

Reblozyl® (Luspatercept-Aamt)

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[U Instructions for Use](#)

Table of Contents	Page
Applicable States	1
Coverage Rationale	1
Applicable Codes	3
Background	3
Benefit Considerations	4
Clinical Evidence	4
U.S. Food and Drug Administration	6
References	6
Policy History/Revision Information	7
Instructions for Use	8

Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

[U See Benefit Considerations](#)

Reblozyl is proven and/or medically necessary for the treatment of anemia in adult patients with beta thalassemia who meet all of the following criteria:¹⁻⁴

- **Initial Therapy**
 - Diagnosis of beta thalassemia including beta⁺ thalassemia, beta⁰ thalassemia, and hemoglobin E/beta thalassemia; **and**
 - Patient is 18 years of age or older; **and**
 - Patient is transfusion dependent as evidenced by **both** of the following in the previous 24 weeks:
 - § Has required regular transfusion of at least six units of packed red blood cells (PRBC); **and**
 - § No transfusion free period greater than 35 days**and**
 - Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of beta thalassemia; **and**
 - Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
 - Diagnosis of beta thalassemia including beta⁺ thalassemia, beta⁰ thalassemia, and hemoglobin E/beta thalassemia; **and**
 - Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of beta thalassemia; **and**

- Patient has experienced a reduction in transfusion requirements from pretreatment baseline of at least 2 units PRBC while receiving Reblozyl; **and**
- Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

Reblozyl is proven and/or medically necessary for the treatment of symptomatic anemia in patients with myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic /myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who meet all of the following criteria:^{7,9-14}

- **Initial Therapy**

- **One** of the following:
 - § Diagnosis of myelodysplastic syndrome with ring sideroblasts (MDS-RS)
 - § Diagnosis of myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)**and**
- Patient has documented lower risk disease as defined as **one** of the following:
 - § Revised International Prognostic Scoring System (IPSS-R): Very Low, Low, Intermediate (Score 0 to ≤ 3.5)
 - § WHO-Based Prognostic Scoring System (WPSS): Very Low, Low, Intermediate (Score 0 to 2)**and**
- Documentation of **both** of the following:
 - § Hemoglobin < 10 g/dL; **and**
 - § Patient requires at least two units of packed red blood cells (pRBCs) in the prior eight weeks**and**
- Prescriber has ruled out and/or addressed other causes of anemia (e.g., gastrointestinal bleeding, hemolysis, renal disease, nutritional deficiency, etc.); **and**
- Patient has failed previous treatment with an erythropoiesis-stimulating agent (ESA) [e.g., Retacrit (epoetin alfa)]; **and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, oncologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes; **and**
- Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 12 months

- **Continuation of Therapy**

- Documentation of a positive clinical response to Reblozyl (e.g., reduction in transfusion burden, increase in hemoglobin from baseline); **and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes; **and**
- Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

Reblozyl is proven and/or medically necessary for the treatment of symptomatic anemia in erythropoiesis stimulating agent-naïve (ESA-naïve) patients with myelodysplastic syndromes (MDS) who meet all of the following criteria:^{9-14, 16}

- **Initial Therapy**

- Diagnosis of myelodysplastic syndrome (MDS); **and**
- Patient has documented lower risk disease as defined as **one** of the following:
 - § Revised International Prognostic Scoring System (IPSS-R): Very Low, Low, Intermediate (Score 0 to ≤ 3.5)
 - § WHO-Based Prognostic Scoring System (WPSS): Very Low, Low, Intermediate (Score 0 to 2)**and**
- Documentation of hemoglobin < 10 g/dL; **and**
- Prescriber has ruled out and/or addressed other causes of anemia (e.g., gastrointestinal bleeding, hemolysis, renal disease, nutritional deficiency, etc.); **and**
- Patient is erythropoiesis-stimulating agent (ESA)-naïve (without prior ESA use); **and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, oncologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes; **and**
- Reblozyl dosing is in accordance with the FDA approved labeling; **and**
- Initial authorization will be for no more than 12 months

- **Continuation of Therapy**

- Documentation of a positive clinical response to Reblozyl (e.g., reduction in transfusion burden, increase in hemoglobin from baseline); **and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes; **and**
- Reblozyl dosing is in accordance with the FDA approved labeling; **and**
- Reauthorization will be for no more than 12 months

Reblozyl is not proven or medically necessary for the treatment of:

- Alpha thalassemia
- Beta thalassemia in pediatric patients
- Non-transfusion dependent beta thalassemia
- Sickle beta thalassemia [hemoglobin S (HbS)/beta thalassemia]

