IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR TRASTUZUMAB PRODUCTS

BACKGROUND
Trastuzumab 150mg (Herceptin®) for intravenous infusion has been available in the UK since 2005, and Trastuzumab 600mg subcutaneous preparation since 2013. In January 2014, Roche launched trastuzumab emtansine (Kadcyla®), an antibody-drug conjugate in which the antibody is trastuzumab and emtansine, is a combination of a cytotoxic agent and a linking agent. More recently, in 2018-19, four trastuzumab intravenous infusion biosimilars (Ontruzant®, Herzuma®, Kanjinti® and Trazimera®) have been launched. This means, at the time of writing, seven preparations of trastuzumab are available on the UK market, with more trastuzumab biosimilar products expected in the coming months and years.

As with other biosimilar monoclonal antibodies, risks are associated with the introduction of the trastuzumab biosimilar preparations. In this case, several presentations are already marketed by Roche which share similar packaging. A higher dose of trastuzumab contained in the subcutaneous formulation Herceptin® (600mg) adds to confusion given the variety of products on market. The trastuzumab emtansine product is a different entity and is indicated only for breast cancer only in patients who have previously received trastuzumab. Although any confusion resulting in the wrong product being administered could lead to patient harm through overdose, underdose or treatment toxicity, the product has now been used for several years as standard practice with successful risk management strategies.

This review summarises practical in-use safety considerations associated with the availability of trastuzumab preparations. Useful background summaries on biosimilar medicines, their science, licensing and commissioning frameworks are available elsewhere1-3.

DETAILS OF PRODUCT (S) ASSESSED
The products assessed using the validated UKMi product assessment tool were:

1. Herceptin® (trastuzumab) 150mg powder for concentrate for solution for infusion; Roche Products Limited
2. Herceptin® (trastuzumab) 600mg/5mL solution for injection in vial (subcutaneous preparation); Roche Products Limited
3. Kadcyla® (trastuzumab emtansine) 100mg & 160mg powder for concentrate for solution for infusion; Roche Products Limited
4. Ontruzant® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion; Merck Sharp & Dohme Limited
5. Herzuma® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion; Napp Pharmaceuticals Ltd [Celltrion Healthcare Hungary Kft]
6. Kanjinti® (trastuzumab biosimilar) 150mg & 420mg powder for concentrate for solution for infusion; Amgen Europe B.V.
7. Trazimera® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion; Pfizer Limited

Assessments were carried out with reference to: high resolution images; summaries of product characteristics 4-10; packaging inserts11-17; risk minimisation materials and the European Medicines Agency Public Assessment Reports (EPARs) for the products10-22. Photographic images are reproduced at the end of the report along with a
summary of the assessment process.

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL
As mentioned above some (largely inherent) risks will be associated with the introduction of biosimilar products. However, in this case the risks may be higher due to the availability of a number of different trastuzumab products; this includes the originator product, a subcutaneous product, an antibody-drug conjugate and three biosimilar products. Safe use will require specific implementation work. Potential risks are identified below; mitigating and other necessary actions are considered in the next section.

Interchangeability between products
Trastuzumab emtansine and trastuzumab are different medicines, with different active substances and different therapeutic indications: Trastuzumab emtansine is indicated for breast cancer only, in patients who have previously received trastuzumab. Trastuzumab emtansine should not be interchanged or confused with other trastuzumab products including the biosimilars.

All known current clinical risks associated with Herceptin® (intravenous infusion) will apply equally to the biosimilars Ontruzant®, Herzuma®, Kanjinti® and Trazimera®. They are all licensed for the same indications, in the same age groups with identical dosage recommendations 4,7-10. Interchangeability between the biosimilars is an area of some potential contention; the specific clinical issues associated with it are beyond the scope of this paper. Considerations for biosimilar switches can be viewed here Link. It is vital to ensure that the intended product is selected correctly for prescribing, dispensing and administration for each patient (steps to achieve this are discussed below).

