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INTRODUCTION

A growing number of medicines are based on biological molecules such as proteins and monoclonal antibodies. These novel drugs have resulted in new, more effective treatments for a number of serious conditions. Yet sometimes these medicines trigger a response from the patient's immune system, which can decrease the effectiveness of the drug or cause severe side effects.

The aim of the IMI-funded ABIRISK project "**Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk**", is to shed new light on the factors behind this immune response. The project, which represents the first concerted effort to solve this problem, officially kicked off March 1st, 2012. ABIRISK project will aid in the creation of new, safer **biopharmaceuticals (BPs)** and also generate tools to determine how individual patients are likely to respond to them both in clinical trials and after release to the market.

The ABIRISK consortium (presently made up of thirty-five partners, twenty-four of which are academic institutions, nine are EFPIA member companies and two are small and medium enterprises, with thirteen countries represented), has been designed to meet all of these requirements in order to target three types of disorders: **Hemophilia A, Multiple sclerosis and Inflammatory diseases: inflammatory rheumatism (including rheumatoid arthritis) and inflammatory bowel diseases.**

ABIRISK Project will collect data both retrospectively from patients suffering from various types of diseases and treated with various BPs at European centers with a high level of experience in clinical research and will prospectively recruit additional patients in dedicated studies during the 5 years of this program. Guidelines and Standard Operating Protocols for the study of anti-drug immunization will be established and used to standardize the collection of prospective data from these patients.

ABIRISK Project thus represents a unique opportunity to create an interdisciplinary task force of clinical centers especially designed to study immune responses against biopharmaceuticals.

WELCOME

Dear Reader,

We would like to welcome you to the **July 2014** issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK topics published around the globe, both inside and outside ABIRISK consortium.

This month, we chose to highlight a paper by Michau *et al.* sought to compare the safety profile of the currently approved TNF α inhibitors (adalimumab, infliximab, golimumab, certolizumab pegol and etanercept) by the mean of a meta-analysis of BPs' safety profiles as defined by overall serious adverse events, malignancy, serious infection, and discontinuation due to adverse events.

In addition, you will find in this issue some regulatory news on biopharmaceuticals.

We look forward to your visit on **ABIRISK** website for more information and updates on the program.

Enjoy reading !

Best wishes

The ABIRISK management team

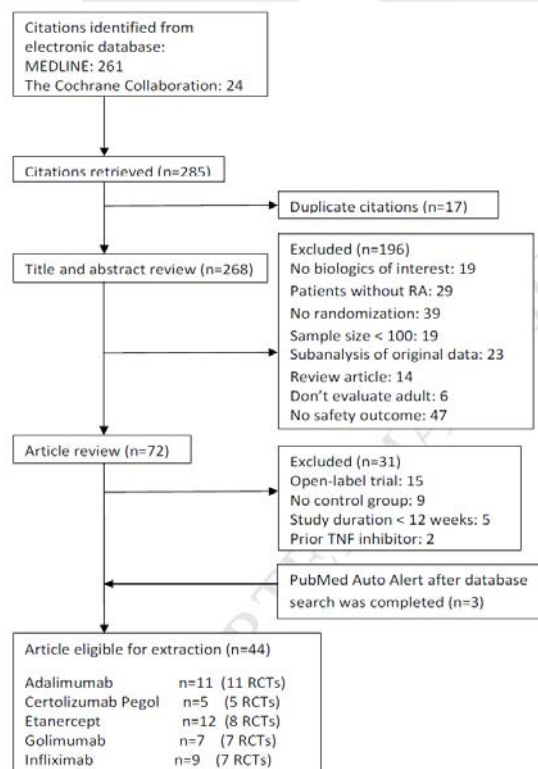
LITERATURE

This month's selected article

Currently approved TNF α inhibitors (adalimumab, infliximab, golimumab, certolizumab pegol and etanercept) exhibit comparable efficacy in rheumatoid arthritis (RA) patients. Based on this observation, Michau *et al.* sought to compare the safety profile of these five biopharmaceuticals (BPs).

