Rituximab Products:
Rituximab (Rituxan®), Rituximab-abbs (Truxima®), Rituximab-pvvr (Ruxience®), Rituximab-arrx (Riabni™)

Prior Authorization Drug Coverage Policy

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This Drug Coverage Policy provides parameters for the coverage of rituximab (Rituxan®), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™). Consideration of medically necessary indications are based upon U.S. Food and Drug Administration (FDA) indications, recommended uses within the Centers of Medicare & Medicaid Services (CMS) five recognized compendia, including the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (Category 1 or 2A recommendations), and peer-reviewed scientific literature eligible for coverage according to the CMS, Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 titled, "Off-Label Use of Anti-Cancer Drugs and Biologics." This policy evaluates whether the drug therapy is proven to be effective based on published evidence-based medicine.

Drug Description[1-4]

Rituximab (Rituxan®), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™) are monoclonal antibodies that target the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to cluster of differentiation (CD) 20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

Rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®), and rituximab-arrx (Riabni™) are FDA approved biosimilar products to rituximab.

FDA Indications[1-4]

Rituximab (Rituxan), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™) are FDA indicated for the following:

- Adult patients with Non-Hodgkin's Lymphoma (NHL)
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP).
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- Adult patients with Chronic Lymphocytic Leukemia (CLL)
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).

NCCN Compendium Supported Indications (Rituxan, Truxima, Ruxience, Riabni)[5-8]

- Acute lymphoblastic leukemia (ALL)
- B-Cell Lymphomas/Non-Hodgkin's lymphomas (NHL)
- Central nervous system cancers
- Chronic lymphocytic leukemia (CLL) / Small lymphocytic lymphoma (SLL)
- Hairy Cell Leukemia
- Hematopoietic Cell Transplantation
- Histiocytic Neoplasms
- Hodgkin Lymphoma
- Management of Immunotherapy-Related Toxicities
- Primary Cutaneous Lymphomas
- Waldenström's macroglobulinemia / Lymphoplasmacytic lymphoma

Coverage Determinations[1-45]

Rituximab (Rituxan®), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™) will require prior authorization. These agents are considered medically necessary for the following oncology indications if all criteria below are met.

In addition to the below criteria, rituximab-arrx (Riabni™) must confirm inadequate response, intolerance, contraindication, or clinical rationale for not using rituximab (Rituxan®), rituximab-abbs (Truxima®), or rituximab-pvvr (Ruxience®).

Acute lymphoblastic leukemia (ALL)

- Induction/consolidation therapy for Philadelphia chromosome-negative ALL in members:
  - 15 years of age to <65 years of age as a component of **ONE** of the following:
    - GRAALL-2005 regimen (daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide) [patients aged <60 years]
    - HyperCVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine)
- Induction therapy for Philadelphia chromosome-negative ALL in members:
  - aged ≥65 years **AND**
  - as a component of GMALL (idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine (moderate intensity)
- Therapy for relapsed/refractory for ALL in members as a component of MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone) with **ONE** of the following:
  - Disease is Philadelphia chromosome-negative (Ph-) **OR**
  - Disease is Philadelphia chromosome-positive (Ph+) refractory to TKIs

<u>Recommended Study doses include:</u>
Administer 375 mg/m² once weekly for 4 - 8 doses.

B-Cell Lymphomas/Non-Hodgkin's lymphomas (NHL), including, but not limited to:

- AIDS-related B-Cell Lymphomas
  - Used in AIDS-related Burkitt Lymphoma as a component of
    - modified CODOX-M/IVAC with rituximab
    - DA-EPOCH-R
    - R-HyperCVAD
  - Second-line or subsequent therapy for relapse of AIDS-related Burkitt lymphoma in combination with
    - DA-EPOCH-R (if not previously given as first-line)
    - RICE (with intrathecal methotrexate if not previously given)
    - RIVAC (with intrathecal methotrexate if not previously given)
    - RGDP
    - High-dose Cytarabine
  - Used in AIDS-related Diffuse Large B-Cell Lymphoma (DLBCL), primary effusion lymphoma, HHV8-positive diffuse large B-cell lymphoma not otherwise specified (NOS) as a component of
    - R-EPOCH
    - CHOP + rituximab
  - Second-line or subsequent therapy in AIDS related diffuse large B-cell Lymphoma, primary effusion lymphoma, HHV8-positive diffuse large B-cell lymphoma not otherwise specified (NOS) in
    - Patients with intention to proceed to transplant in combination with
      - DHAP
      - DHAX
      - ESHAP

        - GDP or (gemcitabine, dexamethasone, carboplatin)
        - GemOX
        - ICE
        - MINE
    - Non-candidates for transplant in combination with
        - Polatuzumab vedotin-piiq with or without Bendamustine AND
            - (after ≥2 prior therapies)
        - Lenalidomide (for non-germinal center DLBCL)
        - Gemcitabine + Vinorelbine
        - CEPP
        - DA-EPOCH
        - CEOP
        - GDP or (gemcitabine, dexamethasone, carboplatin)
        - GemOX
    - Non-candidates for transplant as a single agent
- Burkitt Lymphoma
    - Preferred induction therapy for high-risk disease in patients <60 years of age in combination with
        - CODOX-M/IVAC
        - DA-EPOCH and intrathecal methotrexate
        - HyperCVAD
    - Preferred induction therapy for low-risk and high-risk disease in patients ≥60 years of age in combination with
        - DA-EPOCH and intrathecal methotrexate
    - Preferred induction therapy for low-risk disease in patients <60 years of age in combination with
        - CODOX-M
        - DA-EPOCH and intrathecal methotrexate
        - HyperCVAD
    - Second-line therapy with disease relapse >6-18 months after appropriate first-line therapy or for patients with partial response to second-line therapy as additional therapy (if not previously given) for relapsed/refractory disease as a component of
        - DA-EPOCH-R and intrathecal methotrexate
        - RICE and intrathecal methotrexate if not received previously
        - RIVAC and intrathecal methotrexate if not received previously
    - Useful in certain circumstances as second-line therapy for patients with disease relapse >6-18 months after appropriate first-line therapy or for patients with partial response to second-line therapy as additional therapy (if not previously given) for relapsed or refractory disease in combination with
        - RGDP
        - High-dose Cytarabine
- Castleman's Disease
    - Multicentric disease as primary treatment for patients with fulminant human herpesvirus-8 with or without organ failure in combination with

