# IGA Positioning Statement
# Use of Non-comparable Medicines for Gaucher Disease

This positioning statement outlines the International Gaucher Alliance's (IGA) stance in relation to the use of 'intended copies' of enzyme replacement therapy (ERT) medicines as a treatment for Gaucher disease. These 'copies' are also known as **non-comparables** (the term used in this statement), due to the fact that they have not been directly compared to the original medicine in a clinical trial setting.

This is an important topic to address, given ongoing Gaucher disease patient community concerns around the regulatory approval and use of these medicines. Our recommendations have been developed to support local patient and caregiver communities in preparing and responding to the opportunities and challenges that non-comparables present.

## Background

**Gaucher disease** is a rare inherited (genetic), enzyme deficiency disorder. It is the result of a build-up of fatty substances in certain organs, particularly the spleen and liver. This causes these organs to enlarge and can affect their function. The fatty substances can also build up in bone tissue, weakening the bone and increasing the risk of fractures.[1]

The most common form of Gaucher disease (type 1) affects 1 in 100,000 of the general population but 1 in 850 of people of Jewish (Ashkenazi) descent. [2] In the neuronopathic Gaucher disease (types 2 and 3), neurological symptoms occur which include an eye movement disorder (oculomotor apraxia), unsteadiness (ataxia), fits (seizures), some impairment of thinking (cognitive) and the way the brain handles sounds (central auditory process disorder). Children with type 2 Gaucher disease do not usually live beyond the first few years of life.[2]

At present, there is no cure for Gaucher disease, however, there are a number of medicines available that manage the non-neurological symptoms. First-line treatment options are:

- enzyme replacement therapy (ERT),
- substrate reduction therapy (SRT).[3]

**This statement focuses solely on ERT therapy.** This is because non-comparables of an ERT treatment have been approved in some countries. These non-comparables have not followed the evaluation guidelines recommended by the World Health Organisation (WHO) for the development of biosimilar medicines.[4]

The IGA welcomes the availability of new medicines, as this offers better access and greater treatment choice for patients and providers. However, the IGA is aware of challenges in the way non-comparables could be used or interchanged with other approved medicines. In particular, the IGA is concerned about:

- the lack of safety and efficacy data;
- the lack of accurate product information;
- the lack of clarity and around how country drug approval have been made; and
- how patients are informed about these treatment options, as this has the potential to cause anxiety for the patient community as well as create false expectations.

Therefore, there is a need to clarify the current situation in terms of non-comparable use in Gaucher disease. This document highlights some of the potential issues associated with these medicines and sets out recommendations for consideration moving forward.

*Our aim is to inform and empower the Gaucher community so they can advocate for access to safe and effective treatments.*

### *ERT for Gaucher disease*

The approved ERT medicines in the highly regulated countries (e.g., EU and USA) are:

- Cerezyme® (imiglucerase),
- VPRIV® (velaglucerase alfa),
- Elelyso® (taliglucerase alfa).

*Note: Elelyso® is not licensed for use by the European Medicines Agency (EMA) and therefore is not available in the EU.*[3]

Some people react differently to different ERTs. The rationale behind a change in ERT should be based on the medical needs of the individual and the scientific evidence. The IGA has developed separate best practice guidance on so called treatment 'switching', available via the IGA website.

## Definitions of biologics, biosimilars and non-comparables

### *Biologics*

Biological medicines, shortly biologics (also known as biotherapeutics[7]), are medicines made from living organisms or their components, such as cells, proteins, or DNA.[5] ERT medicines are biologics. Small-molecule medicines can be copied. This means it is possible to make an exact replica of a medicine with a known chemical structure and a fixed number of atoms – this is also known as a generic medicine (shortly generic).[6] Biologics cannot be copied.

### *Biosimilars*

Biosimilar medicines, shortly biosimilars, are biologics that mimic the structure of the original biological medicine (also called "the reference product").[5] Biosimilars should work in a very similar way than their reference product, but they are not 100% identical and cannot technically be classified as generics.[4,6]
Biosimilar development is strictly regulated by the by EMA, the United States Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PDMA), to ensure they are as safe and effective as the reference product.[4] The manufacturers must demonstrate bio similarity to the reference product and provide data on quality, biological activity, safety, and efficacy. The WHO has also provided guidance on the evaluation of biosimilars.[7,8]

### *Non-comparables*

Non-comparables, also known as 'biocopies', 'biomimics', 'intended copies' and 'non-regulated biologics', are copies of licensed biological medicines, but have not followed the rigorous regulatory pathways required for biosimilars.[4,8] Therefore, it is difficult to know how a non-comparable medicine will perform in terms of efficacy, safety, and quality.

