Clinical Policy: Biologic Drug Dose Escalation
Reference Number: GA.PMN.21
Effective Date: 09/1/17
Last Review Date: 7/2021
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.

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**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.

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

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**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

<table>
<thead>
<tr>
<th>Drug/Agent</th>
<th>Normal Drug levels</th>
<th>Normal Drug levels (specific to IBD)</th>
<th>Abnormal Antibody levels</th>
<th>Minimum Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (Remicade, Inflectra)</td>
<td>3-6mcg/ml (≥5mcg/ml suggested)</td>
<td>PI: &gt;3mcg/ml, with ≥7mcg/ml preferred for mucosal healing  M: &gt;3mcg/ml with ≥7mcg/ml for mucosal healing (no need to abandon drug unless &gt;10mcg/ml with active disease</td>
<td>&gt;10ng/ml (Anser Assay) &gt;200ng/ml (RIDAscreen) &gt;200ng/ml (InformTx/Lisa Tracker) <strong>Insufficient data to define other assays</strong></td>
<td>10mg/kg Q 4 weeks</td>
</tr>
<tr>
<td>Adalimumab (Humira, Amjevita)</td>
<td>≥5mcg/ml (≥7.5mcg/ml suggested)</td>
<td>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 &gt;10mcg/ml with active disease</td>
<td>&gt;10ng/ml</td>
<td>40mg Q week</td>
</tr>
<tr>
<td>Certolizumab Pegol (Cimzia)</td>
<td>(≥20mcg/ml studied)</td>
<td>PI: &gt;32mcg/ml  M: ≥15mcg/ml</td>
<td>&gt;20au/ml (rheumatologic diseases)</td>
<td>400mg q 2 weeks</td>
</tr>
</tbody>
</table>
### Golimumab (Simponi, Simponi Aria)
- **Dose**: unavailable
- **PI**: $\geq 2.5 \text{ mcg/ml}$
- **M**: $\geq 1 \text{ mcg/ml}$
- **Maintenance**: 100mg Q 4 weeks

### Natilizumab (Tysabri)
- **Dose**: unavailable
- **PI**: unavailable
- **M**: unavailable
- **Maintenance**: 300mg Q 4 weeks

### Vedolizumab (Entyvio)
- **Dose**: 2-60mcg/ml
- **PI**: $\geq 15 \text{ mcg/ml}$
- **M**: $\geq 12 \text{ mcg/ml}$
- **Maintenance**: 35-500ng/ml

### Ustekinumab (Stelara)
- **Dose**: 2-3.3mcg/ml
- **PI**: $\geq 3.3$
- **M**: 0.8-1.4
- **Maintenance**: 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Responders at end of induction</th>
<th>Once during maintenance phase</th>
<th>Primary Non-responders</th>
<th>Confirmed Secondary Loss of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong> (Remicade, Inflectra)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Adalimumab</strong> (Humira, Amjevita)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Certolizumab Pegol</strong> (Cimzia)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Golimumab</strong> (Simponi, Simponi Aria)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Natilizumab</strong> (Tysabri)</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>Unavailable</td>
</tr>
<tr>
<td><strong>Vedolizumab</strong> (Entyvio)</td>
<td>Yes (incomplete consensus)</td>
<td>Yes (incomplete consensus)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ustekinumab</strong></td>
<td>Yes (incomplete consensus)</td>
<td>Yes (incomplete consensus)</td>
<td>Yes (at 8 weeks)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created and reviewed by GI specialist</td>
<td>10.01.17</td>
<td>10.17</td>
</tr>
</tbody>
</table>
Clinical Policy
Biologic Drug Dose Escalation

<table>
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<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Q 2018 annual review: no significant changes</td>
<td>07.01.18</td>
<td>07.18</td>
</tr>
<tr>
<td>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.</td>
<td>2/19</td>
<td>2/19</td>
</tr>
<tr>
<td>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.</td>
<td>7/19</td>
<td>7/19</td>
</tr>
<tr>
<td>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.</td>
<td>7/2020</td>
<td>7/2020</td>
</tr>
<tr>
<td>Annual review. Added drug level for certolizumab pegol antibodies along with references for rheumatology.</td>
<td>7/2021</td>
<td>7/2021</td>
</tr>
</tbody>
</table>

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
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agents or employees of the Health Plan.

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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.

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