        - CHOP
        - CVAD
        - CVP
        - Doxorubicin Liposomal
        - As a single agent if patient is not a candidate for combination therapy
    - Multicentric disease with no organ failure with or without prednisone for patients who are HIV negative and human herpesvirus-8 **negative** as
        - Primary treatment
        - Alternate treatment for relapsed disease
        - If no response to alternate primary treatment
    - Multicentric disease with no organ failure with or without Doxorubicin Liposomal and/or prednisone for patients who are human herpesvirus-8 **positive** as
        - Primary treatment
        - Alternate treatment for relapsed disease
        - If no response to alternate primary treatment
    - Multicentric disease with no organ failure for progression ≥6 months following completion of rituximab used with or without prednisone
    - Multicentric disease that is refractory or progressive disease as initial treatment or if no response to initial treatment for refractory or progressive disease in combination with
        - Doxorubicin Liposomal
        - CHOP
        - CVAD
        - CVP
    - Multicentric disease that has progressed following treatment of relapsed/refractory or progressive disease as subsequent therapy in combination with
        - Bortezomib
        - Lenalidomide
        - Thalidomide
    - Unicentric disease with or without prednisone and/or cyclophosphamide if used for **ANY ONE** of the following:
        - Surgically unresectable disease
        - Symptomatic disease following incomplete resection
        - Second-line therapy for relapsed or refractory disease
- Diffuse Large B-Cell Lymphoma (DLBCL)
    - First-line therapy for:
        - Extracutaneous primary cutaneous DLBCL, leg type **OR**
        - Grey zone lymphoma **OR**
        - Stage I-II disease**^ OR**
        - Stage III-IV disease
            - As a component of
                - R-CHOP
                - DA-EPOCH-R**^** (not supported for Stage I-II disease)

- For patients with poor left ventricular function as a component of
  - RCEPP
  - RCDOP
  - DA-EPOCH-R
  - RCEOP
  - RGCVP
- For very frail patients and patients >80 years of age with comorbidities as a component of
  - RCEPP
  - RCDOP
  - R-mini-CHOP
  - RGCVP

- First-line therapy for primary mediastinal large B-cell lymphoma as a component of
  - RCHOP
  - DA-EPOCH-R
- Second-line or subsequent therapy for partial response, no response, relapsed, progressive, or refractory disease in
  - Patients with intention to proceed to transplant in combination with
    - DHAP
    - DHAX
    - ESHAP
    - GDP or (gemcitabine, dexamethasone, carboplatin)
    - GemOX
    - ICE
    - MINE
  - Non-candidates for transplant in combination with
    - Polatuzumab vedotin-piiq with or without Bendamustine AND
      - (after ≥2 prior therapies)
    - Lenalidomide (for non-germinal center DLBCL)
    - CEPP
    - DA-EPOCH
    - CEOP
    - GDP or (gemcitabine, dexamethasone, carboplatin)
    - GemOX
  - Non-candidates for transplant as a single agent
- Used for primary cutaneous diffuse large B-cell lymphoma, leg type
  - First-line therapy with involved site radiation therapy **OR**
  - Second-line therapy (if not previously received) for solitary regional, T1-2 disease **OR**
  - First-line therapy for generalized cutaneous, T3 disease
    - As a component of
      - RCHOP
    - For patients with poor left ventricular function as a component of
      - RCEPP

        - RCDOP
        - DA-EPOCH-R
        - RCEOP
        - RGCVP
    - For very frail patients and patients >80 years of age with comorbidities as a component of
        - RCEPP
        - RCDOP
        - R-mini-CHOP
        - RGCVP
- Follicular Lymphoma (FL, grade 1-2)
    - Elderly or Infirm patients:
        - First-line therapy for stage I, contiguous stage II, non-contiguous stage II disease, or for patients with indications for treatment with stage III or IV disease **OR**
        - Second-line or subsequent therapy (if not previously given as first-line) for refractory or progressive disease in patients with indications for treatment
            - As a single agent (when tolerability of combination chemotherapy is a concern) **OR**
            - In combination with Chlorambucil **OR**
            - In combination with Cyclophosphamide
    - First-line consolidation therapy in patients with indications for treatment if initially treated with single-agent rituximab
    - First-line therapy for stage I, II pediatric-type follicular lymphoma in adults with extensive local disease who are not candidates for excision or involved site radiation therapy as a component of RCHOP
    - First-line therapy for stage I, contiguous stage II, non-contiguous stage II disease, or for patients with indications for treatment with stage III or IV disease as
        - Single agent (consider in patients that were initially observed and have progressed with a low tumor burden)
        - In combination with CHOP
        - In combination with RCVP
        - In combination with bendamustine
        - In combination with lenalidomide
    - Maintenance therapy
        - First-line consolidation or extended dosing for patients initially presenting with high tumor burden (stage III, IV) who achieve a complete or partial response following treatment with R-CHOP or RCVP
        - Second-line consolidation or extended dosing
        - Can be considered for patients with histologic transformation to DLBCL that is coexisting with extensive follicular lymphoma who achieve a complete response to chemoimmunotherapy
    - Second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment in combination with/component of

