Humira

Description

Humira (adalimumab), Abrilada* (adalimumab-afzb), Amjevita* (adalimumab-atto), Cyltezo* (adalimumab-adbm), Hadlima* (adalimumab-bwwd), Hyrimoz* (adalimumab-adaz)

*These medications are included in this policy but are not available in the market as of yet

Background
Humira and its biosimilars are grouped within a class of medications called biologic response modifiers ("biologics") also called tumor necrosis factor (TNF) blockers. By working on the immune system, biologics block proteins that contribute to the disease process. TNF blockers suppress the immune system by blocking the activity of TNF, a substance in the body that can cause inflammation and lead to immune-system diseases, such as Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. The drugs in this class include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol) and Simponi (golimumab) (1). Humira and Amjevita reduce levels of the active form of TNF. Humira and its biosimilars may be used alone or in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs) (2-7).

Regulatory Status
FDA-approved indication: Humira and its biosimilars are tumor necrosis factor (TNF) blockers indicated for the treatment of: (2-7)
Rheumatoid Arthritis (RA) – Humira and its biosimilars are indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Humira can be used alone or in combination with methotrexate (MTX) or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Polyarticular Juvenile Idiopathic Arthritis (pJIA) – Humira and its biosimilars are indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA). Humira is indicated in patients aged 2 years or older and Amjevita is indicated in patients aged 4 years and older. Humira and Amjevita can be used alone or in combination with methotrexate (MTX).

Psoriatic Arthritis (PsA) – Humira and its biosimilars are indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PsA). Humira and Amjevita can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis (AS) – Humira and its biosimilars are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

Crohn’s Disease (CD) – Humira and its biosimilars are indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Additionally, Humira and its biosimilars are indicated for reducing signs and symptoms and inducing clinical remission in pediatric patients (6 years of age and older) with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Humira and its biosimilars are indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC) - Humira and its biosimilars are indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of Humira and its biosimilars have not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (Ps) – Humira and its biosimilars are indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis (Ps) who are candidates for systemic
therapy or phototherapy, and when other systemic therapies are medically less appropriate. Humira and its biosimilars should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

FDA-approved indications for Humira only:

- **Hidradenitis Suppurativa (HS)** - The treatment of moderate to severe hidradenitis suppurativa.
- **Uveitis (UV)** - The treatment of non-infectious intermediate, posterior and panuveitis in adults and pediatric patients 2 years of age and older.

Humira and its biosimilars carry boxed warnings regarding serious infections and malignancies. Because Humira and its biosimilars suppresses the immune system, patients are at a greater risk for getting serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. Lymphoma and other malignancies have been reported in children and adolescent patients treated with TNF blockers. Hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including Humira (2-7).

Patients should be screened for latent tuberculosis infection. Patients at risk for hepatitis B virus (HBV) infection should be evaluated for evidence of prior HBV infection. Hepatitis B virus carriers should be monitored for reactivation during and several months after therapy. Humira and its biosimilars should not be used in combination with other biologic agents. Humira should not be initiated in patients with an active infection. Humira and its biosimilars should be discontinued if a patient develops a serious infection or sepsis during treatment (2-7).

Pancytopenia, aplastic anemia, cytopenia, lupus-like syndrome, anaphylaxis reactions, and congestive heart failure (new onset or worsening) may develop during Humira or its biosimilars therapy and therapy should be discontinued (2-7).

Use of Humira or its biosimilars with anakinra, abatacept, or cyclophosphamide is not recommended as the use may increase the risk of serious adverse events, including infections (2-7).

**Off-label use:**
There is sufficient medical literature to support the use of Humira in adolescent for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, ulcerative colitis and plaque psoriasis (8-22).
The use of Humira for pediatric UC (ulcerative colitis) is not uncommon and comes from several sensible conclusions about similar medications that are FDA-approved for pediatric patients with inflammatory bowel disease (IBD) (8-22).

The FDA defines biosimilar as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing the structure and function of both the reference product and the proposed biosimilar. Minor differences between the reference product and the proposed biosimilar in clinically inactive components are acceptable. Manufacturers must also demonstrate that its proposed biosimilar has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness) (23).

