RITUXAN® (rituximab), NONONCOLOGIC USES

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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RITUXAN® (rituximab), NONONCOLOGIC USES (cont.)

Description:

Rituxan (rituximab) is a monoclonal antibody against the CD20 antigen on B-lymphocytes. Rituxan has been used with increased frequency for nononcologic uses, particularly autoimmune diseases that are thought to be B-cell mediated.

Definitions:

Adult: 18 years of age or older.

Criteria:

Effective 02/01/17: For site of service requirements for Rituxan (rituximab), nononcologic uses, see BCBSAZ Medical Coverage Guideline #O1008, “Site of Service Requirements for Certain Medications”.

For Rituxan for B-cell non-Hodgkin Lymphoma (NHL) and Rituxan Hycela for NHL, see BCBSAZ Medical Coverage Guideline #O525, “Uses of Monoclonal Antibodies for Treatment of Non-Hodgkin Lymphoma”.

For Rituxan for treatment of cancers other than B-cell non-Hodgkin lymphoma, including chronic lymphocytic leukemia, see BCBSAZ Medical Coverage Guideline #O603, “Prescription Medications for the Treatment of Cancer”.
RITUXAN® (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Review by the clinical pharmacist is required if individual is currently on Kineret or another biologic as defined by Drug Facts & Comparisons®.

See Resources section for FDA-approved dosage.

Food and Drug Administration–Approved Uses:

Rheumatoid Arthritis:

- Rituxan for adults with rheumatoid arthritis is considered medically necessary with documentation of ALL of the following:
  - Rheumatoid arthritis is moderately to severely active (e.g., ≥8 swollen and ≥8 tender joints)
  - Rituxan is administered in combination with methotrexate
  - Inadequate response to ANY of the following:
    - Methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD) and is not suitable for treatment with TNF inhibitors (e.g., due a recent [e.g., within 5 years] history of lymphoma or other malignancy; latent tuberculosis and contraindications to chemoprophylaxis; or previous demyelinating disease)
    - One or more tumor necrosis factor (TNF) inhibitors
RITUXAN® (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Food and Drug Administration–Approved Uses: (cont.)

Granulomatosis With Polyangiitis (Wegener Granulomatosis) and Microscopic Polyangiitis:

- Rituxan, in combination with glucocorticoids, is considered medically necessary for the treatment of individuals with antineutrophil cytoplasmic antibody-associated vasculitides (i.e., granulomatosis with polyangiitis [Wegener granulomatosis] and microscopic polyangiitis).

Other Uses:

Autoimmune Hemolytic Anemia (AIHA):

- Rituxan is considered medically necessary for individuals with autoimmune hemolytic anemia (AIHA) with documentation of ANY of the following:
  1. Warm AIHA in glucocorticoid-refractory or glucocorticoid-dependent individuals
  2. Cold agglutination syndrome

Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis):

- Rituxan is considered medically necessary for individuals with Churg-Strauss Syndrome (eosinophilic granulomatosis with polyangiitis) with documentation of ANY of the following:
  1. First-line treatment in combination with glucocorticoids for individuals with severe (organ-threatening) disease
  2. Add-on therapy for treatment-refractory disease

Chronic Graft-Versus-Host Disease:

- Rituxan for individuals with glucocorticoid-refractory chronic graft-versus-host disease is considered medically necessary.
RITUXAN® (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Other Uses: (cont.)

Factor Inhibitors in Hemophilia:

➢ Rituxan is considered medically necessary as factor inhibitors in individuals with hemophilia who are refractory to conventional first-line treatments (e.g., immune tolerance induction, glucocorticoids with or without cyclophosphamide), preferably as add-on therapy.

Hepatitis C virus (HCV)–Associated Cryoglobulinemic Vasculitis:

➢ Rituxan is considered medically necessary as an add-on therapy for individuals with hepatitis C with associated cryoglobulinemic vasculitis with documentation of ANY of the following:

1. Active disease resistant to anti-viral drugs
2. Severe or life-threatening cryoglobulinemic vasculitis

Idiopathic Membranous Nephropathy:

➢ Rituxan for individuals with idiopathic membranous nephropathy is considered medically necessary.

Idiopathic Thrombocytopenic Purpura (ITP):

➢ Rituxan is considered medically necessary for individuals with idiopathic thrombocytopenic purpura (also referred to as idiopathic thrombocytopenia purpura) who do not respond to first-line treatments (e.g., corticosteroids).

Lupus Nephritis:

➢ Rituxan as an add-on therapy for individuals with lupus nephritis refractory to at least standard first-line treatment regimens is considered medically necessary.

Multicentric Castleman Disease:

➢ Rituxan for individuals with multicentric Castleman disease (first or second-line therapy) is considered medically necessary.

Neuromyelitis Optica (NMO):

➢ Rituxan for individuals with neuromyelitis optica (for relapse prevention) that is refractory to at least one standard immunosuppressive drug (e.g., azathioprine or mycophenolate mofetil) is considered medically necessary.
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Other Uses: (cont.)

Pemphigoid Diseases:

- Rituxan for individuals with ANY of the following pemphigoid diseases that are treatment-refractory is considered medically necessary.
  