To this aim and following the [Cochrane collaboration guidelines](#) the authors conducted a meta-analysis of BPs' safety profiles as defined by overall serious adverse events, malignancy, serious infection, and discontinuation due to adverse events. Data were extracted from randomized controlled clinical studies published between 1990 and 2013. Selection criteria included safety compared against placebo and/or DMARDs, trial conducted in RA patients only, sample size greater than 100 and a 12-week duration minimum.

As depicted in the diagram below, a total of 44 trials were eligible for the meta-analysis, which amounted to a total of 17 601 patients, 11 700 treated and 5901 in control groups:



Both Arcsine transformation risk differences (ASRDs) and Peto odds ratios (POs) were calculated, heterogeneity between studies was expressed using the chi-square test. Of note, severity of disease could not be taken into account due to heterogeneity of disease severity measures across the trials.

The results of the current study confirmed trends observed in previous meta-analyses showing no statistical increased risk of malignancy and no impact of the BP dose on any of the risks that were estimated. However, an increased risk of serious infection for adalimumab, infliximab and certolizumab pegol compared to that of etanercept, contributing to a higher risk of discontinuation due to adverse events was observed. A similar trend was found for golimumab in combination with methotrexate but not for golimumab given as a monotherapy.

Immunogenicity

[Computationally driven deletion of broadly distributed T cell epitopes in a biotherapeutic candidate.](#)

Salvat RS, Parker AS, Guillems A, Choi Y, Bailey-Kellogg C, Griswold KE.

Cell Mol Life Sci. 2014 Jun 1.

[Development of a Universal Anti-Adalimumab Antibody Standard for Interlaboratory Harmonization.](#)

Gils A, Vande Castele N, Poppe R, Van de Wouwer M, Compennolle G, Peeters M, Brouwers E, **Vermeire S**, Geukens N, J Declerck P.

Ther Drug Monit. 2014 Jun 5.

[The effect of antidrug antibodies on the sustainable efficacy of biologic therapies in rheumatoid arthritis: practical consequences.](#)

Keiserman M, Codreanu C, Handa R, Xibillé-Friedmann D, Mysler E, Briceño F, Akar S.

Expert Rev Clin Immunol. 2014 Jun 25:1-9.

[EBF recommendation for stability testing of anti-drug antibodies; lessons learned from anti-vaccine antibody stability studies.](#)

Pihl S, Michaut L, Hendriks J, Loebbert R, Ryding J, Nemansky M, Vermet L, Companjen A.

Bioanalysis. 2014 May;6(10):1409-13

[Comparison of efficacy, pharmacokinetics, and immunogenicity between infliximab mono- versus combination therapy in ulcerative colitis.](#)

Hayes MJ, Stein AC, Sakuraba A.

J Gastroenterol Hepatol. 2014 Jun;29(6):1177-85.

Methods

[Structure guided homology model based design and engineering of mouse antibodies for humanization.](#)

Kurella VB, Gali R.

Bioinformatics. 2014 Apr 23;10(4):180-6.

[Development of an Algorithm Incorporating Pharmacokinetics of Adalimumab in Inflammatory Bowel Diseases.](#)

Roblin X, Rinaudo M, Del Tedesco E, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S.
Am J Gastroenterol. 2014 Jun 10.

[CHOPPI: A web tool for the analysis of immunogenicity risk from host cell proteins in CHO-based protein production.](#)

Bailey-Kellogg C, Gutiérrez AH, Moise L, Terry F, Martin WD, De Groot AS.
Biotechnol Bioeng. 2014 Jun 2.

[Fecal Biomarkers in the Diagnosis and Monitoring of Crohn's Disease.](#)

Wright EK, De Cruz P, Geary R, Day AS, Kamm MA.
Inflamm Bowel Dis. 2014 Jun 10.

Biomarkers

[Serial changes of serum cytokines in Crohn's disease following treatment with adalimumab.](#)

Abiko Y, Mizutani T, Chiba T.
Hepatogastroenterology. 2014 Mar-Apr;61(130):357-62.