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0896	Injection, luspatercept-aamt, 0.25 mg

Diagnosis Code	Description
D46.1	Refractory anemia with ring sideroblasts
D46.20	Refractory anemia with excess of blasts, unspecified
D46.21	Refractory anemia with excess of blasts 1
D46.22	Refractory anemia with excess of blasts 2
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D56.1	Beta thalassemia
D56.5	Hemoglobin E-beta thalassemia

Background

Beta-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. The total annual incidence of symptomatic individuals is estimated at one in 100,000 throughout the world and one in 10,000 people in the European Union. Three main forms have been described: thalassemia major, thalassemia intermedia and thalassemia minor. Individuals with thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell (RBC) transfusions. Findings in untreated or poorly transfused individuals with thalassemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Regular transfusion therapy leads to iron overload related complications including endocrine complication (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis). Patients with thalassemia intermedia present later in life with moderate anemia and do not require regular transfusions. Main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Thalassemia minor is clinically

asymptomatic but some subjects may have moderate anemia. Beta-thalassemias are caused by point mutations or, more rarely, deletions in the beta globin gene on chromosome 11, leading to reduced (β^+) or absent (β^0) synthesis of the beta chains of hemoglobin. Transmission is autosomal recessive; however, dominant mutations have also been reported. Diagnosis of thalassemia is based on hematologic and molecular genetic testing. Treatment of thalassemia major includes regular RBC transfusions, iron chelation and management of secondary complications of iron overload. In some circumstances, spleen removal may be required. Bone marrow transplantation remains the only definitive cure currently available. Individuals with thalassemia intermedia may require splenectomy, folic acid supplementation, treatment of extramedullary erythropoietic masses and leg ulcers, prevention, and therapy of thromboembolic events. Prognosis for individuals with beta-thalassemia has improved substantially following recent medical advances in transfusion, iron chelation and bone marrow transplantation therapy. However, cardiac disease remains the main cause of death in patients with iron overload.

Myelodysplastic syndromes (MDS) are a heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a risk of transformation to acute leukemia. Patients with MDS have impaired blood cell production and function that often leads to anemia, bleeding, and increased risk of infection. MDS occurs most commonly in male patients 65 years of age and older. Anemia is the most common cytopenia and can manifest as fatigue, weakness, exercise intolerance, angina, etc. Other symptoms include infection, easy bruising, or bleeding. MDS can be classified by one of three prognostic systems, based upon a combination of morphology, immunophenotype, genetics, and clinical features. These scoring systems are: the Revised International Prognostic Scoring System (IPSS-R), International Prognostic Scoring System (IPSS) and the WHO-Based Prognostic Scoring System (WPSS). The IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS. The IPSS-R calculator can be found at <http://www.ipss-r.com> or <https://www.mds-foundation.org/ipss-r-calculator/>.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Beta Thalassemia

The efficacy of Reblozyl was evaluated in adult patients with beta thalassemia in the BELIEVE trial (NCT02604433). BELIEVE is a multicenter, randomized, double-blind, placebo-controlled trial in which (n = 336) patients with beta thalassemia (including β^+ thalassemia, β^0 thalassemia, and hemoglobin E/beta thalassemia; beta thalassemia with mutation and/or multiplication of alpha globin was also allowed) requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period were randomized 2:1 to Reblozyl (n = 224) or placebo (n = 112). In BELIEVE, Reblozyl was administered subcutaneously once every three weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The BELIEVE trial excluded patients with hemoglobin S/beta-thalassemia or alpha-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded. The median age was 30 years (range: 18-66).

The primary efficacy outcome measure was the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 33%, with a reduction of at least two units from week 13 to week 24. Of the patients who received Reblozyl, 21.4% (n = 48) achieved the primary endpoint compared with 4.5% (n = 5) of those who received placebo (risk difference 17.0; 95% CI 10.4, 23.6; p < 0.0001). Secondary outcome measures included the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 33%, with a reduction of at least two units from week 37 to 48 and the proportion of

patients achieving RBC transfusion burden reduction from baseline of at least 50%, with a reduction of at least two units for 12 consecutive weeks from week 13 to week 24 and from week 37 to 48. Of the patients who received Reblozyl, 19.6% (n = 44) achieved a 33% reduction and two unit reduction in transfusion burden from week 37 to 48 compared to 3.6% (n = 4) with placebo (risk difference 16.1; 95% CI 9.8, 22.4; p < 0.0001). 7.6% (n = 17) and 10.3% (n = 23) of patients receiving Reblozyl experienced a 50% reduction in transfusion burden with a 2 unit reduction for 12 consecutive weeks compared to 1.8% (n = 2) and 0.9% (n = 1) from week 13 to 24 and from week 37 to week 48 respectively (p < 0.05 for both comparisons).

