Setting the scene: points to consider when evaluating biosimilars or biopharmaceuticals

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Points to consider when evaluating biosimilars or biopharmaceuticals

- Avonex
- Betaferon
- Rebif

Points to consider?

- Safety
  - Information from patient registers, feedback from NICE
  - Nanofiltration – do products require?
- Cost effectiveness – what is cheapest
- Pre-clinical and Trial information
- Publications
- Structure
- Availability of product and product differentiation
- Handling (ease of) and storage
- SPC considerations
- Hospital expectations
- Patient safety
- Reimbursement issues
- Efficacy of similar products in individual patients
- Post marketing surveillance results

Points to consider when evaluating biosimilars or biopharmaceuticals

Product	Drug substance	Dose per vial	Formulation
Avonex	interferon beta-1a 166 amino acids, 22.5 kDa	30 µg = 6 million IU	Lyophilised powder; contains HSA (15 mg), sodium phosphate, NaCl; 1 ml H_2O – pH 7.3 Prefilled syringe, 0.5 ml H_2O, acetate, arginine-HCl, Tween 20, pH 4.8
Betaferon	interferon beta-1b 165 amino acids, 18.5 kDa	250 µg = 8 million IU	Lyophilised powder; contains HSA (15 mg), mannitol; 1.0 ml 0.54% NaCl
Rebif	interferon beta-1a 166 amino acids, 22.5 kDa	22 µg = 6 million IU	Prefilled syringe, 0.5 ml H_2O, 27.3 mg mannitol, 2 mg HSA, sodium acetate, pH 3.4–4.4

HSA, human serum albumin

Points to consider when evaluating biosimilars or biopharmaceuticals

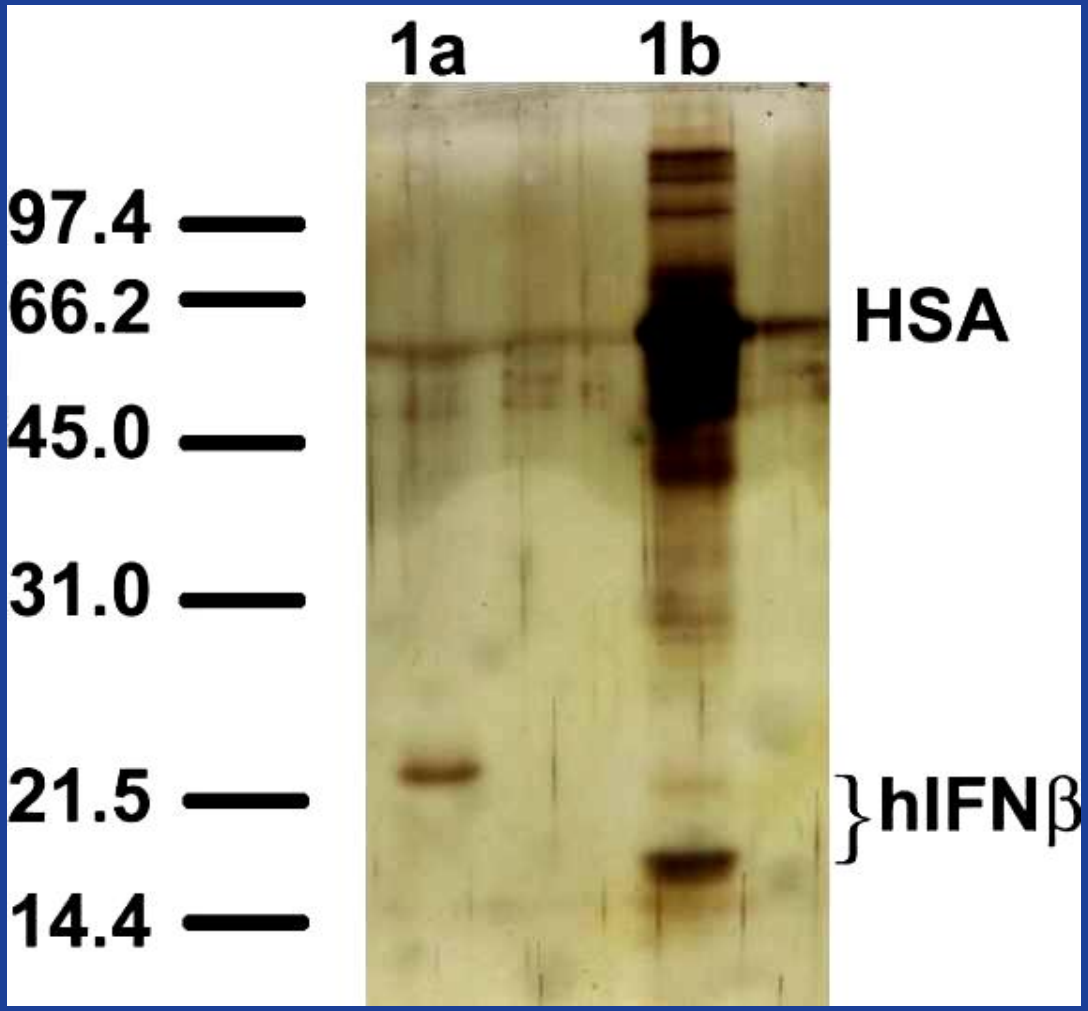
Product	Recommended dose + route	Cost/vial (Eur)	Cost/week/ patient (Eur)
Avonex	30–60 µg, 1x per week, intramuscular	222	222–444
Betaferon	250 µg, 1x per 2 days, subcutaneous	60	210
Rebif	22–44 µg, 3x per week, subcutaneous	88 (22 µg) 97 (44 µg)	264–291

