UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

TYSABRI® (NATALIZUMAB)

Policy Number: CSLA2020D0026L **Effective Date: TBD**

Instructions for Use

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Commercial Policy

- **Tysabri® (Natalizumab)**

APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

Tysabri (natalizumab) is proven for:

Relapsing Forms of Multiple Sclerosis

Tysabri (natalizumab) is medically necessary for the treatment of relapsing forms of multiple sclerosis (MS) when all of the following are met:[1]

- **Initial therapy:**
  - **Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); and**
  - **Patient is not receiving Tysabri in combination with any of the following (used as monotherapy):**
    - **Disease modifying therapy (e.g., interferon beta preparations, glatiramer acetate, fingolimod, cladribine, siponimod, or teriflunomide)**
    - **B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)**
    - **Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone); and**
  - **Tysabri is dosed according to the U.S. FDA labeled dosing: 300 mg intravenous infusion every 4 weeks; and**
  - **Initial authorization is for no more than 6 months**
- **Continuation therapy:**
  - **Patient has previously received treatment with Tysabri; and**
  - **Documentation of positive clinical response to Tysabri therapy; and**
  - **Patient is not receiving Tysabri in combination with any of the following (used as monotherapy):**
    - **Disease modifying therapy (e.g., interferon beta preparations, glatiramer acetate, fingolimod, cladribine, siponimod, or teriflunomide)**
    - **B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)**
    - **Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone);**

and
- **Tysabri is dosed according to the U.S. FDA labeled dosing: 300 mg intravenous infusion every 4 weeks; and**
- **Authorization is for no more than 12 months**

Crohn's Disease

Tysabri (natalizumab) is medically necessary for inducing and maintaining clinical response and remission in patients with moderate to severe Crohn's disease (CD) when all of the following are met:[1,5-6]

- **Initial therapy:**
  - **Diagnosis of moderately to severely active Crohn's disease; and**
  - **Evidence of inflammation (e.g., elevated C-reactive protein [CRP], elevated erythrocyte sedimentation rate, presence of fecal leukocytes[5]); and**
  - **History of inadequate response or intolerance to conventional Crohn's disease therapies and inhibitors of TNF-α. Conventional Crohn's disease therapies may include aminosalicylates (such as mesalamine and sulfasalazine), corticosteroids, immunomodulators (such as azathioprine, 6-mercaptopurine, and methotrexate) and TNF-inhibitors [e.g., infliximab (Remicade®), adalimumab (Humira®), or certolizumab pegol (Cimzia®)]; and**
  - **Patient is not receiving concomitant treatment with immunosuppressants (e.g., 6-MP, azathioprine, cyclosporine, or methotrexate) or TNF-inhibitors [e.g., infliximab (Remicade), adalimumab (Humira), or certolizumab pegol (Cimzia)]; and**
  - **Tysabri is dosed according to the U.S. FDA labeled dosing: 300 mg intravenous infusion every 4 weeks; and**
  - **Initial authorization is for no more than 6 months**
- **Continuation therapy:**
  - **Patient has previously received treatment with Tysabri; and**
  - **Documentation of positive clinical response to Tysabri therapy; and**
  - **Diagnostic and/or clinical documentation (e.g. improved disease activity index) that indicates patient has experienced clinical benefit from receiving (induction) natalizumab therapy by week 12; and**
  - **Patients with Crohn's disease who start natalizumab while on chronic oral corticosteroids must discontinue chronic steroids within 6 months of starting natalizumab therapy or natalizumab therapy should be discontinued; and**
  - **Patient is not receiving concomitant treatment with immunosuppressants (e.g., 6-MP, azathioprine, cyclosporine, or methotrexate) or TNF-inhibitors [e.g., Enbrel (etanercept), Humira (adalimumab), or Remicade (infliximab)]; and**
  - **Tysabri is dosed according to the U.S. FDA labeled dosing: 300 mg intravenous infusion every 4 weeks; and**
  - **Initial authorization is for no more than 12 months**

Natalizumab is unproven for the treatment of other conditions or diseases, including types of MS other than relapsing forms.
Statistically robust randomized controlled trials are needed to address the issue of whether natalizumab has sufficient superiority in clinical efficacy compared to other available treatments to justify the substantial inherent clinical risk in its use.

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 federal, state or contractual requirements 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 Coverage Determination Guidelines may apply.

