Drug Monograph

Drug/Drug Class:	**Renflexis® (infliximab-abda) injection/ Targeted Immunomodulators**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Renflexis® is available in a vial for intravenous injection containing 100 mg lyophilized infliximab-abda in a 20 ml vial. Manufactured for: Merck Sharp & Dohme Corp., Whitehouse Station, NJ 08889
Summary of Findings:	In a randomized, double-blind, multicenter, active-controlled, phase 3 clinical trial, no significant differences were found between infliximab-abda and infliximab in any efficacy criteria. Infliximab-abda had an ACR20 of 64.1%, ACR50 of 35.5%, and ACR70 of 18.2% compared to 66%, 38.1%, and 19% for infliximab.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Renflexis® is the second approved biosimilar to Remicade. A biosimilar product must demonstrate no clinically meaningful differences in safety or efficacy from the reference product. Biosimilar products may not be substituted for the reference product without prescriber intervention.

Dosage Form(s) [1]

Renflexis® is available in a vial for intravenous injection containing 100 mg lyophilized infliximab-abda in a 20 ml vial.

Manufacturer [1]

Manufactured for: Merck Sharp & Dohme Corp., Whitehouse Station, NJ 08889

Indication(s) [1]

Renflexis® is indicated for: reducing signs and symptoms and maintaining clinical remission in adult patients with moderately to severe active Crohn's disease; reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease; reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis; reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis in combination with methotrexate; reducing signs and symptoms in patients with active ankylosing spondylitis; reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis; treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Renflexis® is a chimeric IgG1 kappa monoclonal antibody that is biosimilar to infliximab. It binds with high affinity to TNF-alpha, neutralizing its activity. TNF-alpha functions include induction of pro-inflammatory cytokines, enhancement of leukocyte migration, activation of neutrophils and eosinophils, and induction of acute phase reactants and tissue degrading enzymes made by synoviocytes or chondrocytes.

Pharmacokinetics:

	Renflexis®
Distribution	Primarily within the vasculature

Half Life	7.7 to 9.5 days

Rheumatoid Arthritis

Renflexis® (infliximab-abda) and infliximab were comparable in all measures of efficacy in the treatment of moderate to severe rheumatoid arthritis in adults receiving methotrexate.

STUDY DESIGN	Randomized, double-blind, multicenter, active-controlled, phase 3 clinical trial (N=584)
INCLUSION CRITERIA	Adult patients with moderate to severe rheumatoid arthritis receiving methotrexate.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive Renflexis® (infliximab-abda) or infliximab 3 mg/kg IV at weeks 0, 2, and 6, and then every 8 weeks until week 54.
RESULTS	Efficacy criteria at week 30 showed no significant difference between Renflexis® (infliximab-abda) and infliximab, including the American College of Rheumatology 20% response rate (ACR20, 64.1% vs. 66%), ACR50 (35.5% vs. 38.1%), and ACR70 (18.2% vs. 19%).
SAFETY	Safety profiles were similar between groups.

Contraindications (1)

- Heart failure, moderate to severe; do not administer doses greater than 5 mg/kg.
- Severe hypersensitivity to infliximab products, murine proteins, or any other component of the product

Warnings and Precautions (1)

- Black box warning: Life-threatening and fatal infections (eg, Legionella, Listeria, mycobacterial, invasive fungal, viral, parasitic, and other opportunistic infections) have been reported, especially with concomitant use of immunosuppressants; do not initiate therapy in patients with active infections (including chronic or localized infections); ongoing monitoring recommended both during and after therapy; discontinue if serious infection or sepsis occurs.
- Black box warning: Active TB or reactivation of latent TB may occur, which may present with disseminated disease; increased risk among patients exposed to TB or who have resided
  or traveled in areas of endemic TB; baseline testing and treatment for latent TB is recommended before treatment initiation; conduct ongoing monitoring both during and after

therapy and discontinue if serious infection or sepsis occurs.