The efficacy of Reblozyl was evaluated in a phase 2 open-label, nonrandomized, uncontrolled study in 32 patients with transfusion dependent (requiring > 4 RBC units per 8 weeks) received Reblozyl ranging from 0.6 to 1.25 mg/kg every three weeks. The median age was 38.5 years (range: 20-62). The primary endpoint in the transfusion-dependent population was a 20% reduction in transfusion burden over a 12-week interval. Transfusion dependence was defined as those who received an average of > 4 RBC units every eight weeks over the six-month period before study initiation. Twenty-six (81%) of patients receiving Reblozyl achieved a 20% reduction in transfusion over any 12 weeks on study compared with the 12 weeks before baseline. RBC transfusion burden reduction of ≥ 33% was achieved in 23 patients (72%), and ≥ 50% reduction was achieved in 20 patients (63%) while receiving Reblozyl. An additional secondary endpoint included changes in liver iron concentration (LIC) measured using magnetic resonance imaging. Of nine patients with transfusion dependence with baseline LIC > 3 mg/g dry weight who were treated for > 4 months, 5 (56%) achieved a decrease in LIC > 2 mg/g dry weight. Mean LIC (±SD) for transfusion dependent patients at the end of the initial stage of treatment was -0.27 mg/g dry weight (±1.64), compared with 5.03 mg/g (±5.32) at baseline. All LIC responders were receiving ongoing concomitant iron chelation therapy.

Myelodysplastic Syndromes

The efficacy and safety of Reblozyl for the treatment of patients with symptomatic anemia and lower-risk myelodysplastic syndromes was evaluated in a double-blind, placebo-controlled, phase 3 trial (MEDALIST). Patients with symptomatic anemia and very-low, low, or intermediate-risk myelodysplastic syndromes where erythropoiesis-stimulating agent therapy was not effective, were randomized (n = 229) to receive either luspatercept (n = 153, at a dose of 1.0 mg up to 1.75 mg per kilogram body weight) or placebo (n = 76), administered subcutaneously every three weeks. The primary end point was transfusion independence for eight weeks or longer during weeks 1 through 24, and the key secondary end point was transfusion independence for 12 weeks or longer, assessed during weeks 1 through 24 and 1 through 48. Transfusion independence for eight weeks or longer was observed in 38% of the patients in the luspatercept group, as compared with 13% of those in the placebo group (p < 0.001). A higher percentage of patients in the luspatercept group than in the placebo group met the key secondary end point (28% vs. 8% for weeks 1 through 24, and 33% vs. 12% for weeks 1 through 48; p < 0.001 for both comparisons). The most common luspatercept associated adverse events (of any grade) included fatigue, diarrhea, asthenia, nausea, and dizziness. The authors concluded that luspatercept reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and who had disease that was refractory to or unlikely to respond to erythropoiesis stimulating agents or who had discontinued such agents owing to an adverse event.

In a phase II multicenter, open-label, dose-finding study (PACE-MDS), adult patients (aged ≥ 18 years) with low- or intermediate-1 risk MDS or non-proliferative CMML who had anemia with or without RBC transfusion support were treated with luspatercept (n = 58). Of importance, 78% of the treated patients had greater than or equal to 15% ring sideroblasts, which was a positive predictor of response. Some patients were enrolled in a dose-escalation cohort (n = 27) receiving luspatercept once every 21 days at doses ranging from 0.125 to 1.75 mg/kg over a maximum of 12 weeks. Other patients enrolled in the dose-expansion cohort (n = 31) received luspatercept doses ranging from 1.0 to 1.75 mg/kg, and patients could be treated for up to 5 years. Thirty-two of 51 patients (63%) who received higher doses of luspatercept (0.75–1.75 mg/kg) achieved hematologic improvement-erythroid, defined as: hemoglobin concentration increase of greater than or equal to 1.5 g/dL from baseline for at least 14 days in low transfusion burden patients, and a reduction in RBC transfusion of greater than or equal to 4 RBC units or greater than or equal to 50% reduction in RBC units over 8 weeks versus pre-treatment transfusion burden in high transfusion burden patients.