**Related policies**
Actemra, Cimzia, Cosentyx, Enbrel, Envyvio, Ilumya, Infliximab, Kevzara, Kineret, Olumiant, Orencia, Otezla, Rinvoq, Rituxan, Siliq, Simponi, Stelara, Taltz, Tremfya, Xeljanz

**Policy**
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Humira and its biosimilars may be considered **medically necessary** in patients 2 years of age and older with moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (JIA) or uveitis; in patients 6 years and older with Crohn’s Disease (CD), in patients 12 years of age and older with moderately to severely active Rheumatoid Arthritis (RA), Active Psoriatic Arthritis (PsA), Active Ankylosing Spondylitis (AS), Ulcerative Colitis (UC), Chronic moderate to severe Plaque Psoriasis (Ps), or Hidradenitis Suppurativa (HS); and if the conditions indicated below are met.

Humira and its biosimilars are considered **investigational** in patients that do not meet the above criteria.

**Prior-Approval Requirements**

**Diagnoses**

Patient must have **ONE** of the following:
Age 2 years of age or older

1. Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (JIA)
   a. Inadequate response, intolerance, or contraindication to a 3-month trial of at least ONE conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)

2. Uveitis

Age 6 years of age or older

1. Moderate to severely active Crohn’s Disease (CD)
   a. Inadequate response, intolerance or contraindication to at least ONE conventional therapy option (see Appendix 2)

Age 12 years of age or older

1. Moderately to severely active Rheumatoid Arthritis (RA)
   a. Inadequate response, intolerance, or contraindication to a 3-month trial of at least ONE conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)

2. Active Psoriatic Arthritis (PsA)
   a. Inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD (see Appendix 1)

3. Active Ankylosing Spondylitis (AS)
   a. Inadequate response, intolerance, or contraindication to at least TWO non-steroidal anti-inflammatory drugs (NSAIDs)

4. Ulcerative Colitis (UC)
   a. Inadequate response, intolerance or contraindication to at least ONE conventional therapy option (see Appendix 2)

5. Chronic moderate to severe Plaque Psoriasis (Ps)
5.70.29

**Section:** Prescription Drugs  
**Effective Date:** January 1, 2020

**Subsection:** Analgesics and Anesthetics  
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a. Inadequate response, intolerance, or contraindication to either conventional systemic therapy (see Appendix 1) or phototherapy  
i. If the patient is intolerant or contraindicated to either therapy then the other treatment option needs to be tried  

6. Hidradenitis Suppurativa (HS)

AND ALL of the following:

a. Result for latent TB infection is negative OR result was positive for latent TB and patient completed treatment (or is receiving treatment) for latent TB  
b. Patient is not at risk for HBV infection OR patient is at risk for HBV infection and HBV infection has been ruled out or treatment for HBV infection has been initiated.  
c. Absence of active infection (including tuberculosis and hepatitis B virus (HBV)  
d. NOT to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)  
e. NOT given concurrently with live vaccines

**Prior – Approval Renewal Requirements**

**Diagnoses**

Patient must have **ONE** of the following:

**Age** 2 years of age or older

1. Polyarticular Juvenile Idiopathic Arthritis (JIA)
2. Uveitis

**Age** 6 years of age or older

1. Crohn’s Disease (CD)

**Age** 12 years of age or older

1. Rheumatoid Arthritis (RA)
2. Psoriatic Arthritis (PsA)
3. Ankylosing Spondylitis (AS)
4. Ulcerative Colitis (UC)
5. Plaque Psoriasis (Ps)
6. Hidradenitis Suppurativa (HS)

AND ALL of the following:
  a. Condition has improved or stabilized with Humira
  b. Absence of active infection (including tuberculosis and hepatitis B virus (HBV))
  c. NOT to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
  d. NOT given concurrently with live vaccines

**Policy Guidelines**

**Pre - PA Allowance**
None

**Prior - Approval Limits**

**Duration**
12 months

**Prior – Approval Renewal Limits**

**Duration**
18 months

**Rationale**

**Summary**
Humira and its biosimilars are tumor necrosis factor (TNF) blockers indicated for the treatment of polyarticular juvenile idiopathic arthritis (JIA), moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), active ankylosing spondylitis (AS), Crohn’s disease (CD), ulcerative colitis (UC), or chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy. Humira is also indicated for the treatment of patients with uveitis and Hidradenitis Suppurativa (HS). These patients must have a negative test for latent TB infection or is receiving treatment or has completed treatment for latent TB, not at risk for HBV infection or HBV infection has been ruled out or treatment for HBV has been
initiated, absent of active infection, and not taken in combination with another biologic agent (1-22).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Humira and its biosimilars while maintaining optimal therapeutic outcomes.