Points to consider when evaluating biosimilars or biopharmaceuticals

Product	Patients (%) developing antibodies		
	1 month	3 months	12 months
Avonex	0	3.3	10
Betaferon	60	90	90
Rebif	0	0	25

Perini et al. *Eur Cytokine Netw* 2001;12:56–61

Points to consider when evaluating biosimilars or biopharmaceuticals



Points to consider when evaluating biosimilars or biopharmaceuticals

- Quality aspects…
  - Manufacturer
  - Biological activity
  - Protein and product formulation
  - Batch consistency
  - Good handling practice
- Clinical efficacy
- Clinical safety and tolerability
- Reimbursement and efficiency

Points to consider when evaluating biosimilars or biopharmaceuticals

Manufacturer

- From where and from which manufacturer is the biopharmaceutical produced?
- Is the manufacturer experienced in the production of biopharmaceuticals?
- Does the manufacturer guarantee active information about major changes in the manufacturing process?

- Written statement of the supplier including list of products manufactured, years of experience, number of batches produced

Points to consider when evaluating biosimilars or biopharmaceuticals

Biological activity

- What is the biological activity compared with the reference product and which tests/reference standards were used for measuring?
- On the basis of which parameters is the conclusion drawn of comparable biological activity between the different products?

- Journal publication(s)
- European Public Assessment Report (EPAR)
- Batch certificate

Points to consider when evaluating biosimilars or biopharmaceuticals

Protein and product formulation (1)

- Does the biosimilar comply with the requirements of any applicable pharmacopoeia monograph?
- Which specs are set for batch release (eg protein content, bioactivity, content of aggregates, host cell protein, endotoxin level, pH)?
- Are there any differences in isoform pattern compared with the reference product or other biosimilar product(s)?

Points to consider when evaluating biosimilars or biopharmaceuticals

Protein and product formulation (2)

- Which materials of animal origin or allergenic materials are used during the production process?
- Are there any differences in drug formulation (eg dosage form, excipients such as stabilizers or preservatives) compared with the reference product or other biosimilars?

- Journal publication(s), EPAR
- Batch certificate
- Written statement of supplier (unsolicited in the case of major changes)

Points to consider when evaluating biosimilars or biopharmaceuticals

Batch consistency

- How is consistency between batches ensured?
- Is the manufacturer able or willing to hand over the batch certificates of three recently produced batches?

- Batch certificate
- Written statement of supplier

Points to consider when evaluating biosimilars or biopharmaceuticals

Reliability of supply

- Can the supplier reliably guarantee the provision of the biosimilar over a long time period?