Although non-comparables are less time-consuming to develop than biosimilars and are often available at a significantly lower price than the reference product, there may be hidden

costs. These include if the product does not work as intended, or if it leads to adverse events, which adds pressure to healthcare systems.[4,9]

Non-comparables in Gaucher disease

Currently, no biosimilar for Gaucher disease has been approved by the FDA or EMA. However, some ERTs claiming bioequivalence (aka non-comparables) have been locally approved in a number of countries where regulatory procedures are arguably less stringent. Since 2012, two ERTs have been approved in some countries outside of the USA and EU[4], these are:

- Abcertin®, available in: South Korea, Iran, Bolivia, Peru, Ecuador and Kazakhstan; also registered and marketed as Asbroder® in Mexico, where it has been approved as an orphan drug.
- Glurazyme®, available in Russia.

## Issues surrounding the use of non-comparables for the treatment of Gaucher disease.

In an ideal world, everyone living with Gaucher disease would have access to effective medicines, regardless of location, social circumstances, and local healthcare provisions. The IGA understands there is wide variation in terms of healthcare infrastructure and attitudes to regulation and availability of medicines all over the world. In some cases, political factors may have a role to play.

The IGA acknowledges that non-comparables are often available at a lower cost than biosimilars and the reference products in general and may be the only option available to those living with Gaucher disease in some countries. The IGA also recognises that some non-comparables may be safe and effective, although there is currently insufficient data to support this claim.

While appreciating this context, concerns around the use of non-comparables in Gaucher disease are based on the following issues:

Efficacy and safety

The non-comparables used in Gaucher disease have not undergone the rigorous efficacy, safety and pharmacokinetic-pharmacodynamic (PK-PD) analysis that biosimilars undergo. Therefore, the medicines may not be as effective as the reference product or may cause adverse effects.

Inaccurate labelling and patient information

Some non-comparable medicines include prescribing information and clinical trial data directly copied from the original reference product, without making it clear that this does not relate directly to the non-comparable. This is confusing for patients, health practitioners and local authorities, as they are not always aware that it is a different product, which could be potentially dangerous.

Inaccurate classification

To avoid confusion, the WHO has set out strict guidelines on how new medicines should be named. Each substance must have a unique designated name, its International Non-proprietary Name (INN), that should be used universally. [4,10,11] Abcertin®, Asbroder® and Glurazyme® have the same INN, namely imiglucerase, as the reference product Cerezyme®, without having undergone the testing required for a biosimilar. This could mislead patients into believing they are taking a biosimilar, when they are in fact taking a non-comparable. Again, this raises the possibility of inadvertent switching or substitution.

Lack of transparency

To date, the manufacturers of the non-comparables for Gaucher disease have been reluctant to share data or engage in a dialogue despite repeated approaches from the IGA.

Lack of long-term data

Data collection on both positive and adverse effects in patients taking non-comparables for Gaucher disease is poor - or in some cases non-existent. This problem is compounded by the inaccurate labelling, which makes it difficult for clinicians and patients to compare like with like.

Uncertainty

Current information regarding non-comparables is inconsistent and can be confusing, due to little or no accurate public information available. This can be distressing for those living with Gaucher disease, as this can lead to uncertainty about what medicine they are taking and does not provide reassurance that their medicine is safe and effective.

## IGA recommendations

Non-comparables being used for the treatment of Gaucher disease is the reality in many countries. The current situation is unsatisfactory, but the IGA believes that many of the current issues can be addressed by taking targeted action. As such, recommendations are as follows:

**Medicine naming and labelling should clearly indicate if it is a non-comparable:** there should be a clear and consistent approach to nomenclature in all countries so that it is obvious whether a medicine for Gaucher disease is a biosimilar or a non-comparable. This is the responsibility of the manufacturing companies. The INN should indicate that it is an intended copy of the reference product using a relevant four-letter code at the end. Manufacturers who do not follow guidelines should be held accountable by the pharmaceutical regulatory bodies in their region and local health authorities.

**Accurate product information must be included in all packaging:** patients and clinicians should be able to trust that the information they are given about a medicine is correct. The product information leaflet and labelling on the outside and inside of any packaging in all countries must be directly relevant to the product and the clinical trials it has undergone. This is the responsibility of the manufacturing company and local regulatory authorities should hold them accountable.

**Robust safety and efficacy data should be reported and collected:** manufacturers have a duty to provide accurate information and should be liable to present it. There must be a systematic collection of long-term data on patients taking non-comparables (traceability, reporting and evaluation of adverse events) undertaken by the manufacturers (at a minimum). This can be accomplished via a registry that takes into account factors such as

ethnic differences, ages, molecular tests if available, etc. Adverse event reporting forms should be re-designed to be easier for patients and clinicians to use and ensure that the information reaches manufacturers and is properly recorded.

