09-J1000-36

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Reviewed: 03/13/19

Revised: 04/15/19

Subject: Abiraterone Acetate (Yonsa®, Zytiga®) Tablet

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Prostate cancer remains the most common non-cutaneous malignancy among men worldwide. Prostate cancer is a complex disease, with many variable aspects of management. Prostate cancer is an androgen dependent disease that initially responds but later becomes resistant to established therapies that reduce circulating testosterone levels or inhibit androgen binding to androgen receptor (AR). Reactivation of the disease despite castrate levels of testosterone (<50 ng/dL) represents a transition to the lethal phenotype of castration-resistant prostate cancer (CRPC). This state is now recognized to be driven by AR signaling, in part due to overexpression of the androgen receptor itself. In addition, a small percentage of prostate cancer patients (~3%) may be initially diagnosed with metastatic, castration-sensitive prostate cancer (CSPC) for which management remains a challenge. The addition of docetaxel (for those eligible) to androgen deprivation therapy (ADT) has been shown to improve survival in men with CSPC.

Abiraterone is a small molecule inhibitor of 17 alpha-monooxygenase, which is a member of the cytochrome P450 family that catalyzes the 17 alpha-hydroxylation of intermediates of steroid biosynthesis involved in testosterone synthesis. Abiraterone, as brand name Zytiga, was initially approved by the FDA in April 2011 in combination with low-dose prednisone for the treatment of men with metastatic CRPC who have received prior chemotherapy containing docetaxel. This approved was based principally on the results of a phase III, randomized, placebo controlled trial (COU-AA-301, n=1195) in which subjects were randomized to receive either abiraterone 1,000 mg daily or placebo (both arms received concomitant prednisone). The study was unblinded after a pre-specified interim analysis demonstrated a statistically significant improvement in overall survival in subjects receiving abiraterone. The median survival was 15.8 months vs. 11.2 months in the abiraterone and placebo arm, respectively (HR 0.74; 95% CI 0.64 to 0.86, p<0.0001).

In December 2012, the approval of Zytiga was expanded to include the treatment of men with metastatic CRPC as a first-line option (prior to other chemotherapy). The expanded approval is based on a phase III study (COU-AA-302) of over 1,000 male subjects with late-stage CRPC who had not received prior chemotherapy and was designed to measure the length of overall and progression free survival. The median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone (HR 0.53; 95% CI 0.45 to 0.62, p<0.001). In the extended final survival analysis over a median follow-up period of 49.2 months, overall survival was improved with abiraterone-prednisone (34.7 months) vs. 30.3 months for prednisone alone (HR 0.81; 95% CI 0.7 to 0.93, p=0.0033).

In February 2018, the Zytiga indication was broadened to include the treatment of patients with metastatic high-risk, castration-sensitive prostate cancer (CSPC). The safety and efficacy of abiraterone leading to the FDA approval for CSPC was based on the LATITUDE trial, A total of 11,99 patients with newly-diagnosed, metastatic high-risk CSPC were randomized 1:1 to receive either abiraterone 1,000 mg once daily with prednisone 5 mg once daily, or placebos orally once daily. Metastatic disease was confirmed by a positive bone scan or metastatic lesions on CT scan or MRI. High-risk disease was defined as having at least two of three risk factors at baseline: a total Gleason score of ≥8, presence of ≥3 lesions on bone scan, and evidence of measurable visceral metastases. Patients continued treatment until radiographic or clinical disease progression, unacceptable toxicity, withdrawal or death. The primary efficacy outcome was overall survival (OS). The pre-specified interim analysis was conducted after 406 deaths (median follow-up duration of 30.4 months) and showed a statistically significant improvement in OS in patients on abiraterone with prednisone [169 deaths (28%), median OS = not reached] vs. placebo [237 deaths (39%), median OS = 34.7 months] [HR = 0.62; 95% CI: 0.51-0.76, p<0.001]. Twenty-one percent (21%) of patients on the abiraterone arm and 41% of patients on the placebo arm received subsequent therapies that may prolong OS in metastatic CRPC, including cytotoxic chemotherapy, abiraterone acetate, enzalutamide, and systemic radiotherapy. The survival outcomes was supported by a longer radiographic progression-free survival (PFS) time of 33 months in the abiraterone group vs. 14.8 months in the placebo group [HR = 0.47, 95% CI: 0.39-0.55, p<0.001]. There was also a statistically significant delay in time to initiation of chemotherapy for patients in the abiraterone arm vs. the placebos arm. The median time to initiation of chemotherapy was not reached for patients on abiraterone with prednisone and was 38.9 months for patients on placebos (HR = 0.44; 95% CI: 0.35-0.56, p <0.0001). Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.