- History of back orders or announcements of stock outs
- Production plan

Points to consider when evaluating biosimilars or biopharmaceuticals

Good handling practice (1)

- How does the supplier ensure and document product integrity from production site to point of administration (eg during storage, transport, cold chain)?
- What are the shelf-lives of the products according to the storage conditions?
- Are there any data or recommendations regarding the shelf-life of incorrectly handled biosimilar drug products (eg interruption of cold chain, storage at elevated temperatures)?

Points to consider when evaluating biosimilars or biopharmaceuticals

Good handling practice (2)

- Are there any differences in storage or handling practices compared with the reference product?
- Is the product delivered in or with an administration device (pen, ready-to-use syringe) and how does the administration technique differ from that of the originator product(s) or other biosimilars?

- Written statement of supplier
- Assessment of the supplier according to the pharmacies' quality management system
- History of recalls
- Journal publication(s)

Points to consider when evaluating biosimilars or biopharmaceuticals

Clinical efficacy (1)

- What are the details of the clinical trials performed (patient populations, study designs, endpoints, results)?
- Are the results different compared with the reference product?
- What is the biological activity per unit and the activity index compared with the reference product?

Points to consider when evaluating biosimilars or biopharmaceuticals

Clinical efficacy (2)

- What is the dosing regimen and the route of administration (single dose, frequency) compared with the reference product?
- Is there additional information on efficacy available (eg open-label studies, case reports, data on file)?

- Journal publication(s)
- EMEA/FDA reports
- Clinical investigator brochure (CIB)
- Clinical study reports (CSR)
- Company data on file

EMEA, European Medicines Agency; FDA, Food and Drug Adminstration

Points to consider when evaluating biosimilars or biopharmaceuticals

Clinical efficacy (2)

- List of clinical studies (in table format)

Summary of EU approvals and clinical trials **Product X**				
Reference number **Phase** (eg phase II)	**Population** (eg groups, n=)	**Design** (eg randomized, x arm, regimen, dose)	**Endpoints**	**Results**

Points to consider when evaluating biosimilars or biopharmaceuticals

Clinical safety and tolerability

- Are there any contraindications or warnings that are different to the reference product?
- Differences to the originator product, eg in contraindications, precautions?
- Which (serious) adverse events were reported in clinical trials?
- Were any different safety issues (ie immunogenicity) or tolerability reported in the clinical trials of the biosimilar that are different to the reference product?

Points to consider when evaluating biosimilars or biopharmaceuticals

Post-marketing safety and risk management programme (1)

- Are there any post-marketing commitments? If applicable, which ones?
- Which short- and long-term risk management programmes are established?
  - Pharmacovigilance programme
  - Periodic, safety update reports
  - Phase IV clinical trials/registries

Points to consider when evaluating biosimilars or biopharmaceuticals

Post-marketing safety and risk management programme (2)

- Which (serious) adverse drug events were reported and at which frequency in the post-marketing surveillance studies?
- Which methods of antibody testing were/are established (validated methods, differentiation between Ab and neutralizing Ab)?
  - How many patients were tested for antibodies and what were the findings?
  - Does the manufacturer support antibody testing in patients?

Ab, antibody

Points to consider when evaluating biosimilars or biopharmaceuticals

Clinical safety and tolerability
Post-marketing safety and risk management programme

- Journal publication(s)*
- EMEA (EPAR)/FDA reports
- CIB
- Dear Doctor/pharmacist letter
- Bibliographies by the manufacturer
- National database of AEs, reports of medicine agencies
- Documentation by the manufacturer (safety database from clinical trials, post-marketing surveillance, ‘data on file’)
- National pharmacovigilance reporting system

AE, adverse event; EMEA, European Medicines Agency;
FDA, Food and Drug Administration; CIB, Clinical investigator brochure

Points to consider when evaluating biosimilars or biopharmaceuticals

Reimbursement and efficiency

- What is the reimbursement situation with respect to the biosimilar for inpatients or outpatients?
- What are treatment costs for the biosimilar compared with the reference product?
- Are there any cost–efficacy studies for the biosimilar drug treatment?

- Reimbursement policies
- Pharmacoeconomic studies

Points to consider when evaluating biosimilars or biopharmaceuticals

Many…