**Improved education about non-comparables should be made available:** there should be clear, targeted information about non-comparables for healthcare professionals, patients and decision-makers. Information should be tailored to local circumstances so that all parties can make informed decisions based on their own situation. The IGA is willing to collaborate on the development of such materials with other stakeholders, such as local patient organisations, clinical groups, professional societies, pharmaceutical companies, and non-comparable manufacturers.

**Community groups should engage directly with non-comparable manufacturers:** the IGA seeks to establish a positive dialogue with the manufacturers of non-comparables in Gaucher disease and explore opportunities for mutual collaboration that will benefit all parties. This could include encouraging non-comparable manufacturers to explore the biosimilar regulatory route.

**Wider health economic data on the use of non-comparables should be gathered:** the IGA has a shared responsibility to raise awareness of the data gaps surrounding the long-term economic effects of using less rigorously tested medicines in terms of therapeutic results, adverse events, hospitalisation etc. While community groups are unlikely to be in a position to lead or fund such data collection themselves, the IGA can raise the need with relevant stakeholders. Data collected by academics, researchers and industry groups over time could be used to support and inform other territories considering the non-comparable route.

**Wider discussion among pharmaceutical companies on the cost of biologics should be encouraged:** the IGA aims to engage with medicines manufacturers to explore the possibility of pricing biologics more competitively and transparently, in order to improve patient choice and increase access to medicines, while limiting the risk of compromising patient health by trying to get 'cheaper' medicines.

**Relevant stakeholder groups should come together to reach consensus on the way forward:** the IGA will seek to engage with all stakeholders to raise awareness of the issues surrounding non-comparables in Gaucher disease and generate a positive discussion about how to proceed.

*Our mission is to ensure that all people living with Gaucher disease have equal access to safe and effective medicines, wherever they live. We are committed to exploring the opportunities presented by non-comparables in Gaucher disease, while addressing the significant issues that currently exist. We will work tirelessly to support IGA member organisations so that together we can implement real change.*

*For more information on the IGA and our work, please visit: www.gaucheralliance.org*

## References


1. Mayo Clinic. Gaucher Disease. Available at: https://www.mayoclinic.org/diseases-conditions/gauchers-disease/symptoms-causes/syc-20355546. Last accessed May 2023.
2. International Gaucher Alliance. What is Gaucher Disease. Available at: https://gaucheralliance.org/what-is-gaucher-disease-2/. Last accessed May 2023.
3. International Gaucher Alliance. Treatments available. Available at: https://gaucheralliance.org/treatments-available/. Last accessed May 2023.
4. Drelichman G, Castaneda-Hernandez G, Cem Ar M, et al. The road to biosimilars in rare diseases – ongoing lessons from Gaucher disease. Am J Hematol. 2020;95:233-237.
5. International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Biotherapeutic Medicines - Putting Patients First infographic. 2014. Available at: https://www.ifpma.org/resource-centre/biotherapeutics-medicines-putting-patients-first-infographic/. Last accessed May 2023.
6. FDA. What are Biologics Questions and Answers. Available at: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers. Last accessed May 2023.
7. World Health Organization (WHO). Guideline on Evaluation of Biosimilars. 2022. Available at: https://cdn.who.int/media/docs/default-source/biologicals/who_trs_1043_annex-3_biosimilars_tk.pdf?sfvrsn=998a85d_1&download=true. Last accessed May 2023.
8. Rugo H, Rifkin R, Declerck P, et al. Demystifying biosimilars: development, regulation and clinical use. *Future Oncology*. 2019:15(7),777-790.
9. International Alliance of Patients' Organizations (IAPO). Factsheet: Biosimilars and the Importance of Adherence to International Regulatory Standards. 2017. Available at: https://www.iapo.org.uk/sites/default/files/files/factsheet4.pdf. Last accessed May 2023.
10. Mysler E, Pineda C, Horiuchi T, et al. Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. *Rheumatol Int.* 2016:36,613–625.
11. Tsang S, Pandya S, Barakov, K. et al. Use of Identical INN "Imiglucerase" for Different Drug Products: Impact Analysis of Adverse Events in a Proprietary Global Safety Database. *Drug Saf*. 2022:45,127– 136.


Date issued: 15th June 2023.
Approved by the IGA CEO and by the IGA Board of Directors (list of names here).

Biljana Jovanovic
Irena Znidar
Kristiyan Dimitrov
Suyog Sathe
Aimee-Kate Bosch
Aviva Rosenberg
Francisco Carreiro
Sara Khan
Paulina Pena Aragon
Tanya Collin-Histed (CEO)