HCPCS Code	Description
J2323	Injection, natalizumab, 1 mg

ICD-10 Diagnosis Code	Description
G35	Multiple sclerosis
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications

BACKGROUND

Tysabri (natalizumab) is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). The receptors for the α4 family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. The specific mechanism(s) by which TYSABRI exerts its effects in multiple sclerosis and Crohn's disease have not been fully defined.

CLINICAL EVIDENCE

Proven

Relapsing Multiple Sclerosis

O'Connor et al conducted a prospective, observational, open-label Safety of Tysabri Re-dosing and Treatment (STRATA) Study which evaluated long –term safety and efficacy of patients (n=1,094) treated with natalizumab over 240 weeks.[7] Patients previously enrolled in relapsing-remitting multiple sclerosis (RRMS) natalizumab clinical trials that received natalizumab 300 mg IV every 4 weeks were included. Researchers reported that serious adverse events (including progressive multifocal leukoencephalopathy) were consistent with natalizumab's known safety profile; short exposure with a gap before redosing was associated with higher incidences of anti-natalizumab antibodies and hypersensitivity reactions. Stability of EDSS scores and consistently low relapse rates over 5 years of natalizumab treatment were with its known efficacy profile. Patients originally randomized to placebo/another disease-modifying therapy vs natalizumab in previous studies had significantly higher EDSS scores at STRATA baseline; this difference persisted over 240 weeks. Researchers concluded that this study provided Class III evidence that RRMS patients treated with natalizumab experienced stabilized EDSS scores, decreased relapse rates, and is associated with an increased risk of progressive multifocal leukoencephalopathy.

The Tysabri (natalizumab) Observational Program (TOP) was an open-label, multinational, 10-year prospective study in clinical practice settings which evaluated the safety and efficacy of natalizumab therapy in patients (n=4821) with relapsing-remitting multiple sclerosis (RRMS).[8] Results of the 5-year interim analysis showed that there were no new safety signals. There were 18 cases of progressive multifocal leucoencephalopathy reported, following 11-44 natalizumab infusions. The mean annualized relapse rate decreased from 1.99 in the 12 months prior to baseline to 0.31 on natalizumab therapy ($p<0.0001$), remaining low at 5 years. Lower annualized relapse rates were observed in patients who used natalizumab as first MS therapy, in patients with lower baseline EDSS scores, and in patients with lower pre-natalizumab relapse rates. Mean EDSS scores remained unchanged up to 5 years. Researchers concluded that this interim analysis confirmed natalizumab's overall safety profile and the low relapse rate and stabilized disability levels in natalizumab-treated patients with RRMS in clinical practice

A Cochrane systemic review in 2015 compared the benefit and acceptability of interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine and immunoglobulins for the treatment of people with relapsing-remitting multiple sclerosis (RRMS) and to provide a ranking of these treatments according to their benefit and acceptability, defined as the proportion of participants who withdrew due to any adverse event. The authors included randomized controlled trials (RCTs) that studied one or more of the 15 treatments as monotherapy, compared to placebo or to another active agent, for use in adults with relapsing-remitting multiple sclerosis (RRMS) were included. The authors included 39 studies in this review, in which 25,113 participants were randomized. The majority of the included trials were short-term studies, with a median duration of 24 months. Twenty-four (60%) were placebo-controlled and 15 (40%) were head-to-head studies. Network meta-analysis showed that, in terms of a protective effect against the recurrence of relapses in RRMS during the first 24 months of treatment, alemtuzumab, mitoxantrone, natalizumab, and fingolimod outperformed other drugs. The most effective drug was alemtuzumab (risk ratio (RR) versus placebo 0.46, 95% confidence interval (CI) 0.38 to 0.55; surface under the cumulative ranking curve (SUCRA) 96%; moderate quality evidence), followed by mitoxantrone (RR 0.47, 95% CI 0.27 to 0.81; SUCRA 92%; very low quality evidence), natalizumab (RR 0.56, 95% CI 0.47 to 0.66; SUCRA 88%; high quality evidence), and fingolimod (RR 0.72, 95% CI 0.64 to 0.81; SUCRA 71%; moderate quality evidence). Disability worsening was based on a surrogate marker, defined as irreversible worsening confirmed at three-month follow-up, measured during the first 24 months in the majority of included studies. Both direct and indirect comparisons revealed that the most effective treatments were mitoxantrone (RR versus placebo 0.20, 95% CI 0.05 to 0.84; SUCRA 96%; low quality evidence), alemtuzumab (RR 0.35, 95% CI 0.26 to 0.48; SUCRA 94%; low quality evidence), and natalizumab (RR 0.64, 95% CI 0.49 to 0.85; SUCRA 74%; moderate quality evidence). Almost all of the agents included in this review were associated with a higher proportion of participants who withdrew due to any adverse event compared to placebo. Based on the network meta-analysis methodology, the corresponding RR estimates versus placebo over the first 24 months of follow-up were: mitoxantrone 9.92 (95% CI 0.54 to 168.84), fingolimod 1.69 (95% CI 1.32 to 2.17), natalizumab 1.53 (95% CI 0.93 to 2.53), and alemtuzumab 0.72 (95% CI 0.32 to 1.61). The authors state that alemtuzumab, natalizumab, and