- Black box warning: Lymphoma and other malignancies have developed in children, adolescents, and young adults treated with TNF blockers, usually with concomitant immunosuppressant therapy.
- Black box warning: Hepatosplenic T-cell lymphoma (HSTCL) has been reported, particularly in adolescent and young adult males with Crohn disease or ulcerative colitis treated concurrently with TNF blockers and azathioprine or 6-mercaptopurine.
- Risk of serious infections is increased among patients with comorbid or underlying health conditions that may predispose to infection, older than 65 years of age, with concomitant immunosuppressant use, with a history of opportunistic infection, or who have lived or traveled in areas of endemic mycoses (eg, histoplasmosis, coccidioidomycosis, blastomycosis); monitor and discontinue if serious infection or sepsis occurs.
- Use should generally be avoided in patients with heart failure; monitor and discontinue if new or worsening symptoms develop.
- Concurrent use with anakinra is not recommended due to increased risk of serious infections and neutropenia.
- Concurrent use with abatacept, tocilizumab, live vaccines, biologic agents used to treat the same condition, or therapeutic infectious agents (such as live attenuated bacteria) is not recommended due to increased infection risk.
- Melanoma and Merkel cell carcinoma have been reported; monitoring recommended.
- Use cautiously among patients with a history of significant hematologic abnormalities, as life-threatening or fatal cytopenias (ie, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported; discontinuation may be required.
- Life-threatening or fatal hepatic reactions (ie, hepatitis and autoimmune hepatitis, acute liver failure, jaundice, cholestasis) with or without aminotransferase elevations have been reported; discontinuation may be required.
- Life-threatening or fatal hepatitis B (HBV) reactivation has occurred among chronic carriers, especially with concomitant immunosuppressants; baseline HBV testing and monitoring recommended during and after therapy; discontinuation may be required.
- Malignancies (lymphoma, leukemia, melanoma, nonmelanoma skin, breast, colorectal) have been reported, with increased risk among patients with Crohn disease, rheumatoid arthritis, or plaque psoriasis, particularly those with highly active disease and chronic immunosuppressant exposure; use cautiously in patients with a history of malignancy.
- Nonmelanoma skin cancers have been reported in patients with psoriasis, especially those with prior long-term phototherapy treatment; monitoring recommended.
- Use cautiously among patients with moderate to severe COPD and history of heavy smoking due to increased risk of cancer (especially lung or head and neck malignancies).
- Severe hypersensitivity reactions have usually occurred within 2 hours of infusion, with a higher incidence occurring after a period of no treatment; discontinue if severe reaction develops.
- Serum-sickness like reactions have occurred after initial therapy or upon retreatment following extended treatment interruption and may reduce efficacy; discontinue if severe reaction develops.
- Use caution when switching biological disease-modifying antirheumatic drug (DMARD) treatments; increased infection risk.
- Lupus-like syndrome may develop with autoantibody formation; discontinue if condition occurs.
- New or worsening demyelinating disorders (eg, multiple sclerosis, optic neuritis, peripheral

demyelinating disorders including Guillain-Barre syndrome) have rarely been reported; consider discontinuation if condition occur.
- Seizure has rarely been reported; use cautiously among patients with preexisting disease and consider discontinuation if condition occurs.
- CNS manifestation of systemic vasculitis has rarely been reported; use cautiously among patients with preexisting disease and consider discontinuation if condition occurs.
- Wait at least 6 months following birth before administering live vaccines to infants exposed in utero to infliximab products.
- Update all vaccinations in pediatric patients before treatment initiation when possible.

Adverse Effects [(1)]

Most common, ≥ 10%	Infliximab (n=1129)	Placebo (n=350)
Upper respiratory tract infection	32%	25%
Nausea	21%	20%
Headache	18%	14%
Sinusitis	14%	8%
Abdominal pain	12%	8%
Coughing	12%	8%
Pharyngitis	12%	8%
Bronchitis	10%	9%
Dyspepsia	10%	7%
Rash	10%	5%

Drug Interactions [(1)]

- Abatacept
- Anakinra
- CYP450 substrates with narrow therapeutic indices: Warfarin, cyclosporine
- Live vaccines
- Tocilizumab

Dosage and Administration [(1)]

Depending on the indication, the usual FDA recommended dose ranges from 3 to 5 mg/kg IV over 2 hours as an induction regimen at 0, 2, and 6 weeks; maintenance dosage is 3 to 5 mg/kg every 6 to 8 weeks. Premedication with an antihistamine, acetaminophen, and/or a corticosteroid may be considered.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	DOSE	COST/ VIAL*
Infliximab-abda	Reflexis	Merck	100 mg vial	$760.95
Infliximab-dyyb	Inflectra	Pfizer	100 mg vial	$955.74
Infliximab	Remicade	Jannsen Biotech	100 mg vial	$1,179.50

* Maximum Allowable Cost

Conclusion

Renflexis® is an anti-TNF monoclonal antibody approved as the second biosimilar to agent to Remicade®. It is considered highly similar to infliximab with no clinically meaningful differences. However, it may not be substituted for infliximab without prescriber intervention. It is approved in adults and children 6 years and older for moderately to severe active Crohn's disease, in adults for fistulizing Crohn's disease, ulcerative colitis, active rheumatoid arthritis in combination with methotrexate, active ankylosing spondylitis, psoriatic arthritis, and chronic severe plaque psoriasis. In a large, randomized clinical trial in patients with moderate to severe rheumatoid arthritis, no significant differences in efficacy or safety endpoints were found after 30 weeks between infliximab-abda and infliximab. All of the infliximab products carry black box warnings for the development of serious infections, including tuberculosis, and lymphomas and other malignancies.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Product Information: Reflexis™, infliximab-abda injection. Merck and Co, Inc, Kenilworth, NJ, 04/2017.
2) Choe JY, Prodanovic N, Niebrzydowski J et al: A randomised, double-blind, phase III study comparing SB2, and infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis 2017; 76(1): 58-64.

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