[Prediction of response to interferon therapy in multiple sclerosis.](#)

Sellebjerg F, Søndergaard HB, Koch-Henriksen N, Sørensen PS, Oturai AB.
Acta Neurol Scand. 2014 Jun 18.

[Biomarkers in multiple sclerosis: an update for 2014.](#)

Fernandez O, Martin R, Rovira A, Llufrui S, Vidal-Jordana A, Fernandez-Sanchez VE, Alvarez-Cermeno JC, Izquierdo G, Arroyo-Gonzalez R, Rodriguez-Antiguedad A, Casanova-Estruch B, **Montalban X**.
Rev Neurol. 2014 Jun 16;58(12):553-570.

[The use of cytokine signature patterns: separating drug naïve, interferon and natalizumab-treated multiple sclerosis patients.](#)

O'Connell KE, Mok T, Sweeney B, Ryan AM, Dev KK.
Autoimmunity. 2014 Jun 30:1-7.

[Unraveling Natalizumab Effects on Deregulated miR-17 Expression in CD4\(+\) T Cells of Patients with Relapsing-Remitting Multiple Sclerosis.](#)

Meira M, Sievers C, Hoffmann F, Rasenack M, Kuhle J, Derfuss T, Kappos L, **Lindberg RL**.
J Immunol Res. 2014;2014:897249.

[Leucocyte complement receptor 1 \(CR1/CD35\) transcript and its correlation with the clinical disease activity in rheumatoid arthritis patients.](#)

Anand D, Kumar U, Kanjilal M, Kaur S, Das N.
Clin Exp Immunol. 2014 Jun;176(3):327-35. doi: 10.1111/cei.12274.

[Small non-coding RNA signature in multiple sclerosis patients after treatment with interferon- \$\beta\$.](#)

De Felice B, Mondola P, Sasso A, Orefice G, Bresciamorra V, Vacca G, Biffali E, Borra M, Pannone R.
BMC Med Genomics. 2014 May 17;7(1):26.

Systemic Lupus Erythematosus

[Novel approaches to the development of targeted therapeutic agents for systemic lupus erythematosus.](#)

Stoeger Z, Sharabi A, Mozes E.
J Autoimmun. 2014 Jun 20.

[Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus \(SLE\): 52-week data \(APRIL-SLE randomised trial\).](#)

Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D.
Ann Rheum Dis. 2014 Jun 20.

[When biologics should be used in systemic lupus erythematosus?](#)

Gottenberg JE, Lorenzo N, Sordet C, Theulin A, Chatelus E, Sibia J.
Presse Med. 2014 Jun;43(6 Pt 2):e181-5.

[Systemic lupus erythematosus.](#)

Lisnevskaja L, Murphy G, Isenberg D.

Lancet. 2014 May 29. pii: S0140-6736(14)60128-8.

Rheumatoid Arthritis

[Efficacy and safety of Adalimumab as first and second used biologic agent in juvenile idiopathic arthritis - the German Biologics IIA Registry \(BiKeR\).](#)

Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G.

Arthritis Rheumatol. 2014 Jun 18. doi: 10.1002/art.38741. [Epub ahead of print]

[The Comparative Safety of TNF Inhibitors in Rheumatoid Arthritis - A Meta-Analysis Update of 44 Randomized Controlled Trials.](#)

Michaud TL, Rho YH, Shamliyan T, Kuntz KM, Choi HK.

Am J Med. 2014 Jun 17. pii: S0002-9343(14)00488-4.

[Specific therapy to regulate inflammation in rheumatoid arthritis: molecular aspects.](#)

García-Hernández MH, González-Amaro R, Portales-Pérez DP.

Immunotherapy. 2014 May;6(5):623-36.

[Interleukin-6-receptor polymorphisms rs12083537, rs2228145, and rs4329505 as predictors of response to tocilizumab in rheumatoid arthritis.](#)

Enevold C, Baslund B, Linde L, Josephsen NL, Tarp U, Lindegaard H, Jacobsen S, Nielsen CH.

Pharmacogenet Genomics. 2014 Jun 23.

[Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies.](#)

Hirabara S, Takahashi N, Fukaya N, Miyake H, Yabe Y, Kaneko A, Ito T, Oguchi T, Kida D, Hirano Y, Fujibayashi T, Sugiura F, Hayashi M, Funahashi K, Hanabayashi M, Asai S, Ishiguro N, Kojima T.

Clin Rheumatol. 2014 Jun 28.

[Subcutaneous Tocilizumab vs Placebo in Combination With Disease Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis.](#)

Kivitz A, Olech E, Borofsky M, Zazueta BM, Navarro-Sarabia F, Radominski SC, Merrill JT, Rowell L, Nasmyth-Miller C, Bao M, Wright S, Pope JE.

Arthritis Care Res (Hoboken). 2014 Jun 18.

[Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase.](#)

Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB.

Ann Rheum Dis. 2014 Jun 27.

[Modelling Outcomes of Complex Treatment Strategies Following a Clinical Guideline for Treatment Decisions in Patients with Rheumatoid Arthritis.](#)

Tran-Duy A, Boonen A, Kievit W, van Riel PL, van de Laar MA, Severens JL.

Pharmacoeconomics. 2014 Jun 28

Inflammatory Bowel Disease

[Systematic review of the effectiveness of biological therapy for active moderate to severe ulcerative colitis.](#)

Kawalec P, Mikrut A, Łopuch S.

J Gastroenterol Hepatol. 2014 Jun;29(6):1159-70.

[Implication of miRNAs for inflammatory bowel disease treatment: Systematic review.](#)

Chen WX, Ren LH, Shi RH.

World J Gastrointest Pathophysiol. 2014 May 15;5(2):63-70

[Crohn's disease outpatients treated with adalimumab have an earlier secondary loss of response and requirement for dose escalation compared to infliximab: A real life cohort study.](#)

Ma C, Huang V, Fedorak DK, Kroeker KI, Dieleman LA, Halloran BP, Fedorak RN.

J Crohns Colitis. 2014 Jun 16. pii: S1873-9946(14)00180-9

[The biosimilar road in inflammatory bowel disease: The right way?](#)

Fiorino G, Danese S.

Best Pract Res Clin Gastroenterol. 2014 Jun;28(3):465-471.

[Golimumab in unresponsive ulcerative colitis.](#)

Lippert E, Müller M, Ott C.

Biologics. 2014 May 27;8:207-10.

[Is there a role for vedolizumab in the treatment of ulcerative colitis and Crohn's disease?](#)

Gilroy L, Allen PB.

Clin Exp Gastroenterol. 2014 May 22;7:163-72.

[Targeting T and B lymphocytes in inflammatory bowel diseases: lessons from clinical trials.](#)

Gerner RR, Moschen AR, Tilg H.

Dig Dis. 2013;31(3-4):328-35.

[Efficacy and safety of adalimumab for the Crohn's disease: a systematic review and meta-analysis of published randomized placebo-controlled trials.](#)

Song YN, Zheng P, Xiao JH, Lu ZJ.

Eur J Clin Pharmacol. 2014 Jun 1.

[A 24-month open-label study of canakinumab in neonatal-onset multisystem inflammatory disease.](#)

Sibley CH, Chioato A, Felix S, Colin L, Chakraborty A, Plass N, Rodriguez-Smith J, Brewer C, King K, Zalewski C, Kim HJ, Bishop R, Abrams K, Stone D, Chapelle D, Kost B, Snyder C, Butman JA, Wesley R, Goldbach-Mansky R.

Ann Rheum Dis. 2014 Jun 6

Multiple Sclerosis

[The role of Toll-like receptors in multiple sclerosis and possible targeting for therapeutic purposes.](#)

Gooshe M, Abdolghaffari AH, Gambuzza ME, Rezaei N.

Rev Neurosci. 2014 Jun 7.

[Current and Future Therapies Targeting the Immune System in Multiple Sclerosis.](#)

Loleit V, Biberacher V, **Hemmer B.**

Curr Pharm Biotechnol. 2014 Jun 16.