- A single agent
- Bendamustine
- RCHOP
- RCVP
- Lenalidomide
- DHAP
- DHAX
- ESHAP
- GDP (or gemcitabine, dexamethasone, and carboplatin)
- GemOX
- ICE
- MINE
- CEPP
- DA-EPOCH
- CEOP
- Polatuzumab vedotin-piiq with or without bendamustine
    - (after ≥2 prior therapies)

- Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) with translocations of MYC and BCL2 and/or BCL6 in patients who have received minimal or no prior chemotherapy as a component of
    - DA-EPOCH-R
    - HyperCVAD-R
    - R-CODOX-M alternating with R-IVAC
- Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) without translocations of MYC and BCL2 and/or BCL6 in patients who have received minimal or no prior chemotherapy as a component of
    - RCHOP
    - dose-dense RCHOP-14
    - DA-EPOCH-R
- Treatment of histologic transformation to DLBCL without translocations of MYC and BCL2 and/or BCL6 in patients who have received minimal or no prior chemotherapy and have poor left ventricular function as a component of
    - RCEPP
    - RCDOP
    - DA-EPOCH-R
    - RCEOP
    - RGCVP
- Treatment of histologic transformation to DLBCL without translocations of MYC and BCL2 and/or BCL6 in patients who have received minimal or no prior chemotherapy and are very frail and for patients >80 years of age with comorbidities as a component of
    - RCEPP
    - RCDOP
    - R-mini-CHOP

        - RGCVP
    - Treatment of histologic transformation to diffuse large B-cell lymphoma in patients who have received multiple lines of chemoimmunotherapy for indolent or transformed disease in combination with/component of
        - As a single agent
        - Bendamustine
        - DHAP
        - DHAX
        - ESHAP
        - GDP (or gemcitabine, dexamethasone, and carboplatin)
        - GemOX
        - ICE
        - MINE
        - CEPP
        - DA-EPOCH
        - CEOP
        - Lenalidomide
        - Gemcitabine and Vinorelbine
        - Polatuzumab vedotin-piiq with or without bendamustine
    - Used in combination with Polatuzumab vedotin-piiq with or without bendamustine as treatment of histologic transformation to diffuse large B-cell lymphoma without translocations of MYC and BCL2 and/or BCL6 in patients who have received minimal or no prior chemotherapy prior to histologic transformation and have no response or progressive disease after chemoimmunotherapy
- Gastric MALT Lymphoma
    - Used as a single agent in patients with indications for treatment as
        - Initial therapy (if involved site radiation therapy is contraindicated) for stage I1, or I2, or stage II1 disease in patients who are H-pylori-positive and t(11;18) positive or who are H. pylori-negative
        - First-line therapy for stage IIE, or II2, or stage IV disease (distant nodal, advanced stage)
        - Additional therapy for stage I1, or I2, or stage II1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
        - Additional therapy after involved site radiation therapy ISRT alone for stage I1, or I2, or stage II1 disease that is lymphoma positive after restaging with endoscopy
        - Second-line or subsequent therapy for recurrent or progressive disease (if longer duration of remission)
    - Used as a component of RCHOP, **OR** RCVP, **OR** in combination with Bendamustine in patients with indications for treatment as
        - First-line therapy for stage IIE, or II2, or stage IV disease (distant nodal, advanced stage)

        - As additional therapy for stage I1, or I2, or stage II1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
        - As additional therapy after ISRT or rituximab alone for stage I1, or I2, or stage II1 disease that is lymphoma positive after restaging with endoscopy
    - Used as a single agent **OR** in combination with chlorambucil **OR** cyclophosphamide in elderly or infirm patients with indications for treatment when tolerability of combination chemotherapy is a concern as
        - First-line therapy for stage IIE, or II2, or stage IV disease (distant nodal, advanced stage)
        - Additional therapy for stage I1, or I2, or stage II1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
        - Additional therapy after ISRT or rituximab alone for stage I1, or I2, or stage II1 disease that is lymphoma positive after restaging with endoscopy
        - Second-line or subsequent therapy for recurrent or progressive disease
    - Consolidation as optional first-line extended therapy in patients initially treated with single agent rituximab
    - Preferred second-line or subsequent therapy for recurrent or progressive disease in patients with indications for treatment
        - In combination with bendamustine (not recommended if previously treated with bendamustine)
        - As a component RCHOP
        - As a component of RCVP
        - In combination with lenalidomide (including for the elderly or infirm when tolerability of combination chemotherapy is a concern)
- High Grade B-Cell Lymphoma
    - Used as induction therapy for high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified as a component of
        - DA-EPOCH-R
        - HyperCVAD-R
        - R-CODOX-M /R-IVAC
    - Used as induction therapy for high-grade B-cell lymphomas, not otherwise specified* as a component of RCHOP
        - *RCHOP has been associated with inferior outcomes for patients with high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma)
    - Second-line or subsequent therapy for partial response, no response, relapsed, progressive, or refractory disease in
        - Patients with intention to proceed to transplant in combination with
            - DHAP
            - DHAX
            - ESHAP