In May 2018 a new micronized (smaller particle size) abiraterone acetate product, Yonsa, was approved by the FDA via the 505(b)(2) New Drug Application processes for the treatment of patients with metastatic CRPC in combination with methylprednisolone. Yonsa differs from Zytiga in several important ways: (1) Zytiga has an additional FDA-approved indication of treatment of metastatic high-risk CSPC; (2) Yonsa is labeled to be used in combination with methylprednisolone, while Zytiga is labeled to be used in combination with prednisone; (3) Yonsa is a micronized formulation with increase bioavailability and a labeled dosage of 500 mg daily, while Zytiga has a labeled dosage of 1,000 mg daily; (4) Yonsa is available as a 125 mg tablet only, while Zytiga is available as a 250 mg uncoated tablet, 250 mg film-coated tablet, and 500 mg film-coated tablet; and (5) Yonsa is labeled to be taken with or without food, while Zytiga must be given on an empty stomach either one hour before or two hours after a meal. The approval of Yonsa was based on the results of the STAAR study [Serum Testosterone in Response to AA Fine Particle (AAFP) in Metastatic CRPC]. The STAAR study was an 84-day, open-label study comparing Yonsa + methylprednisolone (n=24) against Zytiga + prednisone (n=29), in patients with metastatic CRPC. The primary endpoint was comparative lowering of total testosterone at pharmacokinetic steady-state. Additional secondary endpoints included safety assessments, PSA and pharmacokinetic measurements. Over 90% of patients in each group achieved absolute testosterone levels of ≤1 ng/dL during the study. The averaged absolute testosterone levels ≤0.1 ng/dL were achieved in 25% of AAFP-

treated patients and 17% of OAA-treated patients. A PSA-50 response was observed in>65% of patients in both groups on days 28, 56, and 84 (p=NS, all time points). Days 9 and 10 averaged rounded-up least squares (LS) mean serum testosterone levels were comparable (1.05 ng/dL AAFP vs. 1.02 ng/dL OAA; p=0.4703). The LS mean differences in abiraterone trough plasma concentrations were not statistically significant at any visit, and adverse event frequency was comparable between arms.

The National Comprehensive Cancer Network (NCCN) Prostate Cancer Guidelines (Version 4.2018) list abiraterone + prednisone as a category 1 option for the treatment of metastatic (M1), castration-naïve (or castration-sensitive) disease when used in combination with ADT. Abiraterone + methylprednisolone + ADT (i.e., Yonsa regimen) is given a category 2B recommendation for this patient population. The guidelines also list abiraterone with prednisone as initial therapy for the treatment of metastatic, castration- resistant disease (without visceral metastases - category 1, with visceral metastases – category 2A). Abiraterone + prednisone is also a category 1 option for the treatment of metastatic CRPC in patients without visceral disease following prior docetaxel therapy. Abiraterone + prednisone is considered a category 2A treatment option for patients with or without visceral metastases following enzalutamide (Xtandi) treatment, and as initial therapy for metastatic CRPC patients with visceral metastases. Abiraterone + methylprednisolone (i.e., Yonsa regimen) is listed for all of these same indications but is given a category 2A recommendation for all. The NCCN recommends that patients whose disease progresses to CRPC during primary androgen deprivation therapy (ADT) should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL) has been achieved. The NCCN also includes ADT with or without abiraterone + prednisone (category 2A) or abiraterone + methylprednisolone (category 2B) as treatment options for prostate cancer with regional lymph node involvement (i.e., regional risk group; any T, N1, M0) in patients with an estimated life expectancy of greater than 5 years.