[IFN- \$\beta\$ alters neurotrophic factor expression in T cells isolated from multiple sclerosis patients - implication of novel neurotensin/NTSR1 pathway in neuroprotection.](#)

Soltys J, Knight J, Scharf E, Pitt D, Mao-Draayer Y.

Am J Transl Res. 2014 May 15;6(3):312-9.

[Expression, Regulation and Function of MicroRNAs in Multiple Sclerosis.](#)

Ma X, Zhou J, Zhong Y, Jiang L, Mu P, Li Y, Singh N, Nagarkatti M, Nagarkatti P.

Int J Med Sci. 2014 Jun 2;11(8):810-818.

[Drug safety evaluation of alemtuzumab for multiple sclerosis.](#)

Willis M, Robertson NP.

Expert Opin Drug Saf. 2014 Jun 16:1-10.

[Rituximab Efficiently Depletes Increased CD20-Expressing T Cells in Multiple Sclerosis Patients.](#)

Palanichamy A, Jahn S, Nickles D, Derstine M, Abounasr A, Hauser SL, Baranzini SE, Leppert D, von Büdingen HC.

J Immunol. 2014 Jun 13

[Alemtuzumab: The advantages and challenges of a novel therapy in MS.](#)

Menge T, Stüve O, Kieseier BC, Hartung HP.

Neurology. 2014 Jun 11.

[Contemporary treatment options for relapsing-remitting multiple sclerosis.](#)

Salhofer-Polanyi S, Leutmezer F.

Drugs Today (Barc). 2014 May;50(5):365-83.

[Metabolic and safety issues for multiple sclerosis pharmacotherapy - opportunities for personalised medicine.](#)

Wiese MD, Suppiah V, O'Doherty C.

Expert Opin Drug Metab Toxicol. 2014 Jun 9:1-15.

[Safety and efficacy of natalizumab in Belgian multiple sclerosis patients: subgroup analysis of the natalizumab observational program.](#)

van Pesch V, Bartholomé E, Bissay V, Bouquiaux O, Bureau M, Caekebeke J, Debruyne J, Declercq I, Decoo D, Denayer P, De Smet E, D'hooghe M, Dubois B, Dupuis M, Sankari SE, Geens K, Guillaume D, van Landegem W, Lysandropoulos A, de Noordhout AM, Medaer R, Melin A, Peeters K, Ba RP, Retif C, Seeldrayers P, Symons A, Urbain E, Vanderdonck P, Van Ingelghem E, Vanopdenbosch L, Vanroose E, Van Wijmeersch B, Willekens B,

Willems C, Sindic C.

Acta Neurol Belg. 2014 Jun 11.

[New regulatory CD19\(+\)CD25\(+\) B-cell subset in clinically isolated syndrome and multiple sclerosis relapse. Changes after glucocorticoids.](#)

de Andrés C, Tejera-Alhambra M, Alonso B, Valor L, Teijeiro R, Ramos-Medina R, Mateos D, Faure F, Sánchez-Ramón S.

J Neuroimmunol. 2014 May 15;270(1-2):37-44.

Hemophilia

[Rituximab for treatment of inhibitors in haemophilia A. A Phase II Study.](#)

Leissinger C, Josephson CD, Granger S, Konkle BA, Kruse-Jarres R, Ragni MV, Journeycake JM, Valentino L, Key NS, Gill JC, McCrae KR, Neufeld EJ, Manno C, Raffini L, Saxena K, Torres M, Marder V, Bennett CM, Assmann SF.

Thromb Haemost. 2014 Jun 12;112(3).

[Effects of Replacement of Factor VIII Amino Acids Asp519 and Glu665 with Val on Plasma Survival and Efficacy In Vivo.](#)

Kosloski MP, Shetty KA, Wakabayashi H, Fay PJ, Balu-Iyer SV.

AAPS J. 2014 Jun 17.

Basic immunology

[TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells.](#)

Gerlach K, Hwang Y, Nikolaev A, Atreya R, Dornhoff H, Steiner S, Lehr HA, Wirtz S, Vieth M, Waisman A, Rosenbauer F, McKenzie AN, Weigmann B, Neurath MF.

