IN-USE PRODUCT SAFETY ASSESSMENT REPORT
REMSIMA® and INFLECTRA® (INFLIXIMAB BIOSIMILARS)

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND
Infliximab is the first monoclonal antibody for which a biosimilar version will be available; it has been developed by Celltrion Pharmaceuticals. UK marketing authorisations have been granted to two products (both of which comprise the same biosimilar) and this review summarises practical in-use safety considerations associated with their introduction. Useful background summaries on biosimilar medicines, their science, and licensing are available elsewhere.

DETAILS OF PRODUCT (S) ASSESSED
The two new products assessed using the validated UKMi product assessment tool are:
1. Inflectra® 100 mg powder for concentrate for solution for infusion; Hospira Pharmaceuticals
2. Remsima® 100 mg powder for concentrate for solution for infusion; Napp Pharmaceuticals

The products were compared with the originator Remicade® 100 mg powder for concentrate for solution for infusion; Merck, Sharp & Dohme (a formal assessment of Remicade® was not undertaken).

Assessments were carried out with reference to: dummy versions of the products and high resolution images supplied by the manufacturers; summaries of product characteristics (SmPC) and packaging inserts; and the European Medicines Agency Public Assessment Reports (EPARs) for the products. The assessment process is summarised at the end of the report.

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL
Overall the presentation, physical characteristics, and accompanying information for both products are considered appropriate. However, some (largely inherent) risks will be associated with the introduction of biosimilar infliximab. These risks should be broadly manageable, but safe introduction will undoubtedly require specific implementation work. Potential risks are identified below; mitigating and other necessary actions are considered in the next section.

Interchangeability and potential for confusion between products
- With three products available—Inflectra®, Remicade®, and Remsima®—confusion between them is possible. Interchangeability is an area of some potential contention; the specific clinical issues associated with it are beyond the scope of this paper. Regardless, it will be vital to identify specifically each individual product intended for, and administered to, each patient at the points of prescribing, dispensing, and administration (steps to achieve this are discussed below). From the assessment, the packaging and presentation between the 3 products is well differentiated and should enable rather than hinder differentiation. There is a small potential for sound and look alike name confusion between Remicade® and Remsima®.

- Infliximab may be used across a range of care settings, and there is hence potential for risk associated with this. For example, where home care use of infliximab is in place or is anticipated, the same issues of potential confusion and identification will be present.

Shelf life and stability issues
- Shelf-lives differ between the products: Remicade® has a 36 month shelf-life, Inflectra® 51 months, and Remsima® 57 months. All three products require storage between 2 to 8°C; in cases of accidental temperature excursion, continued use of Remicade® may be possible.

- All three products have licensed stability for the re-constituted product for 24 hours at 2 to 8°C. Additional NHS stability testing for Remicade® has enabled prolonged storage of the re-constituted product. Extrapolation of stability data between products is not possible; and, at the time of writing, specific guidance was not available for Inflectra® and Remsima®. Work to address this gap is ongoing; however, data that has been assessed by the NHS may not be available at launch.

Similarities with Remicade®
- As with Remicade®, Inflectra® and Remsima® are provided with suitable patient and professional information to support their use. Both are provided with an insert containing a full PIL, as well as information on reconstitution, dilution and administration for professionals; patient alert cards, with...
key caution/contraindication information are also provided for each of the three products.

- All known current risks associated with Remicade® will apply equally to Inflectra® and Remsima®. Both products would be expected to be classified as high risk injectable medicines according to NPSA 20 (Promoting Safer Use of Injectable Medicines) criteria since they will have risks associated with their therapeutic use; use of a concentrate; complex preparation and reconstitution; and use of a part/multiple container, infusion pump/driver, and non-standard infusion set. Stipulations surrounding infusion times for Remicade® will also apply equally to biosimilars; as will the potential for increased susceptibility to infectious diseases such as tuberculosis, and the increased risk of reactivation of latent tuberculosis.

**POTENTIAL NEXT STEPS AND MITIGATION ACTIONS**

Potential next steps and mitigation actions can be considered in two respects: those of particular relevance to the NHS, and those of particular relevance to manufacturers.

**Safe introduction of infliximab biosimilars to the NHS** will need to consider a number of actions:

1. **Brand name prescribing, identification, recording, and traceability needs to be in place**
   - Brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and/or administration. In addition, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made. Many such details are recorded routinely currently for Remicade®; additional recording of the brand should not therefore be onerous. Encouragingly, both Inflectra® and Remsima® include features to facilitate recording (e.g. removable stickers on vial packaging and specific sections in product support material). However, local education and training for prescribers, pharmacists, pharmacy staff, nurses, and others may also be necessary to ensure brand name prescribing, identification, and recording occurs.

2. **Other risk mitigations for Inflectra® and Remsima® to be consistent with measures for Remicade®**
   - Other risk mitigation steps for Inflectra® and Remsima® should be similar to those currently in place for Remicade®. Appropriate processes will be required to assess patient suitability for treatment (particularly in relation to tuberculosis); to ensure administration works within advice on reconstituted stability; and to apply existing practical risk mitigation strategies (for example, local guidance on administration). Existing risk mitigation strategies for Remicade® should be able to be applied to Inflectra® and Remsima® largely without change. The exception, however, is for reconstituted stability: since extrapolation of data from Remicade® extended stability studies is not possible, the licensed information for Inflectra® and Remsima® must be adhered to currently.

3. **Reporting and monitoring of patients through registries and pharmacovigilance**
   - Clinical registries will enable collection of specific data on serious adverse events for Inflectra® and Remsima® in both gastroenterology and rheumatology. These mechanisms will act in addition to routine pharmacovigilance activities (mindful that Inflectra® and Remsima® will initially be under intense regulatory surveillance). Safe introduction and ongoing safe use of Inflectra® and Remsima® requires both practitioner and manufacturer engagement with these processes.

4. **Safe use of the 3 available products across care settings**
   - The risks identified are not particular to any individual care setting; however, the mitigation strategies suggested will apply universally. Governance arrangements may need to be reflected in contracts with homecare providers, for example.

Further actions by manufacturers of Remsima® and Inflectra® are deemed to be fairly limited. The products have been provided in a form which should not fundamentally preclude their safe use. The lack of stability data beyond 24 hours for the re-constituted products is an area manufacturers may wish to consider working with the NHS to develop in the future. Overall, however, the challenges in ensuring safe introduction of these biosimilars sit primarily with commissioning and providers of care.

**PROCESS STATEMENT**

This report was produced in February 2015 following application of the validated UKMi product safety assessment tool using dummy versions of products and photographic images from the manufacturers as described above. This report summarises the results of product assessments undertaken by:

- London Medicines Information Service (Northwick Park)
- North West Medicines Information Service (Liverpool).

We are also grateful for the input of clinical specialists (rheumatology, gastroenterology) and SPS colleagues in QC and procurement in completing this piece of work. Contact b.rehman@nhs.net for comments.
1. What are biosimilars and are they important? Drug Ther Bull May 2013; 51(5): 57-60.
EXAMPLE PRODUCT PHOTOS

Inflectra™ 100 mg
powder for concentrate for solution for infusion

Infliximab

For intravenous use after reconstitution and dilution
Inflectra™ 100 mg
powder for concentrate for solution for infusion
Infliximab

For intravenous use after reconstitution and dilution
1 vial

Remsima™ 100 mg
powder for concentrate for solution for infusion

Infliximab

For intravenous use after reconstitution and dilution.
Remicade®
100 mg
powder for concentrate for solution for infusion
Infliximab
Remicade®
100 mg
powder for concentrate for solution for infusion
Infliximab