fingolimod are the best choices for preventing clinical relapses in people with RRMS, but this evidence is limited to the first 24 months of follow-up. For the prevention of disability worsening in the short term (24 months), only natalizumab shows a beneficial effect on the basis of moderate quality evidence (all of the other estimates were based on low to very low quality evidence). Currently, therefore, insufficient evidence is available to evaluate treatments for the prevention of irreversible disability worsening.

Crohn's Disease

A 2018 update of the 2015 Cochrane systemic review summarizes the current evidence on the use of natalizumab for induction of remission in Crohn's disease (CD). The authors included five randomized controlled trials (RCTs) comparing natalizumab to a placebo o rcontrol therapy for induction of remission in CD. A total of five RCTs (1771 participants) were included. Four studies (1692 participants) compared one, two or three infusions of natalizumab (300 mg or 3 mg/kg or 6mg/kg) to placebo. One study (79 participants) compared three infusions of natalizumab (300 mg) and infliximab (5 mg/kg) to infliximab and placebo. Four studies were rated as low risk of bias. One study was rated as unclear risk of bias for selective reporting. One, two and three infusions of natalizumab were superior to placebo for induction of remission and clinical response. Infusions were administered at weeks zero, four and eight. After one infusion, 76% (849/1117) of natalizumab participants failed to enter remission at 4 weeks compared to 83% (411/494) of placebo participants (RR 0.91, 95% CI 0.86 to 0.96, 3 studies, GRADE high quality). At 4 weeks, the RR for clinical response was 0.78 (95% CI 0.66 to 0.92, 3 studies, 1611 participants, GRADE moderate quality). After two infusions, after 8 weeks, 66% (693/1049) of natalizumab participants failed to enter remission compared to 77% (382/494) of placebo participants (RR 0.85, 95% CI 0.76 to 0.95; 3 studies, GRADE moderate quality). At 8 weeks, the RR for clinical response was 0.73 (95% CI 0.58 to 0.91, 3 studies, 1543 participants, GRADE low quality). After three infusions, at 12 weeks, 61% (596/983) of natalizumab participants failed to enter remission compared to 73% (313/431) of placebo participants (RR 0.85, 95% CI 0.78 to 0.92, 2 studies, GRADE high quality). At 12 weeks, the RR for clinical response was 0.76 (95% CI 0.67 to 0.86, 2 studies, 1414 participants, GRADE high quality). One study (507 participants) reported on change in CDAI from baseline. Natalizumab participants had a larger drop in mean CDAI scores than placebo participants at 4, 8 and 12 weeks. The study comparing combination therapy with natalizumab and infliximab to infliximab and placebo demonstrated similar remission rates at 10 weeks. Sixty-four per cent (33/52) of participants assigned to natalizumab and infliximab failed to achieve remission compared to 70% (19/27) assigned to placebo and infliximab (RR 0.90, 95% CI 0.65 to 1.24, GRADE moderate quality). Natalizumab is associated with the development of progressive multifocal leukoencephalopathy (PML) resulting in some patient deaths. There are currently no tests which can reliably predict those at risk of developing PML. The authors concluded that high quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active CD. However, none of the included studies had the power to detect rare but serious adverse events such as PML. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy. The use of natalizumab in select patients (e.g. patients allergic to different biologics) needs to be carefully considered against the potential risk of developing PML. Further studies of natalizumab are not likely to be done.