POSITION STATEMENT:

Initiation of abiraterone acetate (Yonsa, Zytiga) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “5”):

1. Member is diagnosed with **ANY** of the following (“a”, “b”, “c”, or “d”) – the TNM staging must be provided for any cancer indication:
    a. Prostate cancer with regional lymph node involvement (i.e., regional risk group; any T, N1, M0)
    b. Metastatic, **castration-sensitive** prostate* cancer (CSPC, a.k.a., castration-naïve or hormone-naïve prostate cancer)

        Castration-sensitive is defined as patients who are **NOT on androgen deprivation therapy (ADT) at the time of disease progression. This definition even applies to patients who have had neoadjuvant, concurrent, or adjuvant ADT as part of radion therapy provided they have recovered testicular function.*

    c. Metastatic, **castration-recurrent** prostate cancer (CRPC, a.k.a., castration-resistant or hormone-refractory prostate cancer) – lab documentation of a recent (past 90 days) serum testosterone level at castrate level (<50 ng/dL) must be submitted for members receiving medical castration. A chart note documenting a bilateral orchiectomy must be submitted for members who have received surgical castration.
    d. FDA-approved or NCCN supported diagnosis other than prostate cancer, and **ONE** of the following is met (“i” or ii”):
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product’s FDA-approved prescribing information (or package insert) **AND** member meets

any additional requirements listed in the “Indications and Usage” section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

2. For the prostate cancer indications only- abiraterone will be used in combination with **BOTH** of the following (“a” and “b”):
    a. Either prednisone or methylprednisolone
    b. Androgen deprivation therapy (ADT) [i.e., either medically-induced or surgical-induced castration]
3. For brand Zytiga **ONLY** – **EITHER** of the following (“a” or “b”):
    a. Member has a contraindication to **BOTH** generic abiraterone **AND** Yonsa, and the contraindication is not applicable to brand Zytiga – the specific contraindication(s) and rationale for using brand Zytiga must be provided
    b. Member has tried and had intolerable adverse effects to **BOTH** generic abiraterone **AND** Yonsa, and the intolerance is not expected to occur with brand Zytiga - the specific intolerance(s) and rationale for using brand Zytiga must be provided
4. The dosage does not exceed the following:
    a. Yonsa - 500 mg (four 125 mg tablets) daily
    b. Zytiga (or generic equivalent) - 1,000 mg (four 250 mg tablets or two 500 mg tablets) daily
5. Abiraterone is not used concomitantly with **ANY** of the following:
    a. apalutamide (Erleada)
    b. cabazitaxel (Jevtana)
    c. docetaxel (Taxotere)
    d. enzalutamide (Xtandi)
    e. mitoxantrone (Novantrone)
    f. other abiraterone product
    g. radium-223 (Xofigo)
    h. sipuleucel-T (Provenge)

Approval duration: 12 months

Continuation of abiraterone acetate (Yonsa, Zytiga) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “6”):

1. An authorization or reauthorization for abiraterone has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of regional or metastatic prostate cancer, or FDA-approved or NCCN-supported diagnosis other than prostate cancer, **OR** the member has previously met **ALL** indication-specific criteria
2. For the prostate cancer indications only - member will continue to receive prednisone or methylprednisolone and ADT (i.e., either medically-induced or surgical-induced castration) during treatment with abiraterone
3. Member has demonstrated a beneficial clinical response to abiraterone therapy
4. For brand Zytiga **ONLY** – **EITHER** of the following (“a” or “b”):

a. Member has a contraindication to **BOTH** generic abiraterone **AND** Yonsa, and the contraindication is not applicable to brand Zytiga – the specific contraindication(s) and rationale for using brand Zytiga must be provided

b. Member has tried and had intolerable adverse effects to **BOTH** generic abiraterone **AND** Yonsa, and the intolerance is not expected to occur with brand Zytiga - the specific intolerance(s) and rationale for using brand Zytiga must be provided

5. Abiraterone is not used concomitantly with **ANY** of the following:
   a. apalutamide (Erleada)
   b. cabazitaxel (Jevtana)
   c. docetaxel (Taxotere)
   d. enzalutamide (Xtandi)
   e. mitoxantrone (Novantrone)
   f. other abiraterone product
   g. radium-223 (Xofigo)
   h. sipuleucel-T (Provenge)
6. The dosage does not exceed the following:
   a. Yonsa – 500 mg (four 125 mg tablets) daily
   b. Zytiga (or generic equivalent) - 1,000 mg (four 250 mg tablets or two 500 mg tablets) daily

Approval duration: 12 months

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.