The efficacy Reblozyl for the treatment of MDS with associated anemia in erythropoietin-naïve patients was evaluated in the COMMANDS trial, a phase 3, open-label, randomized controlled trial. Eligible patients were aged 18 years or older, had a diagnosis of myelodysplastic syndromes of very low risk, low risk, or intermediate risk (per the Revised International Prognostic Scoring System), were ESA-naïve, and required red blood cell transfusions (2-6 packed red blood cell units per 8 weeks for ≥ 8 weeks immediately before randomization). Integrated response technology was used to randomly assign patients (1:1, block size 4) to luspatercept or epoetin alfa, stratified by baseline red blood cell transfusion burden (< 4 units per 8 weeks vs ≥ 4 units

per 8 weeks), endogenous serum erythropoietin concentration (≤ 200 U/L vs > 200 to < 500 U/L), and ring sideroblast status (positive vs negative). Luspatercept was administered subcutaneously once every 3 weeks starting at 1.0 mg/kg body weight with possible titration up to 1.75 mg/kg. Epoetin alfa was administered subcutaneously once a week starting at 450 IU/kg body weight with possible titration up to 1050 IU/kg (maximum permitted total dose of 80 000 IU). The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL (weeks 1-24), assessed in the intention-to-treat population. Safety was assessed in patients who received at least one dose of study treatment. A total of 356 patients were randomly assigned to receive luspatercept (178 patients) or epoetin alfa (178 patients), comprising 198 (56%) men and 158 (44%) women [median age 74 years (IQR 69-80)]. The interim efficacy analysis was done for 301 patients (147 in the luspatercept group and 154 in the epoetin alfa group) who completed 24 weeks of treatment or discontinued earlier. 86 (59%) of 147 patients in the luspatercept group and 48 (31%) of 154 patients in the epoetin alfa group reached the primary endpoint (common risk difference on response rate 26.6; 95% CI 15.8-37.4; $p < 0.0001$).

The most frequently reported grade 3 or 4 treatment-emergent adverse events with luspatercept ($\geq 3\%$ patients) were hypertension, anemia, dyspnea, neutropenia, thrombocytopenia, pneumonia, COVID-19, myelodysplastic syndromes, and syncope; and with epoetin alfa were anemia, pneumonia, neutropenia, hypertension, iron overload, COVID-19 pneumonia, and myelodysplastic syndromes. The most common suspected treatment-related adverse events in the luspatercept group ($\geq 3\%$ patients, with the most common event occurring in 5% patients) were fatigue, asthenia, nausea, dyspnea, hypertension, and headache; and none ($\geq 3\%$ patients) in the epoetin alfa group. One death after diagnosis of acute myeloid leukemia was considered to be related to luspatercept treatment (44 days on treatment).

Professional Societies

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium recommend (2A) Reblozyl for the treatment of lower risk* myelodysplastic syndromes associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts $\geq 15\%$ (or ring sideroblasts $\geq 5\%$ with an SF3B1 mutation) and

- With serum erythropoietin > 500 mU/mL
- With serum erythropoietin ≤ 500 mU/mL following no response to the combination of an erythropoiesis-stimulating agent (ESA) and granulocyte-colony stimulating factor (G-CSF)

*Lower risk defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate)

The NCCN Drugs and Biologics Compendium also recommend (2B) Reblozyl for the treatment of myelodysplastic syndromes/myelodysplastic neoplasms associated with symptomatic anemia with ring sideroblasts and thrombocytosis.

NCCN defines a lack of response to luspatercept as a lack of 1.5 g/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by six to eight weeks of treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Reblozyl (luspatercept-aamt) is an erythroid maturation agent indicated for the treatment of:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions
- Anemia failing an erythropoiesis stimulating agent and requiring two or more RBC units over eight weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

Limitations of Use: Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

References

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Policy History/Revision Information

Date	Summary of Changes
05/01/2024	<p>Coverage Rationale</p> <ul style="list-style-type: none"> ● Revised list of unproven and not medically necessary indications; removed: <ul style="list-style-type: none"> ○ Myelodysplastic syndromes without ring sideroblasts ○ Myeloproliferative neoplasm (MPN)-associated myelofibrosis

Date	Summary of Changes
	<p>Anemia in Adult Patients with Beta Thalassemia</p> <ul style="list-style-type: none"> Changed duration for initial authorization from “no more than 6 months” to “no more than 12 months” <p>Symptomatic Anemia in Patients with Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS), Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T), or Erythropoiesis Stimulating Agent-Naïve (ESA-naïve) Patients with Myelodysplastic Syndromes (MDS)</p> <ul style="list-style-type: none"> Changed duration for initial authorization from “no more than 3 months” to “no more than 12 months” <p>Supporting Information</p> <ul style="list-style-type: none"> Archived previous policy version IEXD0084.06

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual[®] criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.