What are the key drivers of reimbursement for biosimilars? An examination of reimbursement processes and recommendations across nine countries

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Definition of ‘Biosimilar’

- European Medicines Agency (EMA) definition*:

  A biosimilar medicinal product is a medicinal product which is similar to a biological medicinal product that has already been authorised (the ‘biological reference medicinal product’). The active substance of a biosimilar medicinal product is similar to the one of the biological reference medicinal product. The name, appearance and packaging of a biosimilar medicinal product may differ to those of the biological reference medicinal product. It may also contain different inactive ingredients’

* 2010 Glossary

Demonstration of biosimilarity

- In Canada, known as *Subsequent Entry Biologics*
- Requirements for authorisation of biosimilars:
  - EMA: Similar to the reference medicine; does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy
  - FDA: A biological product that is "highly similar" to an already-approved biological product
  - Health Canada: A biologic drug that enters the market subsequent to a version previously authorised in Canada, and with demonstrated similarity to a reference biologic drug

Objective

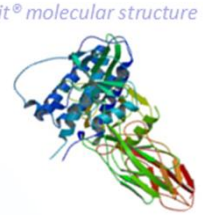
- To obtain insight on the regulatory approval of biosimlars and the approaches to reimbursement of biosimilars in countries using HTA to inform decision-making

- Biosimilars were selected on the basis of product class and assessment by different reimbursement agencies
  - Binocrit® (epoetin alfa, ref: Eprex® Janssen-Cilag)
  - Nivestim® (filgrastim, ref: Neupogen® Amgen Ltd)
  - Ratiograstim® (filgrastim, ref: Neupogen® Amgen Ltd)
  - Omnitrope® (somatropin, ref: Genotropin® Pfizer)

Methods

- Qualitative documentary analysis
- Seven European countries, South Korea and Australia
- Regulatory approval
- HTA reimbursement decisions
  - Processes of appraisal
  - Recommendations by indication
  - Key factors driving the decisions

Overview of Binocrit® – epoetin alfa



- Reference product: Eprex® (Janssen-Cilag)
- Erythropoietin produced by recombinant technology
  - Similar amino acid sequence to endogenous human erythropoietin
  - Differ in the glycosylation pattern
    - Influences pharmacokinetics; may influence efficacy and safety
- Development approach to proving biosimilarity
  - Demonstrating similarity in physicochemical properties and biological activity *in vitro*
  - Confirmation of clinical comparability

Demonstration of clinical comparability

- Five pharmacokinetic/pharmacodynamic studies
- Efficacy and safety: Two double-blind, randomised, parallel-group, multicentre studies
  - Treatment of anaemia in patients with chronic renal failure (equivalence study – Binocrit vs. Erypo; safety study – Binocrit)
  - Treatment of chemotherapy-associated anaemia in cancer patients (non-comparative controlled study)

	Description	Primary endpoint: Mean change in HB from baseline	Safety
Pivotal trial 1	Equivalence study Binocrit vs. Eprex. Efficacy over 24 weeks, safety over 56 weeks. CRF and moderate anemia on hemodialysis. n=478. 2:1 (Bino:Eprex), IV administration.	Bino: 0.147g/dL Eprex: 0.189g/dL Equivalence sought 95% CI, -0.03 to 0.418 Clinical equivalence was suggested (below range of ±0.5 g/dL)	Weeks 1-24: Bino SAEs 36% Eprex SAEs 34% Weeks 29-56: Bino SAEs 35% Eprex + Bino SAEs 36%
Pivotal trial 2	Binocrit (n=74); Eprex (internal control; n=40). Chemotherapy related anaemia (serum ferritin ≥100 µg/l or saturated transferrin levels ≥20%. SC administration	Bino: 2g/dL in 61% of patients (95% CI, 48.2% to 73.9%) Eprex: 2g/dL in 44% of patients (95% CI, 27.2% to 62.1%) Binocrit lower bound >30% (terminal clinical significance)	No increased immunogenicity or appearance of neutralizing antibodies (except in 1 borderline case) in Bino arm

Approval and reimbursement of Binocrit®

- Binocrit was as effective as the reference product in increasing and maintaining red blood cell counts
- EMA approved use in all four indications
  - Epoetin has the same mechanism of action in all indications
- Reimbursement decisions varied for different indications

				
For anaemia in patients with chronic renal failure on haemodialysis or peritoneal dialysis	**Recommend**	**Recommend**	**Recommend**	**Recommend**
For anaemia in patients receiving chemotherapy, reducing need for blood transfusions	**Recommend**	**Restricted Recommend**	**Recommend**	**Restricted Recommend**
To increase the amount of blood allowed in adults with moderate anemia in blood transfusions	**Recommend**	**Restricted Recommend**	**Recommend**	**Not appraised**
To reduce the need for blood transfusions in adults with moderate anemia prior to surgery	**Recommend**	**Recommend**	**Recommend**	**Not appraised**

Appraisal of biosimilars in different countries

- Twenty-one different indications were appraised
  - Automatic recommendation in Germany and The Netherlands
  - Sweden and France appraised and recommended for all indications
  - Scotland and Wales provided a positive decision on all biosimilars but restricted recommendations

									
Binocrit	Not appraised	Not appraised	Restricted Recommend	Not appraised	Not appraised	Not appraised	Restricted Recommend	Recommend	Restricted Recommend
Ratiograstim	Not appraised	Not appraised	Recommend	Not appraised	Not appraised	Not appraised	Recommend	Recommend	Recommend
Nivestim	Restricted Recommend	Not appraised	Recommend	Not appraised	Not appraised	Not appraised	Recommend	Recommend	Recommend
Omnitrope	Restricted Recommend	Recommend	Recommend	Not appraised	Recommend	Not appraised	Recommend	Recommend	Not recommend

Factors influencing HTA appraisal decisions

							
Clinical factors	Clinical comparability demonstrated to reference product	X	X	X	X	X	X
	Safety profile demonstrated to be comparable to reference product	X	X		X	X	X
	Clinical analyses of all subgroups		X				
	Clinical analyses performed on all administrations		X		X		X
	Improved administration (less frequent than ref.prod)			X	X		
	Rarity of disease and/or prevalence of disease		X				
Economic factors	Provide a cost-minimisation analysis	X	X		X		X
	Cost-effectiveness / cost-utility analysis preferred	X					
	Provide a budget impact analysis				X	X	X
	Economic analyses performed on all administrations	X			X		X
	Include potential comparators beyond reference product			X	X		X
	Extrapolation of analyses allowed for other indications				X	X	X

** Germany and Netherlands had no appraisals, whilst decision factors were not publically available for the one Australian appraisal*

Conclusions

- Evolving reimbursement landscape for biosimilars
- Basic principles are similar across regulatory bodies
  - Differences exist with respect to scope
    - Equivalence studies vs. non-inferiority studies
  - And with respect to choice of reference product
    - Regulatory region of authorisation
- HTA evidence important but other decision factors
  - Stakeholder influence
  - Regional decision-makers and local perceptions

Future challenges

- Some agencies require that the reference product is one that is authorised for the specific regulatory region
  - Increased costs in developing biosimilars for global markets
- Assessment of biosimilars of increasing structural complexity
  - Monoclonal antibody-based drugs

Molecular structure of a monoclonal antibody