Potential for confusion between products
There is potential for confusion between the Roche Kadcyla® and Herceptin® products due to the similar livery. There is also potential for confusion between the intravenous and subcutaneous formulations of trastuzumab; the risk is potentially higher between the two Herceptin® formulations. Although Herceptin® 600mg/5ml is labelled in red as being for subcutaneous use on both the outer box and the vial, the labelling of Herceptin® 150mg for intravenous use has remained unchanged despite the increased potential for product mis-selection.

The packaging and presentation between the originator products and Ontruzant® and Kanjinti® are well differentiated and should enable rather than hinder differentiation. There is a small potential for sound and look alike name confusion between Herceptin® and Herzuma®, and this is further compounded by the use of similar orange-red colours on the outer packing and vial. In practice, any risk of harm is unlikely as the efficacy and safety of biosimilars are expected to be similar. Kanjinti® is available in a high strength 420mg product as well as the standard 150mg intravenous formulation; although the packaging and presentation of the two strengths are differentiated by the use of different colours, there is no text on the 420mg product specifically alerting healthcare professionals of this e.g. ‘high strength’.

At present these medicines are either prescribed using electronic systems or are written using pre-populated chemotherapy proformas. In the case of e-prescribing there are risks associated with product selection based on drop down menus based on alphabetical order, search function or name truncation. Similarly there is potential for error when using written prescriptions.

These presentations all need to be stored in a fridge, which also restricts opportunities to physically separate them and therefore educational efforts are needed to avoid picking errors in pharmacy stores, manufacturing departments and amongst nursing staff in units where they reconstitute the products prior to administration.
Administration

Trastuzumab 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\(^2\). Stipulations surrounding infusion times for Herceptin\(^\circ\) 150mg will also apply equally to biosimilars.

Manufacturer product literature

All trastuzumab products are provided with suitable patient and professional information to support their use. Each product is provided with an insert containing a full PIL for patient use. The PILs for Kadcyla\(^\circ\) (trastuzumab emtansine), Ontruzant\(^\circ\), Herzuma\(^\circ\), Kanjinti\(^\circ\) and Trazimera\(^\circ\) each contain a section at the end intended for healthcare care professionals at the point of administration in a clinical setting.\(^13-17\)

Kadcyla\(^\circ\) (trastuzumab emtansine) is provided with risk minimisation material for healthcare professionals to prevent medication errors of confusion between products. It highlights the risk of confusion between Herceptin\(^\circ\), and should be updated to include Ontruzant\(^\circ\), Herzuma\(^\circ\), Kanjinti\(^\circ\) and Trazimera\(^\circ\) biosimilars.\(^18\)

The Herzuma\(^\circ\) and Kanjinti\(^\circ\) packaging include features to facilitate recording of expiry dates, batch numbers and product details in patient notes (e.g. removable stickers on vial packaging).\(^26,27\)

Shelf-life and stability issues

Shelf-lives vary between the products: 21 months (Herceptin\(^\circ\) 600mg), 36 months (Ontruzant\(^\circ\), Kadcyla\(^\circ\), Kanjinti\(^\circ\)) and 48 months (Herzuma\(^\circ\), Herceptin\(^\circ\) 150mg, Trazimera\(^\circ\)). All products require storage between 2 to 8°C; in cases of accidental temperature excursion, continued use may be possible.\(^4-10\) Unopened vials of Trazimera\(^\circ\) are licensed to be stored up to 30°C for a single period of 3 months.\(^10\)

The reconstituted intravenous trastuzumab concentrate for solution products have licensed stability for 48 hours at 2-8°C and the resulting intravenous infusion for 24 hours not exceeding 30°C. Kadcyla\(^\circ\) (trastuzumab emtansine) infusion stability exists for 24 hours at 2-8°C.\(^4-10\) Additional stability data for extended storage of diluted products are available on request from the manufacturer and commercial specials units. NHS Quality Assurance services have approved additional stability of 7 days (Herzuma\(^\circ\)), 21 days (Ontruzant\(^\circ\)), 28 days (Kanjinti\(^\circ\)) and 6 weeks (Trazimera\(^\circ\)) for aseptically compounded products stored at refrigerator temperatures.\(^24-28\)

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.

