Clinical Policy: Biologic Drug Dose Escalation

Reference Number: GA.PMN.21
Effective Date: 09/1/17
Last Review Date: 9/2024 Revision Log
Line of Business: HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that members follow selection elements established by Centene® medical policy for the use of dose frequency escalation as it relates to utilizing biologic medications for autoimmune disorders.

FDA Approved Indication(s)
Most biologic monoclonal antibodies, tumor necrosis factor (TNF) blockers and integrin antagonists are indicated for autoimmune disorders.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that biologic dose escalation is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Dose Escalation of Frequency (must meet all)**:**

1. Prescribed by a specialist for requested disease state;
2. Member meets existing individual drug clinical policy except for the requested dosing frequency;
3. Drug is Food and Drug Administration (FDA) approved for the requested use;
4. Member has tried and failed FDA approved maintenance dosing and one of the following:
   a. Member does not have drug antibodies but has sub-therapeutic drug levels (*see Appendix D*);
   b. Member has developed antibodies to drug but not greater than recommendations (*see Appendix D*);
   c. If drug levels/antibody levels testing is unavailable or not indicated, member must have signs and symptoms of severe disease (disease requiring hospitalization) or ongoing disease activity despite maintenance therapy while on FDA approved maintenance dosing;
5. Symptoms are not due to active infection or other gastrointestinal (GI) disorders;
6. Member is or will be using an applicable immunomodulator concurrently (i.e., methotrexate, hydroxychloroquine, azathioprine) unless contraindicated;

7. Dose escalation does not occur at frequency interval detriments of no more than every 2 weeks from previous requested frequency and no more frequent than what is listed in table 1 (*see Appendix D*).

Approval duration: 6 months or through remainder of the current authorization

B. Other diagnoses/indications

Not applicable.

II. Continued Therapy

A. Dose Escalation of Frequency (must meet all)**:**

1. Prescribed by a specialist for requested disease state;
2. Member previously has met criteria for initiation in individual drug policy and Biologic Drug Dose Escalation policy;
3. Member has had a positive response to current therapy;
4. Member is using an applicable immunomodulator concurrently (i.e., methotrexate, hydroxychloroquine, azathioprine) unless contraindicated;
5. Dose frequency is no more frequent than recommendations from table 1 (*see Appendix D*);

Approval duration: 12 months or through remainder of the current authorization

B. Other diagnoses/indications

Not applicable.

III. Diagnoses/Indications for which coverage is NOT authorized:

Not applicable

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
TDM: Therapeutic Drug Monitoring
TNF: tumor necrosis factor
GI: gastrointestinal
IBD: Inflammatory bowel disease

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: General Information
Anti-TNF alpha blockers and Anti-Integrin Agents are common classes of biologics for inflammatory and autoimmune disorders. Despite these effective biologic medications, patients sometimes continue to demonstrate ongoing symptoms indicative of active inflammation or loss of response. After evaluation of infection and objective evidence of active inflammation is evident, then determining whether symptoms are due to primary non-response versus secondary loss of response is indicated. Primary nonresponse refers to

patients who do not respond adequately to the initial loading doses of a biologic agent. These patients usually have normal drug levels without antibodies present. When this is the case switching to a drug of different class or mechanism is recommended. Secondary loss of response refers to patients who had previously responded to a biologic agent but now has demonstrated evidence of ongoing disease activity despite continued therapy. Those patients found to have low drug levels are recommended to either increase the dose or decrease dosing interval and/or add an immunomodulatory. Therapeutic drug monitoring (TDM) is an assessment of drug concentrations and anti-drug antibodies (ADA) to provide a tool in order to optimize biologic therapy. For all anti-tumor necrosis factor therapy for IBD, there is consensus that it is appropriate to order drug/antibody concentrations testing in 1) responders at the end of induction, 2) at least once during maintenance phase, 3) at the end of induction for primary non-responders, and 4) confirmed secondary loss of response

Table 1: Drug/Antibody levels and minimum dosing frequency

	Normal Drug levels	Normal Drug levels (specific to IBD)	Abnormal Antibody levels	Minimum Dosing Frequency
Infliximab (Remicade, Inflectra)	3-6mcg/ml (≥5mcg/ml suggested)	PI: >3mcg/ml, with ≥7mcg/ml preferred for mucosal healing M: >3mcg/ml with ≥7mcg/ml for mucosal healing (no need to abandon drug unless >10mcg/ml with active disease	>10ng/ml (Anser Assay) >200ng/ml (RIDAscreen) >200ng/ml(InformTx/Lisa Tracker) **Insuffient data to define other assays**	10mg/kg Q 4 weeks
Adalimumab (Humira, Amjevita)	≥5mcg/ml (≥7.5mcg/ml suggested)	PI: ≥5mcg/ml, with ≥7mcg/ml preferred for mucosal healing M: ≥5mcg/ml with ≥8 mcg/ml for mucosal healing (no need to abandon drug unless >10mcg/ml with active disease	>10ng/ml	40mg Q week
Certolizumab Pegol (Cimzia)	(≥20mcg/ml studied)	PI: >32mcg/ml M: ≥15mcg/ml	>20au/ml (rheumatologic diseases)	400mg q 2 weeks

