TYSABRI® FOR CROHN'S DISEASE

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.
TYSABRI FOR CROHN’S DISEASE (cont.)

Description:

Tysabri (natalizumab) is a humanized monoclonal antibody to alpha-4 integrin. Tysabri blocks leukocyte migration from the blood vessels to sites of inflammation by inhibiting the action of cell adhesion molecules.

Risk Evaluation and Mitigation Strategies (REMS):
Use of Tysabri is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

Definitions:

Adult: Age 18 years and older

Moderately to severely active Crohn’s disease:
Crohn’s Disease Activity Index [CDAI] ≥ 220 and ≤ 450
Induction of clinical response (defined as ≥ 70-point decrease in CDAI from baseline)
Clinical remission (defined as CDAI score < 150)

Conventional Crohn's disease therapies include: Sulfasalazine, mesalamine, corticosteroids (budesonide, methylprednisolone, etc), 6-mercaptopurine, azathioprine, methotrexate, and inhibitors of tumor necrosis factor-alpha.
TYSABRI FOR CROHN’S DISEASE (cont.)

Criteria:

TYSABRI IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED THE TOUCH PRESCRIBING PROGRAM.

For Tysabri for treatment of multiple sclerosis, see BCBSAZ Medical Coverage Guideline #O923, “Multiple Sclerosis Injectable Therapy”.

See Resources section for FDA-approved dosage and Crohn’s Disease Activity Index (CDAI) in Adults table.

- Tysabri is considered medically necessary to induce and maintain clinical response and remission in moderately to severely active Crohn’s disease with evidence of inflammation in adults who have had an inadequate response to, or are unable to tolerate, conventional therapy and tumor necrosis factor (TNF) inhibitors with documentation of ALL of the following:

  1. Tysabri is not being used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or TNF inhibitors (e.g., Enbrel, Humira, or Remicade)
  2. For individuals on chronic oral systemic corticosteroids, the corticosteroid will be tapered off within 6 months of starting Tysabri
  3. Absence of ALL of the following contraindications:
     - Hypersensitivity to Tysabri

- Criteria for renewal includes ALL of the following:

  1. Has experienced therapeutic benefit by 3 months of induction
  2. Is in clinical remission (a CDAI score of < 150) or has had a clinical response (reduction of CDAI score of ≥ 70 from baseline)
  3. Not to be used with systemic corticosteroid
  4. Not being used in combination with immunosuppressants or TNF inhibitor medications (e.g., Enbrel, Humira, or Remicade)
  5. No evidence of liver injury
  6. No evidence of opportunistic infections
  7. Not to be used with live vaccines
TYSABRI FOR CROHN’S DISEASE (cont.)

Criteria: (cont.)

➢ Tysabri for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

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

These indications include, but are not limited to:

• Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Resources:

Literature reviewed 03/07/18. We do not include marketing materials, poster boards and non-published literature in our review.

1. Biogen. TOUCH Prescribing Program. Accessed: 01/30/18, 02/04/2017, last updated 10/14/16

Tysabri Package Insert:
Resources: (cont.)

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn’s disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.</td>
<td>Only prescribers registered in the MS TOUCH® Prescribing Program may prescribe Tysabri for Crohn’s disease. Recommended dose: 300 mg intravenous infusion over one hour every four weeks. Discontinue Tysabri in patients who do not show evidence of therapeutic benefit by 12 weeks of induction therapy. For patients with Crohn’s disease who start Tysabri while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of Tysabri has occurred; if the patient with Crohn’s disease cannot be tapered off of oral corticosteroids within six months of starting Tysabri, discontinue Tysabri. Other than the initial six-month taper, prescribers should consider discontinuing Tysabri for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn’s disease.</td>
</tr>
</tbody>
</table>