Nat Immunol. 2014 Jul;15(7):676-86.

[Germinal center reaction: antigen affinity and presentation explain it all.](#)

Oropallo MA, Cerutti A.

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

www.imi.europa.eu



Innovative Medicines Initiative

Trends Immunol. 2014 Jun 13. pii: S1471-4906(14)00096-9.

Opinions/Commentaries/ Across disease reviews

[Can you trust your animal study data?](#)

Peers IS, South MC, Ceuppens PR, Bright JD, Pilling E.
Nat Rev Drug Discov. 2014 Jun 6.

[Alemtuzumab and multiple sclerosis: Is it safe?](#)

Bourdette D.
Neurology. 2014 Jun 11.

[Infliximab for Moderate to Severe Ulcerative Colitis: The Jury Isn't in Yet.](#)

Kamath N, Kamath A, Pai CG.
Gastroenterology. 2014 Jun 25.

[Have biologics changed the natural history of Crohn's disease?](#)

Mandel MD, Miheller P, Müllner K, Golovics PA, Lakatos PL.
Dig Dis. 2014;32(4):351-9.

[Treatment paradigms in multiple sclerosis: who, when and how to treat?](#)

Willis MD, Robertson NP.
J Neurol. 2014 Jun 22.

[Questioning the Use of PEGylation for Drug Delivery.](#)

Verhoef JJ, Anchoroquy TJ.
Drug Deliv Transl Res. 2013 Dec;3(6):499-503.

[The challenge of indication extrapolation for infliximab biosimilars.](#)

Feagan BG, Choquette D, Ghosh S, Gladman DD, Ho V, Meibohm B, Zou G, Xu Z, Shankar G, Sealey DC, Russell AS.

Biologicals. 2014 Jun 21. pii: S1045-1056(14)00045-1.

[Daclizumab in multiple sclerosis: a high-yield extension study.](#)

Barkhof F, Ciccarelli O.

Lancet Neurol. 2014 May;13(5):443-4.

[The rise of biosimilars: potential benefits and drawbacks in rheumatoid arthritis.](#)

Yoo DH.

Expert Rev Clin Immunol. 2014 Jun 25:1-3.

[Loss of response to anti-tumor necrosis factors: what is the next step?](#)

Ben-Horin S.

Dig Dis. 2014;32(4):384-8.

REGULATION

EMA

[Newsletter: News bulletin for small and medium-sized enterprises - Issue 28](#)

[Scientific guideline: Concept paper on qualification and reporting of physiologically based pharmacokinetic \(PBPK\) modelling and analyses](#)

Draft consultation open
Ends 30 September 2014

[Pending EC decision: Enbrel, etanercept](#)

Opinion date: 26-Jun-2014

[Human medicines European public assessment report \(EPAR\): Inflectra, infliximab](#)

Revision: 4, Authorised
June 2014

[Human medicines European public assessment report \(EPAR\): Remsima, infliximab](#)

Revision: 2, Authorised
June 2014

[Opinion/decision on a Paediatric Investigation Plan \(PIP\): Orenzia, abatacept, Therapeutic area: Immunology-Rheumatology-Transplantation](#)

Updated
June 2014

[Human medicines European public assessment report \(EPAR\): ReFacto AF, moroctocog alfa](#)

Revision: 27, Authorised
June 2014

[Human medicines European public assessment report \(EPAR\): Entyvio, vedolizumab](#)

Revision: 0, Authorised
June 2014

[Human medicines European public assessment report \(EPAR\): MabThera, rituximab](#)

Revision: 32, Authorised

June 2014

[Scientific guideline: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues \(revision 1\)](#)

June 2014



WC500167838.pdf

FDA

[New drug approval : Entyvio, vedolizumab](#)

To treat adult patients with moderate to severe ulcerative colitis and adult patients with moderate to severe Crohn's disease

May 2014

[New drug approval : Eloctate](#)

For use in adults and children who have Hemophilia A.

June 2014