

Ontario Association of Gastroenterology Consensus Group: Statement on the Introduction of Subsequent Entry Biologics in Canada

The introduction of subsequent entry biologic (SEB) therapies provides an important opportunity to increase treatment options for both patients and providers and to improve the collective affordability of biologic agents. However, the complex structures of SEBs make generation of biologically identical molecules a challenge (Devlin et al., 2013), and even subtle differences between SEBs and innovators may translate into clinically relevant variations in efficacy, safety, and immunogenicity. Such variations are of significant concern to the Ontario Association of Gastroenterologists (OAG) and several other groups (eg, the Canadian Association of Gastroenterologists [CAG]) (Devlin et al., 2013; Endrenyi et al., 2014), as patients with inflammatory bowel disease (IBD) represent a very sick and vulnerable patient population. With a severe and progressive prognosis and limited therapeutic options, these patients experience a more significant impact of biologic failure and/or novel safety issues than patients with rheumatoid arthritis or psoriasis, for which more therapeutic options are available.

The OAG recognizes several key challenges to the development, marketing, and use of SEBs (Devlin et al., 2013; Endrenyi et al., 2014).

- The need for robust clinical data in all relevant therapeutic indications, and the issues surrounding extrapolation to other indications
- The lack of evidence supporting the interchangeability/substitution of innovators with SEBs
- The need for systems that will capture long-term pharmacovigilance data for innovators and SEBs; SEBs would require distinct, non-proprietary names for proper identification.
- The lack of evidence supporting switching between SEBs of the same innovator product

As noted by other groups, the OAG agrees that the clinical equivalence of SEBs and innovators can only be demonstrated by clinical trials in the therapeutic area of interest (Devlin et al., 2013; Endrenyi et al., 2014). **Similar to CAG's and Health Canada's position statements on SEBs** (Health Canada, 2010a, b; Devlin et al., 2013), **the OAG therefore recommends following:**

1) SEBs should be regarded as stand-alone products and supported by well-designed non-clinical and clinical studies in a population relevant to Canadian patients.

- Robust evidence must demonstrate SEBs to be as safe and effective as innovator products.
- Evidence must be available for every indication in which the SEB's manufacturer is seeking approval.
- Extrapolation of indications must be scientifically supported.

2) SEBs cannot be regarded as interchangeable or substitutable with innovator biologics.

- Non-medical switching of stable patients to an SEB is not recommended without sufficient evidence of efficacy, safety, lack of immunogenicity, and long-term follow-up outcomes.
- Only the treating physician, in consultation with the patient, should make the decision to switch the patient to an alternative regimen.
- The OAG feels strongly that the availability of several distinct yet similarly proven biologic therapies (innovator and SEBs) will increase patient and provider options and improve patient outcomes.

3) Prescriptions for innovator biologics should not be automatically substituted for less expensive SEBs by prescribing pharmacies.

- The OAG acknowledges that, to date, no SEB has interchangeability status and therefore automatic substitution rules do not apply.
- However, future decisions regarding any form of switching must be discussed and approved by the treating physician and patient.

4) SEBs should be supported by long-term pharmacovigilance data in a fashion similar to innovator biologics.

- A robust tracking system should be used for all biologics, including SEBs, to ensure proper tracking of safety and efficacy profiles.
- The system would require all biologics to be easily distinguishable by distinct names, including unique non-proprietary names.
- Adverse events must be correctly attributed to the responsible biologic therapy and manufacturer.

5) Policies should acknowledge the environmental complexities associated with the introduction of multiple SEBs for one innovator biologic.

- There is high potential for accidental switching between SEBs at the pharmacy level.
- Data are currently lacking for the safety and efficacy of switching between two or more SEBs of the same innovator biologic, as SEBs are only required to demonstrate their similarity to the innovator biologic, not to one another.

Patients with IBD should have access to safe, effective, and affordable drugs. The OAG requests careful consideration of the above recommendations when reimbursement decisions are being made regarding the use of SEBs for IBD in Canada, and in Ontario specifically. The OAG hopes to work with the Ontario Public Drug Program to further improve the understanding of these challenges and their potential impact on future policy making and reimbursement.

References

- Devlin SM, Bressler B, Bernstein CN, Fedorak RN, Bitton A et al. (2013) Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. *Can J Gastroenterol* 27 (10): 567-571.
- Endrenyi L, Fakhreddin J, Loebenberg R (2014) Subsequent entry biologics in Canada: Current state of the science. *J Pharm Pharmaceut Sci* 18 (2): 177-183.
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