        - GDP (or gemcitabine, dexamethasone, and carboplatin)
        - GemOX
        - ICE
        - MINE
    - Non-candidates for transplant in combination with
        - Lenalidomide (non-germinal center lymphoma)
        - Bendamustine
        - CEPP
        - DA-EPOCH
        - CEOP
        - GDP
        - GemOX
        - Gemcitabine and Vinorelbine regimen
    - Non-candidates for transplant in combination with Polatuzumab vedotin-piiq with or without bendamustine
        - (after ≥2 prior therapies)
    - Non-candidates for transplant as a single agent
- Histologic transformation of Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma
    - Treatment of patients who have received minimal or no prior chemotherapy as a component of
        - RCHOP
        - dose-dense RCHOP-14
        - DA-EPOCH-R
    - Treatment of patients who have received minimal or no prior chemotherapy and have poor left ventricular function as a component of
        - RCEPP
        - RCDOP
        - DA-EPOCH-R
        - RCEOP
        - RGCVP
    - Treatment of patients who have received minimal or no prior chemotherapy and are very frail and for patients >80 years of age with comorbidities as a component of
        - RCEPP
        - RCDOP
        - R-mini-CHOP
        - RGCVP
    - Treatment for patients who have received multiple lines of chemoimmunotherapy for indolent or transformed disease in combination with/component of
        - As a single agent
        - Bendamustine
        - DHAP
        - DHAX

        - ESHAP
        - GDP (or gemcitabine, dexamethasone, and carboplatin)
        - GemOX
        - ICE
        - MINE
        - CEPP
        - DA-EPOCH
        - CEOP
        - Lenalidomide
        - Gemcitabine + Vinorelbine
    - Used in combination with Polatuzumab vedotin-piiq with or without bendamustine for patients who have received multiple prior therapies including ≥2 lines of chemoimmunotherapy for indolent or transformed disease
- Mantle Cell Lymphoma
    - Less aggressive induction therapy for stage I-II disease (localized presentation, extremely rare) as initial therapy, or for partial response, progression, or relapse after initial treatment with involved site radiation therapy alone, or for aggressive stage II bulky, III, or IV disease, or symptomatic indolent stage II bulky, III, or IV TP53 mutation positive disease in patients who are not candidates for high-dose therapy/autologous stem cell rescue as a component of
        - RBAC500
        - modified HyperCVAD with rituximab regimen in patients older than 65 years
    - Aggressive induction therapy for stage I-II disease that had a partial response, progression, or relapse after initial treatment with involved site radiation therapy alone, or for aggressive stage II bulky, III, or IV disease, or symptomatic indolent stage II bulky, III, or IV TP53 mutation negative* disease in patients who are candidates for high-dose therapy/autologous stem cell rescue (HDT/ASCR) as a component of
        - RDHA + platinum
        - Alternating RCHOP/RDHAP
        - NORDIC regimen
        - R-HyperCVAD**
            - *Aggressive induction therapy followed by HDT/ASCR may not be appropriate for TP53 positive disease. Optimal treatment is unknown.
            - **Rituximab + ibrutinib can be used as a pre-treatment to limit the number of cycles of RHyperCVAD/rituximab maintenance
    - Less aggressive induction therapy for stage I-II disease as initial therapy (localized presentation, extremely rare), or for partial response, progression, or relapse after initial treatment with involved site radiation therapy alone, or for aggressive stage II bulky, III, or IV disease, or symptomatic indolent stage II bulky, III, or IV TP53 mutation positive disease in patients who are not candidates for high dose therapy/autologous stem cell rescue in combination with/component of

        - Bendamustine
        - Lenalidomide
        - VR-CAP
        - RCHOP
        - modified HyperCVAD with rituximab regimen in patients older than 65 years+H58
    - Second-line therapy for patients with stage I-II, aggressive stage II bulky, III, or IV, or symptomatic indolent stage II bulky, III, or IV disease to achieve a complete response after very good partial response (PR) to induction therapy with the goal of proceeding to high-dose therapy/autologous stem cell rescue in combination with
        - Bendamustine (if not previously given)
        - Bortezomib
        - Lenalidomide
        - CHOP with rituximab
        - VR-CAP (if not previously given)
    - Second-line therapy for stage I-II, aggressive stage II bulky, III, or IV, or symptomatic indolent stage II bulky, III, or IV disease in patients who have stable disease or partial response with substantial disease after induction therapy, or who have relapsed or progressed following an extended response duration to prior chemoimmunotherapy (> expected median progression free survival) in combination with
        - Bendamustine (if not previously given)
        - Bortezomib
        - Ibrutinib
        - Lenalidomide
    - Second-line therapy for stage I-II, aggressive stage II bulky, III, or IV, or symptomatic indolent stage II bulky, III, or IV disease in patients who have stable disease or partial response with substantial disease after induction therapy, or who have relapsed or progressed following a short response duration to prior chemoimmunotherapy (< expected median progression free survival) in combination with
        - Ibrutinib
        - Lenalidomide
    - Second-line therapy for stage I-II, aggressive stage II bulky, III, or IV, or symptomatic indolent stage II bulky, III, or IV disease in patients who have stable disease or partial response with substantial disease after induction therapy, or who have relapsed or progressed following an extended response duration to prior chemoimmunotherapy (> expected median progression free survival) in combination with/component of
        - As a single agent
        - Polatuzumab vedotin-piiq with or without bendamustine
            - (after ≥2 prior therapies)
        - PEPC

