



MEDICAL COVERAGE GUIDELINES
SECTION: LABORATORY

ORIGINAL EFFECTIVE DATE: 01/05/11
LAST REVIEW DATE: 01/22/19
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

NEUTRALIZING ANTIBODY TESTS FOR INTERFERON

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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Description:

Individuals undergoing interferon therapy may develop neutralizing antibodies (NABs) that bind to the interferon and inhibit or reduce its therapeutic benefit.

The NAbFeron® test has been investigated in the detection of neutralizing antibodies to interferon beta 1A or interferon beta 1B in individuals with multiple sclerosis and hepatitis C.

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Criteria:

- NAbFeron antibody testing for detection of antibodies to interferon beta 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.

Resources:

Literature reviewed 01/30/18. We do not include marketing materials, poster boards and non-published literature in our review.

1. American Academy of Neurology, Goodin DS, Frohman EM, et al. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. Mar 27 Re-affirmed 01/23/2016, 07/13/2013, 07/10/2010. Issued 03/2007;68(13):977-984.
2. Athena Diagnostics. BAbScreen™/NAbFeron® Antibody Test. Accessed 12/21/2011, 12/29/2014.
3. Athena Diagnostics. NAbFeron® (IFNβ-1) Neutralizing Antibody Test. Accessed 12/21/2011, 12/29/2014, 01/05/2016.
4. Bertolotto A, Capobianco M, Amato MP, et al. Guidelines on the clinical use for the detection of neutralizing antibodies (NABs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group. *Neurol Sci*. Feb 2014;35(2):307-316.
5. Dujmovic I, Hegen H, Paz P, Croze E, Deisenhammer F. Persistency of Neutralizing Anti-Interferon-beta Antibodies in Patients with Multiple Sclerosis Treated with Subcutaneous Interferon-beta Depends on Antibody Titers, IgG Subclasses, and Affinity Maturation. *J Interferon Cytokine Res*. Jul 2017;37(7):317-324.
6. Fujita N, Kaito M, Takeo M, et al. Different hepatitis C virus dynamics of free-virions and immune-complexes after initiation of interferon-alpha in patients with chronic hepatitis C. *J Hepatol*. 2003 Dec 2003;39(6):1013-1019.
7. Gneiss C, Reindl M, Lutterotti A, et al. Interferon-beta: the neutralizing antibody (NAb) titre predicts reversion to NAb negativity. *Mult Scler*. 2004 Oct 2004;10(5):507-510.

NEUTRALIZING ANTIBODY TESTS FOR INTERFERON (cont.)

Resources: (cont.)

8. Hegen H, Millonig A, Bertolotto A, et al. Early detection of neutralizing antibodies to interferon-beta in multiple sclerosis patients: binding antibodies predict neutralizing antibody development. *Mult Scler.* Apr 2014;20(5):577-587.
9. Hegen H, Schleiser M, Gneiss C, et al. Persistency of neutralizing antibodies depends on titer and interferon-beta preparation. *Mult Scler.* Oct 19 2011.
10. Hurtado-Guerrero I, Pinto-Medel MJ, Urbaneja P, et al. Cross-reactivity of antibodies against interferon beta in multiple sclerosis patients and interference of the JAK-STAT signaling pathway. *Sci Rep.* Nov 29 2017;7(1):16585.
11. Jorns C, Holzinger D, Thimme R, et al. Rapid and simple detection of IFN-neutralizing antibodies in chronic hepatitis C non-responsive to IFN-alpha. *J Med Virol.* 2006 Jan 2006;78(1):74-82.
12. Lampasona V, Rio J, Franciotta D, et al. Serial immunoprecipitation assays for interferon--(IFN)-beta antibodies in multiple sclerosis patients. *Eur Cytokine Netw.* 2003 Jul-Sep 2003;14(3):154-157.
13. Link J, Ramanujam R, Auer M, et al. Clinical practice of analysis of anti-drug antibodies against interferon beta and natalizumab in multiple sclerosis patients in Europe: A descriptive study of test results. *PLoS One.* 2017;12(2):e0170395.
14. Paolicelli D, Manni A, Iaffaldano A, et al. The role of neutralizing antibodies to interferon-beta as a biomarker of persistent MRI activity in multiple sclerosis: a 7-year observational study. *European journal of clinical pharmacology.* Aug 2016;72(8):1025-1029.
15. Polman C, Kappos L, White R, et al. Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b. *Neurology.* 2003 Jan 14 2003;60(1):37-43.
16. Up to Date. Treatment of Relapsing-Remitting Multiple Sclerosis in Adults. 2014, 2015.
17. UpToDate.com. Disease-Modifying Treatment of Relapsing-Remitting Multiple Sclerosis in Adults. 01/06/2017.
18. Vartanian TK, Zamvil SS, Fox E, Sorensen PS. Neutralizing antibodies to disease-modifying agents in the treatment of multiple sclerosis. *Neurology.* 2004 Dec 14 2004;63(11 Suppl 5):S42-49.
19. Wadhwa M, Subramanyam M, Goelz S, et al. Use of a standardized MxA protein measurement-based assay for validation of assays for the assessment of neutralizing antibodies against interferon-beta. *J Interferon Cytokine Res.* Nov 2013;33(11):660-671.



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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 nilinígíí Blue Cross Blue Shield of Arizona haada yit'éego bina'idíílkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yina'idíílkidgo beehaz'áanii hólg díí t'áa hazaadk'ehjí háká a'doowołgo bee haz'ą doo baqah ilínígóó. Ata' halne'ígíí kojí' bich'í' hodíilnih 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 thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، ف لديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

