Direct healthcare professional communication (DHPC)

Date: <to be inserted>

Infliximab (Remicade, Flixabi, Inflectra, Remsima and Zessly): 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 <National Competent 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, 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
<include the details (e.g. name, postal address, fax number, web address) on how to access the national spontaneous reporting system>
Please report the product name and batch details.

Company contact points

<Table with the companies concerned, their contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address (company contact point in the concerned EU MS should be included, respectively)>

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.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	infliximab Remicade (originator) Flixabi Inflectra Remsima Zessly
Marketing authorisation holder(s)	Janssen Biologics B.V. Samsung Bioepis NL B.V. Pfizer Europe MA EEIG Celltrion Healthcare Hungary Kft. Sandoz GmbH
Safety concern and purpose of the communication	Updated recommendations for the use of live vaccines in infants exposed in utero or during breastfeeding
DHPC recipients	Prescribers of infliximab: including but not limited to rheumatologists, adult and pediatric gastroenterologists, dermatologists, paediatricians. Exact target audience to be defined and agreed at national level. Professional societies and national associations to be defined and agreed at national level. These should preferably include national associations for the above-mentioned specialists, and also for general practitioners, specialists in obstetrics and HCP or related HCP organisations who are responsible for national immunisation programs for children.
Member States where the DHPC will be distributed	All EU member states (unless not marketed).

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	10 February 2022
DHPC and communication plan (in English) agreed by CHMP	14 February 2022
Submission of translated DHPCs to the national competent authorities for review	21 February 2022
Agreement of translations by national competent authorities	28 February 2022
Dissemination of DHPC	From 7 March 2022