        - Bendamustine + Bortezomib
        - Gemcitabine + Vinorelbine
        - DHAP
        - DHAX
        - ESHAP
        - GDP (or gemcitabine, dexamethasone, and carboplatin)
        - GemOX
        - ICE
        - MINE
        - CEPP
        - DA-EPOCH
        - CEOP
        - RCHOP (if not previously given)
        - VR-CAP (if not previously given)
    - Consider single-agent maintenance therapy for aggressive stage II bulky, III, or IV disease, or symptomatic indolent stage II bulky, III, or IV disease following complete response or very good partial response to less aggressive induction therapy* or following high-dose therapy with autologous stem cell rescue
        - ***Prospective trial data suggests no benefit of maintenance therapy following induction therapy with bendamustine + rituximab**
            - Maintenance therapy following VR-CAP or RBAC500 therapy has not been tested
- Nodal Marginal Zone Lymphoma (MZL)
    - First-line therapy for stage I, contiguous stage II, non-contiguous stage II, or stage III, IV disease in patients with indications for treatment in combination/component of
        - As a single agent
        - Lenalidomide
        - Bendamustine
        - RCHOP
        - RCVP
    - Second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment in combination/component of
        - As a single agent (if longer duration of remission)
        - Bendamustine (not recommended if previously treated with bendamustine)
        - Lenalidomide including for the elderly or infirm when tolerability of combination chemotherapy is a concern
        - RCHOP
        - RCVP
    - First-line therapy **OR** second-line or subsequent therapy for refractory or progressive disease for stage I, contiguous stage II, non-contiguous stage II, or stage III, IV disease in elderly or infirm patients with indications for treatment when tolerability of combination chemotherapy is a concern as

        - As a single agent
        - In combination with chlorambucil
        - In combination with cyclophosphamide
    - Consolidation as optional first-line extended therapy in patients initially treated with single agent rituximab
- Non-gastric MALT Lymphoma (Noncutaneous)
    - First-line therapy for stage I-II disease in selected cases
    - First-line therapy for stage IV disease or recurrent stage I-II disease in patients with indications for treatment in combination/component of
        - As a single agent
        - RCHOP
        - RCVP
        - Bendamustine
    - Second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment in combination with/component of
        - As a single agent (if longer duration of remission)
        - Bendamustine (not recommended if previously treated with bendamustine)
        - RCHOP
        - RCVP
        - Lenalidomide (including for the elderly or infirm when tolerability of combination chemotherapy is a concern)
    - Used as first-line therapy **OR** second-line or subsequent therapy for stage IV disease or recurrent stage I-II disease in elderly or infirm patients with indications for treatment when tolerability of combination chemotherapy is a concern
        - As a single agent
        - In combination with Chlorambucil
        - In combination with Cyclophosphamide
    - Consolidation as optional first-line extended therapy in patients initially treated with single agent rituximab
- Post-transplant lymphoproliferative disorder (PTLD)
    - As concurrent chemoimmunotherapy for CD20+ disease for frail patients who cannot tolerate anthracyclines in combination with/component of CHOP, CVP, CEPP, CEOP therapy for
        - First-line therapy for monomorphic (B-cell type) or systemic polymorphic (B-cell type) PTLD **OR**
        - Second-line therapy for partial response, persistent or progressive monomorphic (B-cell type) or polymorphic (B-cell type) PTLD
    - Single agent therapy as
        - First-line therapy for monomorphic (B-cell type) or polymorphic (B-cell type) PTLD **OR**
        - Second-line therapy for partial response, persistent or progressive non-destructive lesions or for partial response, persistent or progressive

monomorphic (B-cell type) PTLD if immunosuppressive was reduced in first-line therapy **OR**
- Maintenance therapy for polymorphic (B-cell type) PTLD achieving complete response on first-line therapy

- Used in combination with high-dose methotrexate for primary CNS PTLD (B-cell type)
- Sequential chemoimmunotherapy as a single agent followed by CHOP with or without rituximab as
  - First-line therapy for monomorphic (B-cell type) or systemic polymorphic (B-cell type) PTLD **OR**
  - Second-line therapy for partial response, persistent or progressive monomorphic (B-cell type) or polymorphic (B-cell type) PTLD
- Second-line and subsequent therapy for patients with partial response, persistent or progressive disease after receiving chemoimmunotherapy as first-line treatment for monomorphic PTLD (B-cell type) in combination with/component of
  - As a single agent
  - Bendamustine
  - DHAP
  - DHAX
  - ESHAP
  - GDP (or gemcitabine, dexamethasone, and carboplatin)
  - GemOX
  - ICE
  - MINE
  - CEPP
  - DA-EPOCH
  - CEOP
  - Lenalidomide
  - Gemcitabine and Vinorelbine
  - Polatuzumab vedotin-piiq with or without bendamustine
    - (after ≥2 prior therapies

- Splenic Marginal Zone Lymphoma
  - Single agent therapy for symptomatic patients with splenomegaly who are
    - Hepatitis C negative
    - Hepatitis C positive with contraindications for hepatitis treatment
    - Hepatitis C positive with no response to appropriate hepatitis treatment
  - First-line therapy for disease recurrence following initial management of splenomegaly in treatment naïve patients with indications for treatment in combination with/component of
    - As a single agent
    - Bendamustine
    - RCHOP
    - RCVP

- First-line therapy (if treatment naïve) **OR** second-line or subsequent therapy for disease recurrence following initial management of splenomegaly in elderly or infirm patients with indications for treatment when tolerability of combination chemotherapy is a concern as
  - As a single agent
  - In combination with Chlorambucil
  - In combination with Cyclophosphamide
- Second-line (if previously treated with rituximab) or subsequent therapy for disease recurrence in patients with indications for treatment in combination with/component of
  - As a single agent (if previously treated with rituximab with a longer duration of remission)
  - Bendamustine (not recommended if previously treated with bendamustine)
  - RCHOP
  - RCVP
  - Lenalidomide (including the elderly or infirm when tolerability of combination chemotherapy is a concern)
- Consolidation as optional first-line extended therapy in patients initially treated with single agent rituximab

Recommended dosage:

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
Administer 375 mg/m^2 once weekly for 4 or 8 doses, given as single agent therapy.

Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
Administer 375 mg/m^2 once weekly for 4 doses, given as single agent therapy.

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
Administer 375 mg/m^2 on Day 1 of each cycle of chemotherapy for up to 8 doses, given in combination with Bendamustine days 1 and 2 OR CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) OR CVP (cyclophosphamide, vincristine, and prednisone).

May be initiated as single-agent therapy first-line for elderly or if chemotherapy deemed to be intolerable to patient.

In patients with complete or partial response, initiate rituximab maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. Administer rituximab as a single-agent every 8 weeks for 12 doses.

Non-progressing, Low-Grade, CD20-Positive, B-Cell NHL, after first-line CVP chemotherapy
Following completion of 6-8 cycles of CVP chemotherapy, administer 375 mg/m^2 once weekly for 4 doses at 6-month intervals to a maximum of 16 doses, given as single-agent therapy.

Diffuse Large B-Cell NHL

Administer 375 mg/m^2 on Day 1 of each cycle of chemotherapy for up to 8 infusions, given in combination with CHOP.

May be initiated as single-agent therapy first-line for elderly or if chemotherapy deemed to be intolerable to patient.

Rituximab is NOT indicated for maintenance therapy in patients who achieved CR (complete response).

Central nervous system cancers (CNS)

- Diagnosis of CNS cancer and **ANY ONE** of the following:
    - Leptomeningeal metastases from lymphomas and rituximab will be administered intrathecally
    - Primary CNS lymphoma as **ANY ONE** of the following:
        - Induction therapy
            - in combination with a methotrexate-containing regimen **OR**
            - as a single agent if member unsuitable or intolerant to methotrexate **OR**
            - in combination with temozolomide or lenalidomide if member unsuitable or intolerant to methotrexate
        - Consolidation therapy - in combination with a methotrexate-containing regimen with a complete response (CR) or a complete response unconfirmed (CRu) to induction therapy
        - Treatment in combination with high-dose methotrexate with or without ibrutinib for relapsed or refractory disease
        - Treatment as a single agent, or in combination with either temozolomide or lenalidomide for relapsed or refractory disease

<u>Recommended Study doses include:</u>

Intravenous

Newly diagnosed:

- 375 mg/m^2 on day 3 every 14 days (in combination with high-dose methotrexate) until disease progression or unacceptable toxicity, or for 2 doses beyond a complete response followed by monthly treatments for up to a total of 1 year **OR**
- 500 mg/m^2 on day 1 of each cycle for 5 to 7 induction cycles (in combination with high-dose methotrexate, vincristine, and procarbazine, followed by whole-brain radiotherapy and cytarabine consolidation) **OR**
- 375 mg/m^2 once per week beginning on day 3 of remission induction and continuing for 6 doses (in combination with high-dose methotrexate, leucovorin, and temozolomide and followed by etoposide and cytarabine consolidation therapy).

Refractory disease: 375 mg/m^2 on day 1 every 28 days (in combination with temozolomide) for 4 cycles, then followed by temozolomide monotherapy.

Intrathecal/Intraventricular

Study doses include ranges from 10-50 mg weekly to every 4 weeks

Chronic lymphocytic leukemia (CLL) / Small lymphocytic lymphoma (SLL), CD20-positive disease

- Diagnosis of CLL/SLL and **ANY ONE** of the following:
  - Initial therapy for treatment of histologic (Richter's) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) as a component of **ANY ONE** of the following:
    - R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab regimen
    - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) with rituximab regimen
    - OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen
  - Therapy for relapsed or refractory disease without del(17p)/TP53 mutation in frail patients with significant comorbidity or age ≥65 years and younger patients with significant comorbidities with **ANY ONE** of the following:
    - Idelalisib
    - Venetoclax
    - Alemtuzumab
    - Chlorambucil
    - Lenalidomide
    - High-dose methylprednisolone
    - Reduced-dose FCR (fludarabine, cyclophosphamide, and rituximab)
    - Reduced-dose PCR (pentostatin, cyclophosphamide, and rituximab)
  - Therapy for relapsed or refractory disease with del(17p)/TP53 with **ANY ONE** of the following:
    - Idelalisib
    - Venetoclax
    - Alemtuzumab
    - Lenalidomide
    - High-dose methylprednisolone
  - Therapy for relapsed or refractory disease without del(17p)/TP53 mutation in patients <65 years without significant comorbidities with **ANY ONE** of the following:
    - Idelalisib
    - Venetoclax
    - Alemtuzumab
    - High-dose methylprednisolone
    - Lenalidomide
    - Component of FCR
    - Component of PCR

- First-line therapy for **ANY ONE** of the following individuals:
  - Without del(17p)/TP53 mutation if <65 years of age without significant comorbidities as a component of **ANY ONE** of the following:
    - FCR regimen (preferred with IGHV mutated CLL)
    - FR regimen [not recommended for CLL with del(11q)]
  - Without del (17p)/TP53 mutation if ≥65 years and younger patients with or without significant comorbidities in combination with bendamustine (not recommended for frail individuals)
  - With del(17p)/TP53 mutation in combination with **ANY ONE** of the following:
    - Alemtuzumab
    - High-dose methylprednisolone

Recommended dosage:

- Administer 375 mg/m² weekly x 4-8 doses; **OR**
- 375 mg/m² cycle 1, then 500 mg/m² every 28 days cycles 2-6 (6 total doses).
- Treatment with Rituximab given in combination with above noted agents.

