
IV. Continuation of deutetrabenazine meets the definition of medical necessity for the indications in Table 2 when ALL of the following criteria are met:

1. The member has a beneficial response to deutetrabenazine
2. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage
3. The dose does not exceed 48 mg daily using the fewest number of tablets per day to permit twice daily dosing

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER’S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

Tetrabenazine:

Chorea associated with Huntington’s disease: The dose is individualized and requires careful weekly titration. The first week’s dose is 12.5 mg daily, followed by 25 mg (12.5 mg twice daily) in the second week; slowly titrate at weekly intervals by 12.5 mg to a tolerated dose that reduces chorea. Doses of 37.5 mg and up to 50 mg per day should be administered in three divided doses per day with the maximum recommended single dose not to exceed 25 mg.
If serious adverse reactions occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consider withdrawal of tetrabenazine.

**Dose Adjustment**

**CYP2D6 metabolism:** Member’s requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if they are a poor metabolizer (PM) or an extensive metabolizer (EM)

The maximum daily dose in PMs is 50 mg, with a maximum single dose of 25 mg

The maximum daily dose in EMs and intermediate metabolizers (IMs) is 100 mg with a maximum single dose of 37.5 mg

**Hepatic Impairment:** The safety and efficacy of the increased exposure to tetrabenazine and other circulating metabolites are unknown, and it is not possible to adjust the dose of tetrabenazine in persons with hepatic impairment. The use in patients with hepatic impairment is contraindicated.

**Strong CYP2D6 Inhibitors:** The dose of tetrabenazine should not exceed 50 mg daily or 25 mg as a single dose when used in members administered strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine).

**Drug Availability:** tetrabenazine is available at 12.5- and 25 mg tablets.

Deutetrabenazine:

**Chorea associated with Huntington’s disease:** The starting dose is 6 mg once daily and should be titrated up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea up to a maximum daily dose of 48 mg (24 mg twice daily).

**Tardive dyskinesia:** The starting dose is 12 mg daily (6 mg twice daily) and should be titrated up at weekly intervals by 6 mg per day to a tolerated dose that reduces tardive dyskinesia up to a maximum daily dose of 48 mg (24 mg twice daily).

Doses of 12 mg or above should be given in two divided doses and swallowed whole.

See prescribing information for converting patients from tetrabenazine.

Deutetrabenazine can be discontinued without tapering but must be retitrated if stopped for greater than one week.

Administer with food and swallow tablets whole; do not crush, break or chew.

**Dose Adjustment**

**QT prolongation:** assess the QT interval before and after increasing total dose above 24 mg per day.

**CYP2D6 metabolism:** In patients who are poor metabolizers of CYP2D6, the maximum daily dose is 36 mg (18 mg twice daily).
**Hepatic Impairment:** The safety and efficacy of the increased exposure to deutetrabenazine and other circulating metabolites are unknown, and it is not possible to adjust the dose in persons with hepatic impairment. The use in patients with hepatic impairment is contraindicated.

**Strong CYP2D6 Inhibitors:** The dose should not exceed 36 mg daily (18 mg twice daily) when used in members administered strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine, bupropion).

**Drug Availability:** Deutetrabenazine is available as 6, 9, and 12 mg tablets.

**PRECAUTIONS:**

**Boxed Warning:**

**Tetrabenazine and Deutetrabenazine**

Treatment with either agent can increase the risk of depression and suicidal thoughts and behavior (suicidality) in persons with Huntington’s disease.

Balance risk of depression and suicidality with the clinical need for control of choreiform movements when considering use of either agent.

Monitor members for the emergence or worsening of depression, suicidality, or unusual changes in behavior.

Inform members, caregivers, and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician.

Exercise caution when treating members with a history of depression or prior suicide attempts or ideation.

Treatment is contraindicated in persons who are actively suicidal, and in those with untreated or inadequately treated depression.

**Contraindications**

**Tetrabenazine and Deutetrabenazine**

Contraindicated in persons with Huntington’s disease who are actively suicidal, or who have depression which is untreated or undertreated.

Contraindicated in those with impaired hepatic function.

Contraindicated in persons receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), reserpine (Serpalan), or an additional VMAT2 inhibitor.

**Warnings**

**Tetrabenazine and Deutetrabenazine**

Periodically reevaluate the benefit of treatment and potential for adverse effects such as worsening mood, cognition, rigidity and functional capacity.
Neuroleptic Malignant Syndrome (NMS). Discontinue therapy if this occurs.

Restlessness, agitation, akathisia and parkinsonism. Reduce dose or discontinue if this occurs.

Sedation/somnolence. May impair the patient's ability to drive or operate complex machinery. Alcohol or other sedating drugs can worsen sedation and somnolence.

Therapy may prolong the QTc interval. Avoid use with a history of congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. Do not prescribe in combination with other drugs that prolong QTc.

Hyperprolactinemia may occur and possibly result in low estrogen and increased risk for osteoporosis.

Binding to melanin-containing can occur and possible ophthalmologic toxicity with long term exposure.

Tetrabenazine

Postural dizziness has occurred. Monitor vital signs on standing in patients vulnerable to hypotension.

Treatment may exaggerate extrapyramidal disorders when used with drugs that reduce or antagonize dopamine. Discontinue if this occurs.

There are no adequate and well-controlled studies in pregnant women.