Professional Societies

In 2018, the American Academy of Neurology developed recommendations for disease-modifying therapy (DMT) for multiple sclerosis (MS). Thirty recommendations were developed. The following recommendations applied to natalizumab:[4]

- **Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).**
- **Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indexes above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML (Level C).**
- **Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use (Level B).**
- **Clinicians should counsel people with MS considering natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B).**
- **Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or become JCV antibody–positive, especially with an index of above 0.9 while on therapy (Level B).**

- **Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B).**
- **People with MS with serious infections potentially linked to their DMT should switch DMTs (does not pertain to PML management in people with MS using DMT) (Level B).**
- **Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B).**
- **Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies (Level B).**
- **Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A).**
- **Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8–12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity (Level B).**

According to the 2018 American College of Gastroenterology Practice Guidelines for the Management of Crohn's Disease in Adults (ACG Practice Guideline), patients with moderate-severe disease usually have a Crohn's Disease Activity Index (CDAI) of 220-450. They have failed to respond to treatment for mild-moderate disease, or have more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. They typically have moderate to severely active endoscopic mucosal disease.[5]

The 2018 ACG Practice Guideline states that:

- **Natalizumab is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation, high level of evidence).**
- **Natalizumab should be used for maintenance of natalizumab-induced remission of Crohn's disease only if serum antibody to John Cunningham (JC) virus is negative. Testing for anti-JC virus antibody should be repeated every 6 months and treatment stopped if the result is positive. (strong recommendation, moderate level of evidence).**
- **Natalizumab should be considered for maintaining remission of natalizumab-induced remission of Crohn's disease patients only if John Cunningham (JC) virus is negative (conditional recommendation, moderate level of evidence).**

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.

Tysabri (natalizumab) is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[1] Tysabri increases the risk of PML and therefore, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk when initiating and continuing treatment with Tysabri. In multiple sclerosis patients, an MRI scan should be obtained prior to initiating therapy with Tysabri. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.

Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.[1] Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α. In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on Tysabri therapy are uncommon.[1]

The FDA issued a Drug Safety Communication dated February 5, 2010 to communicate that the risk of developing progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection associated with the use of Tysabri, increases with the number of Tysabri infusions received.[13] This safety information, based on reports of 31 confirmed cases of PML received by the FDA as of January 21, 2010, is

included in the Tysabri drug label and patient *Medication Guide.* However, based on the available information, the FDA believes that the clinical benefits of Tysabri continue to outweigh the potential risks.

The FDA issued a second Drug Safety Communication dated April 22, 2011 to provide a safety update on PML associated with Tysabri.[14] The Tysabri label has been revised to include new information about the risk of PML. The updated drug label includes a table summarizing rates of PML with Tysabri use according to the number of infusions (duration of exposure). The new label also includes information on a newly identified PML risk factor. Patients who took an immune system suppressing medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and mycophenolate) prior to taking Tysabri have been shown to be at an increased risk for developing PML. Based on the available information to date, the FDA continues to believe that the benefits of taking Tysabri outweigh the potential risks.

The FDA issued a third Drug Safety Communication dated January 1, 2012 to provide a safety update on risk factors for developing PML.[15] Testing positive for anti-JC virus (JCV) antibodies has been identified as a risk factor for progressive multifocal leukoencephalopathy (PML). The risks and benefits of continuing treatment with Tysabri should be carefully considered in those patients who are found to be anti-JCV antibody positive and have one or more of the other known risk factors for PML. Patients with all three known risk factors have an estimated risk of PML of 11/1,000 users. The risk factors are:[16]

- **The presence of anti-JCV antibodies.**
- **Longer duration of Tysabri treatment, especially beyond 2 years.**
- **Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil).**

A patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated, and has been ordered by a healthcare professional. The Stratify JCV Antibody ELISA test was cleared by FDA on January 20, 2012.[17]

Tysabri is available only through a risk minimization plan called Tysabri Outreach Unified Commitment to Health (the TOUCH® Prescribing Program) which registers prescribers, infusion centers, and pharmacies associated with infusion centers. Additionally, Tysabri can only be prescribed to patients who are enrolled in and meet all the requirements of the program.[1]

- **For prescribers and patients, the TOUCH® Prescribing Program has two components: MS TOUCH® (for patients with multiple sclerosis) and CD TOUCH® (for patients with Crohn's disease).**
- **Patients must be enrolled in the TOUCH® Prescribing Program, read the Medication Guide, understand the risks associated with Tysabri, and complete and sign the Patient-Prescriber Enrollment Form.**
- **Pharmacies and infusion centers must be specially certified to dispense or infuse TYSABRI.**

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	• New Medical Benefit Drug Policy

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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 MCG™ Care Guidelines, to assist us in administering health benefits. The 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.