Golimumab (Simponi, Simponi Aria)	unavailable	PI: ≥2.5mcg/ml M: ≥1mcg/ml	unavailable	100mg Q 4 weeks
Natilizumab (Tysabri)	unavailable	unavailable	unavailable	300mg Q 4 weeks
Vedolizumab (Entyvio)	2-60mcg/ml	PI: ≥15mcg/ml with ≥17mcg/ml preferred for mucosal healing M: ≥12mcg/ml with ≥14 mcg/ml preferred for mucosal healing	35-500ng/ml	300mg Q 4 weeks
Ustekinumab (Stelara)	2-3.3mcg/ml	PI: ≥3.3 M: 0.8-1.4	unavailable	90mg Q 4 weeks

M: maintenance dosing in remission, PI: post induction

Table 2: Scenarios of applying TDM of Biologic Therapy in patients with IBD

	Responders at end of induction	**Once during maintenance phase**	**Primary Non-responders the end of inductionAbnormal Antibody levels**	**Confirmed Secondary Loss of Response**
Infliximab (Remicade, Inflectra)	Yes	Yes	Yes	Yes
Adalimumab (Humira, Amjevita)	Yes	Yes	Yes	Yes
Certolizumab Pegol (Cimzia)	Yes	Yes	Yes	Yes
Golimumab (Simponi, Simponi Aria)	Yes	Yes	Yes	Yes
Natilizumab (Tysabri)	Unavailable	Unavailable	Unavailable	Unavailable
Vedolizumab (Entyvio)	Yes (incomplete consensus)	Yes (incomplete consensus)	Yes	Yes
Ustekinumab	Yes (incomplete consensus)	Yes (incomplete consensus)	Yes (at 8 weeks)	Yes

V. Dosage and Administration

Please refer to the respective policies and package inserts for dosing and administration.

VI. Product Availability

Please refer to the respective policies and package inserts for products availability.

VII. References

1. D Roda G, Jharap B, Neeraj N, et al. Loss of response to anti-TNFs: Definition, epidemiology, and managament. Clinical and Translational Gastroenterology 2016; 7: e135.
2. Feuerstein J, Nguyen G, Kupfer S, et al. Therapeutic drug monitoring in inflammatory bowel disease. Gastroeneterology 2017;1-8.
3. De Vries H, Van Oijen M, Driessen R, et. al. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists, and gastroenterologists. Br J Clin Pharmacology 2011;71(1):7-19.
4. Oxford University Hospitals Diagnostic Tests. Available at: http://www.ouh.nhs.uk/immunology/diagnostic-tests/tests-catalogue/infliximab-levels.aspx. Accessed September 1, 2017.www.goo
5. The University of Iowa Department of Pathology Laboratory Services Handbook. Available at: https://www.healthcare.uiowa.edu/path_handbook/handbook/test3424.html. Accessed September 1, 2017.
6. Goel, Niti, and Sue Stephens. Certolizumab Pegol. MAbs 2010; 2(2): 137–147.
7. Curtis J, Chen L, Luijtens K, et. al. Dose escalation of certolizumab from 200mg to 400mg every other week provided no additional efficacy in rheumatoid arthritis: an analysis of individual patient level data. Arthritis Rheumatology 2011; 63(8): 2203–2208.
8. Dalal S, Cohen R. What to do when biologic agents are not working in inflammatory bowel disease patients. Gastroenterol Hepatol (N Y) 2015; 11(10):657-65.
9. Papamichael K, Cheifetz A, Memlmed G, et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients with Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology 2019;17:1655-1668
10. Papmichael K and Cheifetz A. Therapuetic drug monitoring in inflammatory bowel disease: for every patient and every drug? Curr Opin Gastroenterol 2019, 35:302-310
11. Berkhout LC, Vogelzhang EH, Hart MH. Et al. The effect of Certolizumab drug concentration and anti-drug antibodies on TNF neutralization. Clin and Experimental Rheumatology 2020; 38: 306-313
12. Jano Meghna, Isaacs J, Morgan A, et. Al. High Frequency of antidrug antibodies and association of random drug levels with efficacy in certolizumab pegol-treated patients with rheumatoid arthritis: results from the BRAGGSS cohort. Ann Rheum Dis. 2017 Jan;76(1):208-213

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created and reviewed by GI specialist	10.01.17	10.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: no significant changes	07.01.18	07.18
Changed current Georgia policy templates to corporate standard templates for drug coverage criteria to meet corporate compliance. Changes/revisions included; new formatting, font size, use of standard policy language for each section of policy, and rearranged order of certain steps in criteria and sections.	2/19	2/19
Added section for drug level suggestions specific IBD in table and updated references. Updated general information section to include consensus on when to monitor drug/antibody levels for anti-TNF drugs.	7/19	7/19
Annual review. Updated general information to include TDM definition and to provide clarity on utilization of appropriate drug level/antibody testing. Added Ustekinumab TDM recommendations. Created table on when to apply TDM. Updated Drug/Antibody levels and minimum dosing frequency table for infliximab specific assay testing for abnormal antibody levels.	7/2020	7/2020
Annual review. Added drug level for certolizumab pegol antibodies along with references for rheumatology.	7/2021	7/2021
4Q 2021 annual review. No changes made.	10/2021	10/2021
4Q 2022 annual review. No changes made.	10/2022	10/2022
4Q 2023 annual review. No changes made.	10/2023	10/2023
4Q 2024 annual review. No changes made.	09/2024	09/2024

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.