1. Trastuzumab products should be prescribed using both generic name and brand name to help reduce the likelihood of error and prevent automatic substitution. This is in line with current regulatory advice about biological medicines when there is more than one version available on the market.\(^29\) 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 Herceptin\(^\circ\); additional recording of the brand should not therefore be onerous.

2. Organisations should consider which trastuzumab presentations to stock in the Trust with a view to minimise errors of mis-selection through restricting to one biosimilar product. If Kanjinti\(^\circ\) is to be the
preferred option, a local decision should be made regarding which strength of vials to stock.

3. **Local education and training** for prescribers, pharmacy staff, nurses, and others will be necessary to ensure that they are aware that a number of trastuzumab products are available and the potential for errors of mis-selection to occur. Staff will also need to be educated to ensure brand name prescribing, identification, and recording occurs for the biosimilar products.

4. Staff should be familiar with all trastuzumab presentations used in their Trust (including clinical trial supplies and dose branded presentations, if relevant). Ideally independent **double checks** of product selection should be considered at each stage of the supply and dispensing processes. At the point of administration, the infusion bag label should be checked against the prescription.

5. Strategies to mitigate the risk of picking errors between the trastuzumab products should be considered. These may include review of the stock’s **storage** in pharmacy departments.

6. **Prescribing systems** need to be reviewed to reduce the risk of prescribing the wrong product.

7. Local monitoring schemes should be developed to ensure adverse events associated with Ontruzant®, Herzuma®, Kanjinti® and Trazimera® are notified appropriately via routine pharmacovigilance schemes. Kadcyla® (trastuzumab emtansine), Ontruzant®, Herzuma®, Kanjinti®, and Trazimera® are black triangle products and will be subject to additional monitoring under intense MHRA regulatory surveillance to allow quick identification of new safety information. Safe introduction and ongoing safe use of trastuzumab biosimilar requires both practitioner and manufacturer engagement with these processes. Details of brand names will be necessary for reporting adverse drug reactions via the MHRA.

**Further actions by the manufacturers** are deemed to be fairly limited. The products have been provided in a form which should not fundamentally preclude their safe use. Manufacturers should consider:

- Changing the colour of the Herzuma® product packaging (Napp) and vial to improve differentiation with the Herceptin® product.

- Including information for healthcare professionals on reconstitution, dilution and administration within the package insert for Herceptin® (Roche).

- Update the Kadcyla® risk minimisation materials to include the biosimilars Ontruzant®, Herzuma®, Kanjinti® and Trazimera® (Roche).

- Providing removable labels on Herceptin®, Ontruzant®, and Trazimera® products to facilitate recording of brand, batch number and expiry dates (Roche, MSD, Pfizer).
References

1. What are biosimilars and are they important? Drug Ther Bull May 2013; 51(5): 57-60.
24. Personal Communication. NHS Pharmacy Aseptics Department, May 2018
26. Personal communication. Medicines Information at Napp Pharmaceutical Limited. May-August 2018
27. Personal communication. Medicines Information at Amgen UK Limited. May-August 2018
28. Personal communication. Medicines Information at Merck Sharpe & Dohme Limited. May-August 2018

This report was produced in August 2018 (and updated in April 2019 to include Trazimera®) using photographic images (not physical products) of licensed trastuzumab available at the time of assessment. Images were obtained primarily from pharmaceutical companies but also from various sources within the NHS.

This report summarises product assessments undertaken by: London Medicines Information service and London & South East Medicines Information Service. For comments email lnwh-tr.medinfo@nhs.net.

The UKMI product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey: https://www.surveymonkey.com/r/UKMiProductSafetyAssessments.
Roche Products Limited:
Kadcyla® (trastuzumab emtansine) 100mg & 600mg powder for concentrate for solution for infusion
Herceptin® (trastuzumab) 150mg powder for concentrate for solution for infusion
Herceptin® (trastuzumab) 600mg/5mL solution for injection in vial (subcutaneous preparation)

Merck Sharp & Dohme Limited:
Ontruzant® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion
Napp Pharmaceuticals Ltd [Celltrion Healthcare Hungary Kft]:
Herzuma® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion

Pfizer Limited:
Trazimera® (trastuzumab biosimilar) 150mg powder for concentrate for solution for infusion
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