Northern Health Interim Strategy
Reference Biologic and Biosimilar Insulin Interchangeability

Situation in British Columbia

In 2018, Pharmacare approved coverage of the first biosimilar insulin glargine (BASAGLAR®). At this time, less was known in Canada regarding interchangeability between the insulin reference biologic (e.g LANTUS®) and the biosimilar products. The approach was to deem non-interchangeable in the hospital setting until further information was reviewed provincially.

In December 2021, Pharmacare announced the change in coverage to the new rapid acting biosimilar insulins, insulin aspart (TRURAPI®) and insulin lispro (ADMELOG®), with a six month transition period in the community. Since there is more information regarding switching biosimilar insulins and the new approach regarding enoxaparin provincially, the BC P&T and DRS will be reviewing the biosimilar insulin approach; however, this will not likely occur until April 2022.

In the interim, several other health authorities in B.C. are considering the rapid-acting biosimilar insulin products as therapeutically equivalent and interchangeable to the reference biologics. This means that patients admitted to hospital will receive whichever brand the hospital carries, regardless of what brand they are receiving in community (originator brand will be kept in NH for time being).

Background on Biosimilar Insulin[1-3]

Biosimilar insulins have been used internationally for many years in various countries such as Europe and the U.S.A. and come to market after the patent on a reference biologic expires. Insulin is manufactured using recombinant DNA technology that utilizes living organisms to synthesize the insulin. The first version of this is termed the “reference biologic” and subsequent iterations are termed “biosimilar”. This is close to brand versus generic for chemically synthesized medications except that a biologic and biosimilar are not chemically “identical”. This is due to the complex process of using live organisms to manufacturer biologics, meaning there is expected natural variability not only between a reference biologic and a biosimilar but also between different lots/batches of the same biologic drug.

As such, Health Canada deems biosimilar products as “highly similar” to the reference biologic and they must meet specific criteria to ensure there is no clinically meaningful difference between the safety and efficacy of the 2 products. It is felt that the expected variabilities during manufacturing are not clinically meaningful.

Jessica Granberg BSP, ACPR
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Further, biologic drugs and these “heterogeneities” have sparked discussion regarding the potential for immunogenicity and development of antibodies not only with respect to the properties themselves but also switching between products. In general, the larger molecule products, like infliximab, were more of a concern for eliciting immunogenicity compared to the smaller insulin molecules of which it is noted in the monographs that there is a low potential for immunogenicity.

Assessment[4-7]

A comparison of the reference biologic and biosimilar insulin aspart in the table below shows identical structure and molecular weight with the only difference being the production organism used during manufacturing.

	NOVORAPID®	**TRURAPI®**
Molecular weight	5825.8 g/mole	5825.8 g/mole
Production organism	Recombinant DNA technology via *Saccharomyces cerevisiae*	Recombinant DNA technology via *E.coli*
Structure (see below)	Insulin analogue, amino acid proline in position B28 has been replaced by aspartic acid.	Insulin analogue, amino acid proline in position B28 has been replaced by aspartic acid.

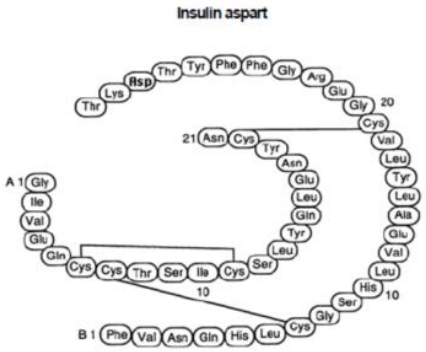

Image 1: identical molecular structure of both insulin aspart products

In reviewing other international agencies, the U.S. Food and Drug Administration (FDA) deemed biosimilar insulin glargine to be interchangeable with the reference biologic, meaning automatic substitution is permitted. An industry guidance document on considerations regarding clinical immunogenicity published in 2019 highlighted the following excerpts for biosimilar and interchangeable insulins:

- “…if state-of-the-art technology supports a demonstration of “highly similar” for a proposed biosimilar or interchangeable insulin product, there would be little or no residual uncertainty regarding immunogenicity; in such instances, the proposed biosimilar or interchangeable insulin product, like the reference product, would be expected to have minimal or no risk of clinical impact from immunogenicity.”

- "This updated recommendation is based on an extensive multidisciplinary evaluation involving several considerations, including:
  - the relatively small, structurally uncomplicated and well-characterized nature of insulin products in comparison to the vast majority of biologics, which generally allows for a comprehensive analytical evaluation, leaving little or no residual uncertainty regarding risk of clinical impact from immunogenicity,
  - extensive experience and literature survey that confirm minimal or no clinical relevance of immunogenicity with insulin product use; and scientific thinking on the lack of clinical impact of immunogenicity with insulin product use, as reflected in:
    - decades of clinical experience with approved insulin products, including the lack of a correlation between immunogenicity and safety or effectiveness as reflected in approved product labeling for insulin products
    - updated recommendations from the European Medicines Agency, which published a revised guideline in 2015 that no longer recommends a clinical immunogenicity study to support a biosimilar marketing application
    - published literature, including reports of clinical trial results in adults and pediatric patients with diabetes and retrospective reviews, which indicated a poor correlation between immunogenicity in insulin-treated patients and clinical impact on safety and efficacy and confirmed minimal or no risk of clinical impact from immunogenicity"

In summary, the concern of immunogenicity when switching between reference and biosimilar insulins is unlikely to be impactful to patient care. TRURAPI® has identical indications to the NOVORAPID® reference biologic, shares an identical structure, and is easily monitored in both inpatient and outpatient settings. Further, the current precedent for authorizing therapeutic equivalence with biosimilar enoxaparin injections and the standing insulins interchangeability in both European and America policies further supports therapeutic equivalence and interchangeability amongst biosimilar insulins. Lastly, a current provincial therapeutic interchange from insulin aspart (NOVORAPID®) to insulin lispro (HUMALOG®) and vice versa is performed without concern for immunogenicity, even though these two insulins are more different than changing between the TRURAPI® and NOVORAPID® insulin aspart products. The same is true when changing patients admitted on insulin analogues to a regular human insulin infusion (e.g. HUMULIN R®) in the critically ill population.

Action Plan as endorsed by NH Endocrinologist (Dr. Ksseiry)

1. NH will consider the rapid-acting insulin aspart product (TRURAPI®) as highly similar, therapeutically equivalent, and interchangeable with the reference biologic (NOVORAPID®).

2. NH will consider the biosimilar long-acting insulin glargine product (BASAGLAR®) to be considered highly similar, therapeutically equivalent, and interchangeable with the reference biologic (LANTUS®).

References

1. JDRF Canada. Biosimilar Insulins – What you need to know. 2021. Accessed December 23, 2021 via https://www.jdrf.ca/biosimilar-insulins-what-you-need-to-know/
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4. Health Canada. NovoRapid: Insulin Aspart. 2018. Accessed via Product information (canada.ca)
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FDA. Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products: Guidance for Industry. 2019. Accessed December 23, 2021 via https://www.fda.gov/media/133014/download

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