Hairy Cell Leukemia

- Preferred therapy in patients with indications for treatment in combination with **ANY ONE** of the following:
  - Cladribine for less than complete response or relapse within 2 years of complete response following initial treatment with pentostatin
  - Pentostatin for less than complete response or relapse within 2 years of complete response following initial treatment with cladribine
  - Cladribine for relapse ≥2 years following initial treatment
  - Pentostatin for relapse ≥2 years following initial treatment
  - Vemurafenib for progression after therapy for relapsed/refractory disease
- Used as a single agent in patients with indications for treatment who are unable to receive purine analogs for
  - Less than complete response following initial treatment with cladribine or pentostatin **OR**
  - For relapsed disease

Recommended Study doses include:

- Pentostatin: Rituximab was given intravenously at a dose of 375 mg/m^2 concurrently with pentostatin every 2 weeks or sequentially for 8 weekly doses, beginning 1 month after the completion of pentostatin treatment.
- Cladribine: Rituximab was given intravenously at a dose of 375 mg/m2 weekly either from the start or from 2 months after the end of cladribine treatment.

Hematopoietic Cell Transplantation

- For chronic graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Recommended Study doses include:

- Administer 375 mg/m² once weekly for 4 doses; a second course of 4 weekly doses may be administered 8 weeks after initial therapy for lack of or incomplete response **OR**
- 375 mg/m^2 once weekly for 4 to 8 doses.

Hodgkin's lymphoma

- Primary treatment as a single agent for stage III-IV disease
- Second-line or subsequent systemic therapy (if not previously used) for progressive, relapsed, or refractory disease as a single agent with or without ISRT **OR**
    - in combination with **ANY ONE** of the following:
        - DHAP (dexamethasone, cisplatin, high-dose cytarabine)
        - ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)
        - ICE (ifosfamide, carboplatin, etoposide)
        - IGEV (ifosfamide, gemcitabine, vinorelbine)
- Primary treatment as a component of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab, or CVP (cyclophosphamide, vinblastine, prednisolone) + rituximab
    - with ISRT for stage IA (bulky) or IIA disease (bulky or non-contiguous)
    - with ISRT for stage IB or IIB disease
    - with or without ISRT for stage III-IV disease (based on clinical judgment)
- May be considered as maintenance therapy for patients treated with second-line systemic therapy with rituximab alone for progressive, relapsed, or refractory disease

Recommended Study doses include:

Administer 375 mg/m^2 once weekly for 4 weeks **OR** 375 mg/m^2 once weekly for 4 weeks followed by maintenance dosing of 375 mg/m^2 once weekly for 4 weeks every 6 months for 2 years.

Primary Cutaneous B-Cell Lymphomas

- Therapy for generalized disease (skin only) **AND ONE** of the following
    - T3 primary cutaneous marginal zone
    - Follicle center lymphoma

Recommended Study doses include:

Administer 375 mg/m² once weekly for 4 - 8 doses, given as single-agent.

Management of Immunotherapy-Related Toxicities

- The member has been treated with an immuno-oncology therapy **AND**
- Diagnosis of non-viral encephalitis due to immuno-oncology treatment is made **AND**

- The member has encephalitis after viral etiology is ruled out in patients positive for autoimmune encephalopathy antibody ***or***
- The member has toxicities refractory to methylprednisolone with or without intravenous immunoglobulin (IVIG)

Recommended Study doses include:
Administer 375 mg/m² once weekly for 4 treatments in a six-month period

Waldenström's macroglobulinemia / lymphoplasmacytic lymphoma

- Consider for maintenance therapy following a complete, very good partial, partial, or minor response to primary therapy if regimen included rituximab
- Used as primary therapy, or consider for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response, or as alternative therapy for previously treated disease that does not respond to primary therapy or for progressive or relapsed disease
    - in combination with bendamustine
    - in combination with bortezomib and dexamethasone
    - in combination with ibrutinib
    - in combination with cyclophosphamide and dexamethasone
    - as a single agent
    - in combination with bortezomib
    - in combination with cyclophosphamide and prednisone
    - as a component of R-CHOP regimen
    - in combination with cladribine in patients who are not potential autologous stem cell transplant candidates
    - in combination with fludarabine in patients who are not potential autologous stem cell transplant candidates
    - as a component of FCR regimen in patients who are not potential autologous stem cell transplant candidates
- Used as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen or in combination with ixazomib and dexamethasone **AND ONE** of the following:
    - as primary therapy
    - for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response

Recommended Study doses include:

- Single-agent rituximab: 375 mg/m^2 once weekly for 4 weeks as a single agent; may repeat cycle one time after 12 weeks.
- In combination with cyclophosphamide and dexamethasone: 375 mg/m^2 on day 1 every 21 days for 6 cycles.
- In combination with bortezomib: 375 mg/m^2 on days 1, 8, 15, and 22 every 28 days during cycles 1 and 4; treatment is continued for 6 cycles, with a total of 8 rituximab doses.
- In combination with bortezomib and dexamethasone:

  - 375 mg/m^2 on days 1, 8, 15, and 22 every 35 days during cycles 2 and 5; treatment is administered for 6 cycles, with a total of 8 rituximab doses **OR**
  - 375 mg/m^2 on day 11 every 21 days for 4 cycles (induction); after a 12-week break, 4 additional maintenance cycles (spaced 12 weeks apart) were administered.
- In combination with bendamustine: 375 mg/m^2 on day 1 every 28 days for 4 cycles; single rituximab doses were also administered 1 week prior to the first cycle and 4 weeks after the last cycles (for a total of 6 rituximab doses).
- In combination with carfilzomib and dexamethasone: 375 mg/m^2 on days 2 and 9 every 21 days for 6 induction cycles, followed by 375 mg/m2 on day 2 every 8 weeks for 8 maintenance cycles.
- In combination with ibrutinib: 375 mg/m^2 once weekly during weeks 1-4 and weeks 17-20.