YONSA

FDA-approved: in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer. The recommended dose is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. To avoid medication errors and overdose, be aware that Yonsa tablets may have different dosing and food effects than other abiraterone acetate products. Unlike Zytiga, Yonsa tablets can be taken with or without food. The tablets should be swallowed whole with water. Do not crush or chew tablets.

Dose Adjustments

- **Baseline moderate hepatic impairment**: For members with moderate hepatic impairment (Child-Pugh class B), the initial dose should be reduced to 125 mg once daily. Do **NOT** use in patients with severe baseline hepatic impairment (Child-Pugh Class C). Monitor ALT, AST and bilirubin prior to therapy initiation, every week for 1 month, every 2 weeks for the following 2 months and monthly thereafter; if elevation in ALT and/or AST exceed 5 times the upper limit of normal (ULN) or total bilirubin exceeds 3 times the ULN, discontinue therapy and do not reinitiate.

- **Hepatotoxicity**: For members with normal hepatic function who develop hepatotoxicity while on therapy:
    - **First elevation**: ALT and/or AST greater than 5 times ULN or total bilirubin 3 times ULN interrupt therapy and reinitiate at 375 mg daily once members levels return to baseline or less than or equal to 2.5 times the ULN for ALT and/or AST or 1.5 times ULN for bilirubin. Monitor ALT, AST and bilirubin at a minimum of every two weeks for three months and monthly thereafter.
    - **Recurrence after reduction to 375 mg**: reinitiate at 250 mg once daily once members LFTs to baseline or less than or equal to 2.5 times the ULN for ALT and/or AST or 1.5 times ULN for bilirubin
    - **Recurrence after reduction to 250 mg**: discontinue therapy
    - Permanently discontinue for patients who develop a concurrent elevation of ALT greater than 3 times ULN and total bilirubin greater than 2 times ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.
- **Strong CYP3A4 Inducers**: Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment if possible. Although there are no clinical data with this dose adjustment, because of the potential for an interaction, if a strong CYP3A4 inducer **MUST** be co-administered, increase the dosing frequency to twice a day only during the co-administration period (e.g., from 500 mg once daily to 500 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued.

Drug Availability: Yonsa is supplied as a 125 mg tablet.

ZYTIGA

FDA-approved: abiraterone is indicated for use in combination with prednisone for the treatment of persons with: (1) metastatic castration-resistant prostate cancer (CRPC), and (2) metastatic high-risk castration-sensitive prostate cancer (CSPC). Although initially approved for CRPC following chemotherapy, the indication was expanded in December 2012 to include treatment prior to treatment with chemotherapy, and then in February 2018 to include metastatic high-risk castration-sensitive prostate cancer (CSPC). Abiraterone should be administered as a 1,000 mg dose (two 500 mg or four 250 mg tablets) once daily in combination with prednisone (5 mg once daily for CSPC or 5 mg twice daily for CRPC). Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Additionally, it should always be taken on an empty stomach to prevent supratherapeutic concentrations. The package insert advises against eating 2 hours before or 1 hour after administration. The tablets should be swallowed whole; do not crust or chew tablets.

Dose Adjustments

- **Baseline moderate hepatic impairment:** For members with moderate hepatic impairment (Child-Pugh class B), the initial dose should be reduced to 250 mg once daily. Do **NOT** use in patients with severe baseline hepatic impairment (Child-Pugh Class C). Monitor ALT, AST and bilirubin prior to therapy initiation, every week for 1 month, every 2 weeks for the following 2 months and monthly thereafter; if elevation in ALT and/or AST exceed 5 times the upper limit of normal (ULN) or total bilirubin exceeds 3 times the ULN, discontinue therapy and do not reinitiate.
- **Hepatotoxicity:** For members with normal hepatic function who develop hepatotoxicity while on therapy:
    - **First elevation:** ALT and/or AST greater than 5 times ULN or total bilirubin 3 times ULN interrupt therapy and reinitiate at 750 mg daily once members levels return to baseline or less than or

equal to 2.5 times the ULN for ALT and/or AST or 1.5 times ULN for bilirubin. Monitor ALT, AST and bilirubin at a minimum of every two weeks for three months and monthly thereafter

- **Recurrence after reduction to 750 mg:** reinitiate at 500 mg once daily once members LFTs to baseline or less than or equal to 2.5 times the ULN for ALT and/or AST or 1.5 times ULN for bilirubin
- **Recurrence after reduction to 500 mg:** discontinue therapy
- Permanently discontinue for patients who develop a concurrent elevation of ALT greater than 3 times ULN and total bilirubin greater than 2 times ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

- **Strong CYP3A4 Inducers:** Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment if possible. Although there are no clinical data with this dose adjustment, because of the potential for an interaction, if a strong CYP3A4 inducer **MUST** be co-administered, increase the dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued.