**BILLING/CODING INFORMATION:**

The following codes may be used to describe:

**HCPCS Coding:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J8499</td>
<td>Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified</td>
</tr>
</tbody>
</table>

**ICD-10 Diagnosis Codes That Support Medical Necessity:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G10</td>
<td>Huntington’s chorea</td>
</tr>
<tr>
<td>G24.01</td>
<td>Drug-induced subacute dyskinesia</td>
</tr>
</tbody>
</table>

**REIMBURSEMENT INFORMATION:**

Refer to section entitled **POSITION STATEMENT**

**PROGRAM EXCEPTIONS:**

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.
Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**DEFINITIONS:**

Chorea: the ceaseless occurrence of a wide variety of rapid, highly complex, jerky, dyskinetic movements that appear to be well coordinated but are performed involuntarily.

Huntington disease: an autosomal dominant disease characterized by chronic progressive chorea and mental deterioration terminating in dementia; the age of onset is variable but usually in the fourth decade of life, with death within 15 years.

**RELATED GUIDELINES:**

09-J2000-81, Valbenazine (Ingrezza)

**OTHER:**

<table>
<thead>
<tr>
<th>Abnormal Involuntary Movement Scale (AIMS)</th>
<th>Movement Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 = none, 1 = minimal, 2 = mild</td>
</tr>
<tr>
<td></td>
<td>3 = moderate, 4 = severe</td>
</tr>
</tbody>
</table>

I. Facial and Oral Movements

1. Muscles of Facial Expression (e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing) 0 1 2 3 4

2. Lips and Perioral Area (e.g., puckering, pouting, smacking) 0 1 2 3 4

3. Jaw (e.g., biting, clenching, chewing, mouth opening, lateral movement) 0 1 2 3 4

4. Tongue Rate only increases in movement both in and out of mouth, not inability to sustain movement 0 1 2 3 4

II. Extremity Movements

5. Upper (arms, wrists, hands, fingers) Include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous); athetoid movements (i.e., slow, irregular, complex, serpentine). Do not include tremor (ie, repetitive, regular, rhythmic). 0 1 2 3 4

6. Lower (legs, knees, ankles, toes) (e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot) 0 1 2 3 4

III. Trunk Movements

7. Neck, shoulders, hips (e.g., rocking, twisting, squirming, pelvic gyrations) 0 1 2 3 4

IV. Global Judgement

8. Severity of abnormal movements overall 0 1 2 3 4

9. Incapacitation due to abnormal movements 0 1 2 3 4

10. Patient’s awareness of abnormal movements (rate only patient’s report) 0 1 2 3 4
### V. Dental Status

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes or No</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Current problems with teeth and/or dentures?</td>
<td></td>
</tr>
<tr>
<td>12. Does patient usually wear dentures?</td>
<td></td>
</tr>
<tr>
<td>13. Endentia?</td>
<td></td>
</tr>
<tr>
<td>14. Do movements disappear with sleep?</td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES:**


COMMITTEE APPROVAL:
This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19.

GUIDELINE UPDATE INFORMATION:

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/15/09</td>
<td>New Medical Coverage Guideline.</td>
</tr>
<tr>
<td>09/15/09</td>
<td>Revision of guideline; consisting of adding coverage criteria and contraindications.</td>
</tr>
<tr>
<td>04/15/10</td>
<td>Review and revision to guideline; consisting of updating references.</td>
</tr>
<tr>
<td>04/15/11</td>
<td>Review and revision to guideline; consisting of updating references.</td>
</tr>
<tr>
<td>04/15/12</td>
<td>Review and revision to guideline; consisting of add maximum dosage to position statement, updating precautions and references.</td>
</tr>
<tr>
<td>04/15/13</td>
<td>Review and revision to guideline; consisting of reformatting and revising position statement to include treatment of tardive dyskinesia and approval duration; reformatting and revising description, dosage/administration, and precautions section; updated references.</td>
</tr>
<tr>
<td>05/11/14</td>
<td>Revision: Program Exceptions section updated.</td>
</tr>
<tr>
<td>10/15/14</td>
<td>Review and revision to guideline; consisting of reformatting position statement and updating references.</td>
</tr>
<tr>
<td>05/15/15</td>
<td>Revision; updated billing/coding.</td>
</tr>
<tr>
<td>10/15/15</td>
<td>Review and revision to guideline; consisting of revising position statement, updating dosing, coding and references.</td>
</tr>
<tr>
<td>11/01/15</td>
<td>Revision: ICD-9 Codes deleted.</td>
</tr>
<tr>
<td>10/15/16</td>
<td>Review and revision to guideline; consisting of revising position statement and updating references.</td>
</tr>
<tr>
<td>06/15/17</td>
<td>Review and revision to guideline; consisting of revising position statement and updating dosing, warnings/precautions and references.</td>
</tr>
<tr>
<td>07/15/17</td>
<td>Review and revision to guideline; consisting of revising position statement.</td>
</tr>
<tr>
<td>10/15/17</td>
<td>Review and revision to guideline; consisting of updating position statement and references.</td>
</tr>
<tr>
<td>07/15/18</td>
<td>Review and revision to guideline; consisting of updating references.</td>
</tr>
<tr>
<td>07/15/19</td>
<td>Review and revision to guideline; consisting of updating position statement and references.</td>
</tr>
</tbody>
</table>