London, 19 January 2006
Product name: **REBIF**
Procedure no: **EMEA/H/C/00136/X/0051**

SCIENTIFIC DISCUSSION

1. Introduction

Currently, the registered strengths of Rebif are 22 µg and 44 µg in 0.5 ml. The recommended posology of Rebif is 44 micrograms given three times weekly by subcutaneous injection. The currently approved SPC also indicates that:

"When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions, it is recommended that 8.8 micrograms (0.1 ml of the 44 micrograms strength or 0.2 ml of the 22 micrograms strength) be administered during the initial 2 weeks of therapy, 22 micrograms (0.25 ml of the 44 micrograms strength or the total of the 22 micrograms strength) be administered in weeks 3 and 4, and the total of the 44 micrograms strength be administered from the fifth week onwards."

The new strength product will be provided in a "Initiation pack", containing 6 syringes of the 8.8 µg and 6 syringes of the 22 µg presentation, respectively. Each pre-filled syringe (1ml) is designed to deliver 0.2 ml (for 8.8 µg) or 0.5 ml (for 22 µg) of a sterile, clear aqueous solution. The interferon-ß-1a 8.8 µg finished product batches have been manufactured using the same compounding, manufacturing process, equipment and quality control procedures as for the currently marketed Interferon-ß-1a finished product (22 and 44 µg) and are differing only in the syringe fill volume (0.2 ml instead of 0.5 ml per 22 µg syringe).

2. Quality aspects

Active substance

No changes to the approved dossier.

Finished product

Description and composition of the finished product

Rebif solution for injection in a pre-filled syringe is available in syringes delivering 8.8 µg in 0.2 ml, or 22 µg in 0.5 ml, or 44 µg in 0.5 ml. Each pre-filled syringe (1ml) is designed to deliver 0.2 ml (for 8.8 µg) or 0.5 ml (for 22 µg and 44 µg) of a sterile, clear aqueous solution. The compositions are given below:

Composition of Rebif 8.8 mcg

NAME OF INGREDIENTS	UNIT FORMULA OR PERCENTAGE	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Interferon beta-1a	8.8 mcg		Reference House Standard
Other ingredients			
Human serum albumin	0.8 mg	Prevention of adsorption, stabiliser	Ph. Eur./USP
Mannitol	10.9 mg	Tonicity agent	Ph. Eur./USP
0.01 M Sodium acetate buffer pH 3.5	q.s. to 0.2 ml	Buffer	Ph. Eur./USP[1]

Composition of Rebif 22 mcg

NAME OF INGREDIENTS	UNIT FORMULA OR PERCENTAGE	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Interferon beta-1a	22 mcg		Reference House Standard
Other ingredients			
Human serum albumin	2.0 mg	Prevention of adsorption, stabiliser	Ph. Eur./USP
Mannitol	27.3 mg	Tonicity agent	Ph. Eur./USP
0.01 M Sodium acetate buffer pH 3.5	q.s. to 0.5 ml	Buffer	Ph. Eur./USP[1]

Composition of Rebif 44 mcg

NAME OF INGREDIENTS	UNIT FORMULA OR PERCENTAGE	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Interferon beta-1a	44 mcg		Reference House Standard
Other ingredients			
Human serum albumin	4.0 mg	Prevention of adsorption, stabiliser	Ph. Eur./USP
Mannitol	27.3 mg	Tonicity agent	Ph. Eur./USP
0.01 M Sodium acetate buffer pH 3.5	q.s. to 0.5 ml	Buffer	Ph. Eur./USP[1]

Pharmaceutical Development
No changes to the approved dossier.

Manufacture
IFN-ß-1a finished product solution for injection in pre-filled syringe is manufactured at the currently approved finished product manufacturers.

Manufacturing process
IFN-ß-1a solution for injection 8.8 µg / 0.2 ml in pre-filled syringe, is manufactured according to the process used for Rebif 22 µg but with a filling volume of 0.2 ml instead of 0.5 ml.
The same in-process controls are applied for control in the manufacture of all three product strengths, except that the filling volume acceptance range is adapted to the target filling volume of 0.2 ml.

Process validation
Studies were performed to demonstrate that IFN-ß-1a solution for injection 8.8 µg in a pre-filled syringe (0.2 ml fill) manufactured at LSA consistently delivers a product that meets the approved in-process control and the intended finished product specifications.

Control of Excipients
No changes to the approved dossier.

Control of Finished product
Compared to the currently approved 22 µg and 44 µg strengths, the specifications were adapted to the smaller volume of the 8.8 µg strength as applicable. There are no other changes.

Reference Standards or Materials
No changes to the approved dossier.

Container Closure System
No changes to the approved dossier.

Stability
Based on the real time stability data a shelf life for the finished product has been accepted.

3. Non clinical aspects

No new data or studies were submitted for this application.

4. Clinical aspects

No new data or studies were submitted for this application.

5. Overall conclusions, benefit/risk assessment and recommendation

Close to identical processes are used for manufacture of the 22 µg and 8.8 µg presentations. The use of a smaller fill volume is not considered likely to have any large effect on product quality.

Based on the CHMP review of data on quality, the CHMP considered that the benefit/risk ratio of Rebif in the treatment of "patients with multiple sclerosis and with 2 or more relapses within the last two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity" was favourable and therefore recommended the extension of the marketing authorisation for Rebif 8.8 µg and 22 µg.