References
Section: Prescription Drugs Effective Date: January 1, 2020
Subsection: Analgesics and Anesthetics Original Policy Date: November 11, 2013
Subject: Humira Page: 9 of 13

20. Afif W et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response to infliximab. Inflam Bowel Dis 2009;Apr 30:[Epub ahead of publication].
   https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#generic

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>October 2013</td>
<td>Addition to PA</td>
</tr>
<tr>
<td>December 2013</td>
<td>Annual editorial review by the PMPC</td>
</tr>
<tr>
<td>September 2014</td>
<td>Age limit lowered to 12 and older for RA, PsA, AS, UC, PsO and renewal limit to 18 months, age limit lowered to 6 and older for CD Annual editorial review and reference update</td>
</tr>
<tr>
<td>October 2014</td>
<td>Age limit lowered to 2 and older for JIA</td>
</tr>
<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>June 2015</td>
<td>Annual review and reference update</td>
</tr>
<tr>
<td>August 2015</td>
<td>Addition of off-Label indications: uveitis and hidradenitis suppurativa (HS)</td>
</tr>
<tr>
<td>December 2015</td>
<td>Annual review and reference update</td>
</tr>
<tr>
<td>September 2016</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td></td>
<td>Addition of not to be used in combination with any other biologic DMARD or targeted synthetic DMARD</td>
</tr>
<tr>
<td></td>
<td>Addition of not given concurrently with live vaccines per SME Policy number change from 5.18.01 to 5.70.29</td>
</tr>
<tr>
<td>October 2016</td>
<td>Addition of Amjevita (biosimilar) to criteria</td>
</tr>
<tr>
<td>December 2016</td>
<td>Annual review and reference update</td>
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<td>Analgesics and Anesthetics</td>
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<td><strong>Subject:</strong></td>
<td>Humira</td>
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- **March 2017**  
  Annual review
- **June 2017**  
  Annual review
- **December 2017**  
  Annual review
- **March 2018**  
  Annual editorial review and reference update
  Addition of Appendix 1 - List of DMARDs
- **June 2018**  
  Annual editorial review
  Addition of Appendix 2 - List of Conventional Therapies and Appendix 3 - Examples of Contraindications to Methotrexate
  Addition of additional requirements to initiation criteria
  - For diagnoses of RA and pJIA: inadequate treatment response, intolerance, or contraindication to at least ONE conventional disease-modifying antirheumatic drugs (DMARDs)
  - For diagnoses of UC and C: inadequate treatment response, intolerance, or contraindication to at least one conventional systemic therapy
  - For diagnosis of AS: inadequate response, intolerance, or contraindication to at least 2 NSAIDs
  - For diagnosis of PsA: inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD
  - For diagnosis of Ps: if the patient is intolerant or contraindicated to either therapy then the other treatment option needs to be tried
- **September 2018**  
  Annual editorial review and reference update
  Change of age limit for uveitis to 2 years and older
  Addition of off-label indications to Amjevita per SME
- **November 2018**  
  Annual review and reference update. Addition of Cyltezo and Hyrimoz (biosimilars) to criteria
- **March 2019**  
  Annual review and reference update
- **August 2019**  
  Addition of biosimilar Hadlima
- **September 2019**  
  Annual review
- **December 2019**  
  Annual review and reference update. Addition of biosimilar Abrilada

**Keywords**

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective on January 1, 2020.
### Appendix 1 - List of DMARDs

#### Conventional disease-modifying antirheumatic drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>azathioprine</td>
<td>Azasan, Imuran</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Cytoxan</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>Neoral, Gengraf, Sandimmune</td>
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<td>hydroxychloroquine</td>
<td>Plaquenil</td>
</tr>
<tr>
<td>leflunomide</td>
<td>Arava</td>
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<tr>
<td>methotrexate</td>
<td>Rheumatrex, Trexall</td>
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<tr>
<td>mycophenolate</td>
<td>Cellcept</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>Azulfidine, Sulfazine</td>
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#### Biological disease-modifying antirheumatic drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>abatacept</td>
<td>Orencia</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira</td>
</tr>
<tr>
<td>anakinra</td>
<td>Kineret</td>
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<tr>
<td>brodalumab</td>
<td>Siliq</td>
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<tr>
<td>certolizumab</td>
<td>Cimzia</td>
</tr>
<tr>
<td>etanercept</td>
<td>Enbrel</td>
</tr>
<tr>
<td>golimubumab</td>
<td>Simponi/Simponi Aria</td>
</tr>
<tr>
<td>guselkumab</td>
<td>Tremfya</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade/Renflexis/Inflectra</td>
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<tr>
<td>ixekizumab</td>
<td>Taltz</td>
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<td>risankizumab-rzaa</td>
<td>Skyrizi</td>
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<td>rituximab</td>
<td>Rituxan</td>
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<td>sarilumab</td>
<td>Kevezara</td>
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<td>secukinumab</td>
<td>Cosentyx</td>
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<tr>
<td>tildrakizumab-asnn</td>
<td>Ilumya</td>
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<tr>
<td>tocilizumab</td>
<td>Actemra</td>
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<tr>
<td>ustekinumab</td>
<td>Stelara</td>
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<tr>
<td>vedolizumab</td>
<td>Entyvio</td>
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#### Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