Drug Availability: abiraterone is supplied as 250 mg film-coated and uncoated tablets and 500 mg film-coated tablets.

PRECAUTIONS:

YONSA and ZYTIGA

CONTRAINDICATIONS

- Pregnancy - can cause fetal harm and potential loss of pregnancy

WARNINGS

Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess: Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Use abiraterone with caution in members with a history of cardiovascular disease. The safety of abiraterone in members with a LVEF less than 50% or NYHA Class III or IV heart failure has not been established. Control hypertension and correct hypokalemia prior to treatment initiation. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly .In the LATITUDE trial which used prednisone 5 mg daily in combination with 1000 mg abiraterone acetate daily, grades 3-4 hypokalemia were detected in 10% of patients on the abiraterone arm and 1% of patients on the placebo arm, grades 3-4 hypertension were observed in 20% of patients on the abiraterone arm and 10% of patients on the placebo arm. Grades 3-4 fluid retention occurred in 1% of patients each arm.

Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue abiraterone dosing as recommended.

Food effect (Zytiga ONLY) - Zytiga must be taken on an empty stomach. Exposure may increase up to 10-fold when abiraterone is taken with meals.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J8999	Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C61	Malignant neoplasm of prostate

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 review 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:

Castrate-resistant/recurrent prostate cancer (CRPC): disease progression despite androgen deprivation therapy (ADT) with either medication or surgery (i.e., removal/destruction of testicles, and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

TNM Classification of Malignant Tumors (TNM): a notation system that describes the stage of a cancer which originates from a solid tumor with alphanumeric codes. T describes the size of the original (primary) tumor and whether it has invaded nearby tissue. N describes nearby (regional) lymph nodes that are involved, M describes distant metastasis (spread of cancer from one part of the body to another).

RELATED GUIDELINES:

Apalutamide (Erleada), 09-J3000-03

Cabazitaxel (Jevtana), 09-J1000-77

Cryosurgical Ablation of the Prostate (CSAP), 02-54000-14

Docetaxel (Taxotere) IV, 09-J0000-95

Enzalutamide (Xtandi), 09-J1000-85

Gonadotropin Releasing Hormone Analogs and Antagonists, 09-J0000-48

Radium Ra 223 (Xofigo) Injection, 09-J2000-01

Sipuleucel-T (Provenge), 09-J1000-29

OTHER:

None

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16. Zytiga (abiraterone acetate) [package insert]. Janssen Biotech, Inc. Horsham (PA): April 2018.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 03/13/19.

GUIDELINE UPDATE INFORMATION:

09/15/11	New Pharmacy Coverage Guideline.
11/15/11	Revision to guideline; consisting of removing 18 years of age requirement for coverage.
09/15/12	Review and revision to guideline; consisting of updating position statement, precautions and references.
02/15/13	Revision to guideline; consisting of adding additional indication to position statement, revising and reformatting description, dosage/administration, precautions section; adding definition and related guidelines; updating references.
04/15/13	Review and revision to guideline; consisting of revising position statement to include approval duration; updating description section and references.
04/15/14	Review and revision to guideline; consisting of reformatting position statement, updating description section, references and program exceptions.
04/15/15	Review and revision to guideline; consisting of description section, position statement to include continuation criteria, dosage/administration, definitions, and references.
04/15/16	Review and revision to guideline consisting of description section, position statement, definitions, and references.
04/15/17	Review and revision to guideline consisting of description section, position statement, precautions section, and references.
07/01/17	Revision to guideline consisting of updating the position statement and dosage/administration section as a result of a new 500 mg tablet strength.
04/15/18	Review and revision to guideline consisting of description section, position statement, precautions section, definitions, and references.
09/15/18	Revision to guideline consisting of description section, position statement, dosage/administration section, precautions section, definitions, and references based on the approval of Yonsa.
12/15/18	Revision to guideline consisting of updating the position statement.
04/15/19	Review and revision to guideline consisting of updating the description section, position statement, and references.