  1. Bullous pemphigoid
  2. Epidermolysis bullosa acquisita
  3. Mucous membrane pemphigoid, including ocular cicatricial pemphigoid

Pemphigus Diseases:

- Rituxan for individuals with ANY of the following pemphigus diseases is considered medically necessary.
  
  1. Paraneoplastic pemphigus
  2. Pemphigus foliaceus
  3. Pemphigus vulgaris

Primary Sjogren Syndrome:

- Rituxan for individuals with primary Sjogren syndrome that is refractory to glucocorticoids and other immunosuppressive agents is considered medically necessary.

Renal Transplant Candidates:

- Rituxan for desensitization of human leukocyte antigen (HLA) ‒ sensitized renal transplant candidates before transplantation is considered medically necessary.

Systemic Lupus Erythematosus (SLE):

- Rituxan as an add-on therapy for individuals with systemic lupus erythematosus refractory to standard first-line treatment is considered medically necessary.

Systemic Sclerosis (Scleroderma):

- Rituxan for individuals with systemic sclerosis (scleroderma) refractory to first-line treatment is considered medically necessary.
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Other Uses: (cont.)

Thrombotic Thrombocytopenic Purpura (TTP):

- Rituxan for individuals with thrombotic thrombocytopenic purpura (TTP) with refractory disease or relapse (i.e., lack of response to plasma exchange therapy and glucocorticoids) is considered medically necessary.

- Rituxan is considered medically necessary for individuals 18 years of age or older with Evans syndrome with documentation of ALL of the following:
  
  1. Individual has failed ANY of the following therapies:
     
     - Corticosteroids
     - Intravenous immune globulin
     - Other immunosuppressants such as Cyclosporine or Mycophenolate or Vincristine or Cyclophosphamide

  2. Splenectomy has failed or is otherwise determined by the treating provider that surgery poses a greater risk to the individual than medical treatment with Rituxan

  3. Results of HBsAg and anti-HBc are documented in the medical records

  4. Dosage is no greater than 375 mg/m^2 given as an intravenous (IV) infusion once weekly for 4 doses
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Criteria: (cont.)

Other Uses: (cont.)

➢ Rituxan for all other nononcologic uses not previously listed or if above criteria not met is considered experimental or investigational based upon:

1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
2. Insufficient evidence to support improvement of the net health outcome, and
3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
4. Insufficient evidence to support improvement outside the investigational setting.

These uses include, but are not limited to:

- Induction immunosuppressive therapy for kidney transplantation
- Mixed connective tissue disease (MCTD)
- Multiple Sclerosis
- Myasthenia gravis
- Minimal change nephropathy
- Paroxysmal cold hemoglobinuria
- Prophylaxis for graft-versus-host disease
- Treatment of antibody-mediated rejection (ABMR) after pancreatic islet transplantation
- Treatment of ABMR in solid organ transplant recipients
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Resources:

Literature reviewed 11/14/17. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 03/31/15 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Resources: (cont.)


Rituxan (rituximab) Package Insert:
- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Two-1000 mg IV infusions separated by 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.</td>
</tr>
<tr>
<td></td>
<td>Rituxan is given in combination with methotrexate.</td>
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<tr>
<td></td>
<td>Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wegener’s Granulomatosis (also referred to as Granulomatosis with polyangiitis [GPA])</th>
<th>375 mg/m² as an intravenous (IV) infusion once weekly for 4 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic Polyangiitis (MPA)</td>
<td>Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment.</td>
</tr>
<tr>
<td>Safety and efficacy of treatment with subsequent courses of Rituxan have not been established.</td>
<td></td>
</tr>
</tbody>
</table>
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah niiłiiłii Blue Cross Blue Shield of Arizona haadá yit’éego bina’idílkiidgo éi doodago Háída biiá aniyeediíí t’àadoo le'é yina’idílkiidgo bee hazh’äníí hólo díí t’àâ hazaadk’ehí háká a’dooowolgo bee haz’a doo baah niiłigóó. Atá’ halné’ííí kojí bích’í’ hodiihí 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thợ dịch viễn, xin gọi 877-475-4799.

Arabic: إن كان لديك أو أدى شخص تساذه أسئلة بشخص المعلومة Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أي تكلفة . للتحدث مع مترجم التصل ب 877-475-4799.
RITUXAN (rituximab), NONONCOLOGIC USES (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinituunan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 무담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 매개하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳をお手伝いする場合、877-475-4799 までお電話ください。

Farsi:

آگ کشیده، یا کسی که شما به او کمک می‌کنید، سوالی نمودید که ممکن است اطلاعاتی به زبان خود را به دوستان دوستان خویش دهد. 877-475-4799.

Assyrian:

Stas, gii ko paya dada neka kekk na Blue Cross Blue Shield of Arizona, nekkene paya dada, nekkene nekkene, wina nekkene, nekkene. 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคุณช่วยเหลือผู้ติดยา Blue Cross Blue Shield of Arizona มีสิทธิ์ได้รับความช่วยเหลือและข้อมูลภาษาของคุณได้โดยไม่เสียค่าใช้จ่าย โทร 877-475-4799