<table>
<thead>
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<th>Generic Name</th>
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</thead>
<tbody>
<tr>
<td>apremilast</td>
<td>Otezla</td>
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</tbody>
</table>
Appendix 2 - List of Conventional Therapies

**Conventional Therapy Options for CD**

1. Mild to moderate disease - induction of remission:
   a. Oral budesonide, oral mesalamine
   b. Alternatives: metronidazole, ciprofloxacin

2. Mild to moderate disease - maintenance of remission:
   a. Azathioprine, mercaptopurine
   b. Alternatives: oral budesonide, methotrexate intramuscularly (IM)

3. Moderate to severe disease - induction of remission:
   a. Prednisone, methylprednisolone intravenously (IV)
   b. Alternatives: methotrexate IM

4. Moderate to severe disease - maintenance of remission:
   a. Azathioprine, mercaptopurine
   b. Alternative: methotrexate IM

5. Perianal and fistulizing disease - induction of remission
   c. Metronidazole ± ciprofloxacin

6. Perianal and fistulizing disease - maintenance of remission
   d. Azathioprine, mercaptopurine
   e. Alternative: methotrexate IM

**Conventional Therapy Options for UC**

1. Mild to moderate disease - induction of remission:
   a. Oral mesalamine (e.g., Asacol, Lialda, Pentasa), balsalazide, olsalazine
   b. Rectal mesalamine (e.g., Canasa, Rowasa)
   c. Rectal hydrocortisone (e.g., Colocort, Cortifoam)
   d. Alternatives: prednisone, azathioprine, mercaptopurine, sulfasalazine

2. Mild to moderate disease - maintenance of remission:
   a. Oral mesalamine, balsalazide, olsalazine, rectal mesalamine
   b. Alternatives: azathioprine, mercaptopurine, sulfasalazine

3. Severe disease - induction of remission:
   a. Prednisone, hydrocortisone IV, methylprednisolone IV
   b. Alternatives: cyclosporine IV, tacrolimus, sulfasalazine

<table>
<thead>
<tr>
<th>baricitinib</th>
<th>Olumiant</th>
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<tbody>
<tr>
<td>tofacitinib</td>
<td>Xeljanz</td>
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<tr>
<td>upadactinib</td>
<td>Rinvoq</td>
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</tbody>
</table>
4. Severe disease - maintenance of remission:
   a. Azathioprine, mercaptopurine
   b. Alternative: sulfasalazine

5. Pouchitis:
   a. Metronidazole, ciprofloxacin
   b. Alternative: rectal mesalamine

**Appendix 3 – Examples of Contraindications to Methotrexate**

<table>
<thead>
<tr>
<th>Contraindications to Methotrexate</th>
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<tbody>
<tr>
<td>1. Alcoholism, alcoholic liver disease or other chronic liver disease</td>
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<tr>
<td>2. Breastfeeding</td>
</tr>
<tr>
<td>3. Blood dyscrasias (e.g., thrombocytopenia, leukopenia, significant anemia)</td>
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<tr>
<td>4. Elevated liver transaminases</td>
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<tr>
<td>5. History of intolerance or adverse event</td>
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<tr>
<td>6. Hypersensitivity</td>
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<tr>
<td>7. Interstitial pneumonitis or clinically significant pulmonary fibrosis</td>
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<tr>
<td>8. Myelodysplasia</td>
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<tr>
<td>9. Pregnancy or planning pregnancy (male or female)</td>
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<tr>
<td>10. Renal impairment</td>
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<tr>
<td>11. Significant drug interaction</td>
</tr>
</tbody>
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