Initial Approval Duration: 6 months

Renewal Approval Duration: 12 months
**TYSABRI FOR CROHN’S DISEASE (cont.)**

**Resources**: (cont.)

**Crohn’s Disease Activity Index in Adults:**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient reported stool pattern over seven days</strong></td>
<td>14 points per stool</td>
</tr>
<tr>
<td>Using diphenoxylate or loperamide for diarrhea</td>
<td>30 points</td>
</tr>
<tr>
<td><strong>Average abdominal pain rating over seven days</strong></td>
<td>0 points</td>
</tr>
<tr>
<td>None</td>
<td>0 points</td>
</tr>
<tr>
<td>Mild pain</td>
<td>35 points</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>70 points</td>
</tr>
<tr>
<td>Severe pain</td>
<td>105 points</td>
</tr>
<tr>
<td><strong>General wellbeing each day over seven days</strong></td>
<td>0 points</td>
</tr>
<tr>
<td>Well</td>
<td>0 points</td>
</tr>
<tr>
<td>Slightly below average</td>
<td>49 points</td>
</tr>
<tr>
<td>Poor</td>
<td>98 points</td>
</tr>
<tr>
<td>Very poor</td>
<td>147 points</td>
</tr>
<tr>
<td>Terrible</td>
<td>196 points</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>20 points</td>
</tr>
<tr>
<td>Iritis or uveitis</td>
<td>20 points</td>
</tr>
<tr>
<td>Erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis</td>
<td>20 points</td>
</tr>
<tr>
<td>Anal fissure, fistula, or abcess</td>
<td>20 points</td>
</tr>
<tr>
<td>Other fistula</td>
<td>20 points</td>
</tr>
<tr>
<td>Temperature over 100°F (37.8°C) in the last week</td>
<td>20 points</td>
</tr>
<tr>
<td><strong>Finding of an abdominal mass</strong></td>
<td></td>
</tr>
<tr>
<td>No mass</td>
<td>0 points</td>
</tr>
<tr>
<td>Possible mass</td>
<td>20 points</td>
</tr>
<tr>
<td>Definite mass</td>
<td>50 points</td>
</tr>
<tr>
<td><strong>Anemia and weight change</strong></td>
<td></td>
</tr>
<tr>
<td>Absolute deviation of hematocrit* from 47 percent in males or 42 percent in females</td>
<td>6 points per percent deviation</td>
</tr>
<tr>
<td>Percentage deviation from standard weight**</td>
<td>1 point for each percent deviation</td>
</tr>
</tbody>
</table>

**Total criteria point count:**

- 0 to 149 points: Asymptomatic remission
- 150 to 220 points: Mildly to moderately active Crohn's disease
- 221 to 450 points: Moderately to severely active Crohn's disease
- 451 to 1100 points: Severely active to fulminant disease
TYSABRI FOR CROHN’S DISEASE (cont.)

Resources: (cont.)

Crohn’s Disease Activity Index in Adults: (cont.)

Notes
* Absolute deviation of hematocrit is simply the difference in hematocrit from standard. A male patient with a hematocrit of 40 percent has an absolute deviation of 7.
** Percent deviation from standard weight is (1 - weight/standard weight) * 100, thus positive percent deviation represents weight loss, adding points to the CDAI.
Patients requiring steroids to remain asymptomatic are not considered to be in remission, but are referred to as being “steroid dependent.”
TYSABRI FOR CROHN’S DISEASE (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/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 níilíngíí Blue Cross Blue Shield of Arizona haada yíí éego bíí na’díldíldgo éí doodago Háída bíjá aníyeediígíí t’àadoo le’e yina’díldíldgo beehaz’áaníi hóliq díí t’àá hazaad’ehíí háká a’doooolgo beez’á doo bąqhq ilílingóó. Atá’ halne’íígií kojí’ bích’íj’ hodíilíníí 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插補項目的名稱 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 người dịch, xin gọi 877-475-4799.

Arabic: إن كان لديك أو أدى شخصيًا أسئلة بخصوص Blue Cross Blue Shield of Arizona للاستفسار، فممكن الحصول على المساعدة والمعلومات الضرورية بعنوان دون دفع كلفة. للاستفسار، تواصل مع محترف الترجمة باستخدام الاتصال بمخرج 877-475-4799.
MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 03/07/18
LAST REVIEW DATE:
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

TYSABRI FOR CROHN’S DISEASE (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutuuanan, ay may mga katarungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatang 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 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 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。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:

آگه شما، یا کسی که شما به یا کمک می‌خواهید، سوالاتی در مورد Blue Cross Blue Shield of Arizona اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799-475-4799.

Assyrian:

Blue Cross Blue Shield of Arizona ئادامەیان دەتوانێتەوە چەندە بەبەرێشەیەکە بەسەر بەسەرەکەیەکە، کە بەسەرەکەیەکە بەسەرەکەیەکە، کە بەسەرەکەیەکە بەسەرەکەیەکە، کە بەسەرەکەیەکە بەسەرەکەیەکە.

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

Thai: หากคุณ หรือคนอื่นที่คุณช่วยเหลือถามคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ขอความช่วยเหลือและข้อมูลภาษา ของคุณได้โดยไม่เสียเงิน ติดต่อที่ 877-475-4799.