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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Direct healthcare professional communication (DHPC)

Date: 07-March-2022

Infliximab (Remicade, Flixabi, Inflectra, and Remsima): Use of live vaccines in infants exposed *in utero* or during breastfeeding

Dear Healthcare Professional,

The marketing authorization holders of infliximab, in agreement with the European Medicines Agency and the Health Products Regulatory Authority, would like to inform you about the following:

Summary

Infants exposed to infliximab *in utero* (i.e., during pregnancy)

- **Infliximab crosses the placenta and has been detected in infant serum up to 12 months after birth. After *in utero* exposure, infants may be at increased risk of infection, including serious disseminated infection that can become fatal.**
- **Live vaccines (e.g., BCG vaccine) should not be given to infants after *in utero* exposure to infliximab for 12 months after birth.**
- **If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint if infant infliximab serum levels are undetectable or if infliximab administration was limited to the first trimester of pregnancy.**

Infants exposed to infliximab via breast milk

- **Infliximab has been detected at low levels in breast milk. It has also been detected in infant serum after exposure to infliximab via breast milk.**
- **Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable.**

Background on the safety concern

Infliximab is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to human TNFα. In the European Union, it is indicated for the treatment of rheumatoid arthritis,

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Crohn's disease (adult and pediatric), ulcerative colitis (adult and pediatric), ankylosing spondylitis, psoriatic arthritis, and psoriasis.

Administration of live vaccines to infants exposed to infliximab *in utero*

Infliximab crosses the placenta and has been detected in the serum of infants exposed to infliximab *in utero* for up to 12 months after birth (Julsgaard et al, 2016). These infants may be at increased risk of infection, including serious disseminated infection that can become fatal. This includes disseminated Bacillus Calmette Guérin (BCG) infection which has been reported following administration of BCG live vaccine after birth.

A 12-month waiting period starting at birth is therefore recommended before live vaccines are administered to infants who have been exposed to infliximab *in utero*. If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered earlier if infant infliximab serum levels are undetectable or if infliximab administration was limited to the first trimester of pregnancy (when placental transfer of IgG is considered minimal).

Administration of live vaccines to infants exposed to infliximab via breast milk

Limited data from published literature indicate that infliximab has been detected at low levels in breast milk at concentrations up to 5% of the maternal serum level (Fritzsche et al, 2012).

Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. Systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract.

Administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable.

Product information

The infliximab SmPC, patient leaflets and patient reminder cards are being updated to reflect the current recommendations on live vaccination of infants following *in utero* exposure or whilst breastfeeding. Patients treated with infliximab should be given the package leaflet and the patient reminder card. Women treated with infliximab should be educated on the importance of discussing (live) vaccines with their infants' physicians, should they become pregnant or choose to breastfeed while using infliximab.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of infliximab in accordance with the national spontaneous reporting system. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

Adverse reaction reports should also be reported to the company contacts listed in Table 1, for applicable products. Please report the product name and batch details.

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Company contact points

Table 1 provides a list of Companies, their concerned products and contact points. Healthcare professionals should report adverse drug reactions to the respective marketing authorization holder.

References

Fritzsche J, Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46:718-9. doi: 10.1097/MCG.0b013e31825f2807. PMID: 22858514.

Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology. 2016;151:110-119. doi: 10.1053/j.gastro.2016.04.002. Epub 2016 Apr 8. PMID: 27063728.

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Table 1: Contact details for the Marketing Authorisation Holders for reporting adverse drug reactions

Product Name	Marketing Authorisation Holder	Local Representative	Email Contact	Phone Number
Remicade 100 mg powder for concentrate for solution for infusion. EU/1/99/116/001	Janssen Biologics B.V. Einsteinweg 101 2333 CB Leiden The Netherlands	Merck Sharp & Dohme Ireland (Human Health) Limited	medinfo_ireland@merck.com	+353 (0)1 2998700
Remsima 100 mg powder for concentrate for solution for infusion EU/1/13/853/001-005 Remsima 120 mg/mL solution for injection EU/1/13/853/006-017	Celltrion Healthcare Hungary Kft. 1062 Budapest Váci út 1-3. WestEnd Office Building B torony Hungary	Rosina Zahoor (National Contact Person for UK) Michelle Ergin (Deputy National Contact Person for UK)	rosina.zahoor@biomapas.com PV.IE@biomapas.com michelle.ergin@biomapas.com PV.IE@biomapas.com	+447711 884408 +44 7500 117005
Flixabi (infliximab) 100mg powder for concentrate for solution for infusion EU/1/16/1106/001-005	Samsung Bioepis NL B.V. Olaf Palmestraat 10, 2616 LR Delft, The Netherlands	Biogen Idec (Ireland) Ltd	Medinfo.europe@biogen.com	+353 (0)1 513 33 33
Inflectra 100 mg powder for concentrate for solution for infusion EU/1/13/854/001-005	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium	Pfizer Healthcare Ireland, 9 Riverwalk, Citywest Business Campus, Dublin 24	medical.information@pfizer.com	1800 633 363, & ask for Medical Information