All indications:

- Rituximab (Rituxan), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™) will be approved for up to a 12-month duration, or as determined through clinical review.

Coverage Limitations

Treatment with rituximab (Rituxan), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®), and rituximab-arrx (Riabni™) is not considered medically necessary for members with the following concomitant conditions:

- Rituximab (Rituxan), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience®) and rituximab-arrx (Riabni™) are not recommended for use in patients with severe, active infections.
- Indications not supported by NCCN category 2A or higher recommendations may not be considered medically necessary

Contraindications/Warnings/Precautions[1]

- There are no contraindications listed in the US manufacturer's labeling.
- Warnings/precautions:
  - Fatal infusion reactions*
  - Severe mucocutaneous reactions*
  - Hepatitis B virus reactivation*
  - Progressive multifocal leukoencephalopathy*
  - Tumor lysis syndrome
  - Infections
  - Cardiovascular adverse reactions
  - Renal toxicity
  - Bowel obstruction and perforation
  - Embryo-Fetal toxicity

*Black Box Warnings

For specific recommendations on contraindications, warnings and precautions, patient monitoring, and on dose adjustments and discontinuation, please refer to the current prescribing information.

Billing

- Description: Inj., rituximab 10mg
  - HCPCS: J9312
- Description: Inj., rituximab-abbs (Truxima) 10mg
  - HCPCS: Q5115
- Description: Inj., rituximab-pvvr (Ruxience) 10mg
  - HCPCS: Q5119
- Description: Inj., rituximab-arrx (Riabni) 10mg
  - HCPCS: Q5123

Disclaimer

Drug Coverage Policies are developed as needed, regularly reviewed, updated at least annually, and are subject to change. Other policies and coverage determination guidelines may apply. Federal and state regulatory requirements and member specific benefit plan documents, if applicable, must be reviewed prior to this Drug Coverage Policy. This Drug Coverage Policy is for informational purposes only and does not constitute medical advice or dictate how providers should practice medicine. This policy should not be reproduced, stored in a retrieval system, or altered from its original form without written permission from Oncology Analytics, Inc.

Chemotherapy Regimens

ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
CEOP	cyclophosphamide, etoposide, vincristine, and prednisone
CEPP	cyclophosphamide, etoposide, prednisone, and procarbazine
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone)
CODOX-M	cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate
CODOX-M/IVAC	cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate regimen alternating with ifosfamide, cytarabine, etoposide, and intrathecal methotrexate
CVAD	cyclophosphamide, vincristine, doxorubicin, and dexamethasone
CVP	cyclophosphamide, vincristine, and prednisone
DA-EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
DA-EPOCH-R	rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
DHAP	dexamethasone, cisplatin, and cytarabine
DHAX	dexamethasone, cytarabine, and oxaliplatin
ESHAP	etoposide, methylprednisolone, cytarabine, and cisplatin

FCR	fludarabine, cyclophosphamide, and rituximab
FR	fludarabine, rituximab
GDP	gemcitabine, dexamethasone, cisplatin or gemcitabine, dexamethasone, carboplatin
GemOX	gemcitabine and oxaliplatin
GMALL	idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine, with or without rituximab
HyperCVAD	hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine
HyperCVAD-R or R-HyperCVAD	rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine
ICE	ifosfamide, carboplatin, and etoposide
IGEV	ifosfamide, gemcitabine, vinorelbine
IVAC	ifosfamide, cytarabine, etoposide, and intrathecal methotrexate
MINE	mesna, ifosfamide, mitoxantrone, and etoposide
NORDIC regimen	dose-intensified induction immunochemotherapy with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone [maxi-CHOP] alternating with rituximab and high-dose cytarabine
OFAR	oxaliplatin, fludarabine, cytarabine, and rituximab
PCR	pentostatin, cyclophosphamide, and rituximab
PEPC	prednisone, etoposide, procarbazine, and cyclophosphamide
RBAC500	rituximab, bendamustine and cytarabine
RCDOP	rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone
RCEOP	rituximab, cyclophosphamide, etoposide, vincristine, and prednisone
RCEPP	rituximab, cyclophosphamide, etoposide, prednisone, and procarbazine
RCHOP OR R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CODOX-M	rituximab, cyclophosphamide, vincristine, and doxorubicin with methotrexate
RCVP	rituximab, cyclophosphamide, vincristine, and prednisone
RDHA	rituximab, dexamethasone, cytarabine
RDHAP	rituximab, dexamethasone, cytarabine, and cisplatin
R-EPOCH	rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
RGCVP	rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone
RGDP	rituximab, gemcitabine, dexamethasone, cisplatin
RICE	rituximab, ifosfamide, carboplatin, and etoposide
RIVAC or R-IVAC	rituximab, ifosfamide, etoposide, and cytarabine
R-mini-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
VR-CAP	bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone

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