PUBLIC SUMMARY DOCUMENT

Product: Interferon Beta – 1b, injection set comprising 1 vial powder for injection 8,000,000 i.u. (250 micrograms) and solvent, Betaferon®

Sponsor: Schering Pty Limited

Date of PBAC Consideration: March 2007

1. Purpose of Application

The submission requested a review of the eligibility criteria of drugs for the treatment of Multiple Sclerosis (MS) to allow patients diagnosed using the McDonald criteria to access treatment. This would allow for a second attack in time to be defined by a new lesion appearing on Magnetic Resonance Imaging (MRI) rather than a second clinical attack.

2. Background

Interferon beta-1b was first listed on the PBS on 1 November 1996 after consideration at the September 1996 PBAC meeting.

3. Registration Status

Betaferon is registered for:

- the treatment of ambulatory patients with relapsing-remitting multiple sclerosis (MS) characterised by at least two attacks of neurologic dysfunction over a two year period followed by complete or incomplete recovery.

- the reduction of frequency and severity of clinical relapses, and for the slowing of progression of disease in patients with secondary progressive multiple sclerosis.

- the treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent magnetic resonance imaging (MRI) lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.

4. Listing Requested and PBAC's View

Two listing alternatives were proposed:

Alternative One:
Authority required
Initial treatment of relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients who have experienced documented neurological dysfunction believed to be due to the multiple sclerosis.

- Two or more attacks believed to be due to multiple sclerosis with objective clinical evidence of two or more lesions.

- Two or more attacks believed to be due to the multiple sclerosis with objective clinical evidence of one lesion plus dissemination in space demonstrated by MRI, or two or more MRI lesions plus positive CSF or a further clinical attack implicating a different site.

- One attack believed to be due to the multiple sclerosis with objective clinical evidence of two or more lesions plus dissemination in time demonstrated by MRI or a second clinical attack suggestive of multiple sclerosis.

- One attack believed to be due to the multiple sclerosis with objective clinical evidence of one lesion plus dissemination in space demonstrated by MRI or two or more MRI-detected lesions plus positive CSF and dissemination in time demonstration by MRI or a second clinical attack.

- MRI lesions should be consistent with multiple sclerosis. MRI dissemination in space criteria should include three of the following, (1) at least one gadolinium-enhancing lesion or nine T2 hyperintense lesions (2) at least one infratentorial lesion (3) at least one juxtacortical lesion (4) at least three periventricular lesions. A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered equivalent to an enhancing brain lesion and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions. MRI dissemination in time criteria can be satisfied by (a) detection of gadolinium enhancement at least three months after the onset of the initial clinical event at a new site or (b) detection of a new T2 lesion if it appears at any time compared to a reference scan done at least 30 days after the onset of the initial clinical event.

The dates of scans must be included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

Continuing treatment of multiple sclerosis patients previously issued with an authority prescription for this drug who do not show continuing progression of disability while on treatment with this drug and who have demonstrated compliance with, and an ability to tolerate, this therapy. The authority will be limited to the maximum quantity and number of repeats indicated in the schedule.

Alternative two:
Authority required
Initial treatment of relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients who have experienced one or more documented attacks of neurological dysfunction believed to be due to the multiple sclerosis.

The diagnosis must be confirmed by magnetic resonance imaging (MRI) unless there have been two attacks with objective evidence of two or more lesions. MRI lesions should be consistent with multiple sclerosis.

For a single neurological attack with objective clinical evidence of two or more lesions, a positive MRI disseminated in time is required. For a single neurological attack with

objective clinical evidence of one lesion, positive MRIs disseminated in space and time are required.

The dates of MRI scans must be included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

Continuing treatment of multiple sclerosis patients previously issued with an authority prescription for this drug who do not show continuing progression of disability while on treatment with this drug and who have demonstrated compliance with, and an ability to tolerate, this therapy. The authority will be limited to the maximum quantity and number of repeats indicated in the schedule.

See Recommendation and Reasons for PBAC's view

5. Clinical Place for the Proposed Therapy

By revising the current eligibility criteria, patients who are already diagnosed with multiple sclerosis using the McDonald criteria would have access to treatment.

6. Comparator

The submission nominated placebo as the appropriate comparator.

7. Clinical Trials

The primary source of evidence was a single trial (the BENEFIT trial) comparing interferon beta-1b (INFN beta-1b) (8 million IU every other day) and placebo over 24 months in the treatment of patients with one clinical attack of neurological dysfunction suggestive of demyelinating disease within the last 60 days and at least two clinically silent lesions on MRI.

The BENEFIT trial had been published at the time of submission as follows:

First author	Publication title	Publication citation
Kappos et al.	Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.	Neurology; 2006;67(7):1242-124
Blaeser-Kiel et al.	First clinical manifestation of multiple sclerosis. BENEFIT: Good prospects of therapy 'on suspicion'.	Neurologue & Rehabilitation 2005; 6:356-357.
Anonymous	The BENEFIT study: Betaferon can delay outbreak of multiple sclerosis.	Deutsche Apotheker Zeitung 2005; 145(44):47-49

8. Results of Trials

The results of the BENEFIT trial are summarised below:

Cumulative probability (%, Kaplan-Meier estimates) of being diagnosed with MS according to the McDonald criteria and CDMS according to the altered Poser criteria

	Cumulative probability of CDMS according to the modified Poser criteria (%)		Cumulative probability of being diagnosed with MS according to the McDonald criteria (%)	
Days of treatment	**INFN-1b (N=292)**	**Placebo (N=176)**	**INFN-1b (N=292)**	**Placebo (N=176)**
0	0	0	0	0
90	6.6	9.2	12.2	21.2
180	11.2	19	28	50.6
270	14.4	26	46.5	66.1
360	18.4	31.9	55.6	73.1
450	22.1	34.3	62.6	76.6
540	24	39.1	63.4	77.8
630	25.8	40.9	76	79.7
720	27.5	45.3	69.4	84.5

The Kaplin-Meier estimates for the probability of MS according to the McDonald criteria over time suggest that the majority of patients in both groups were diagnosed with MS in the first year of the trial.

The following table shows mean and median scores for the Kurtzke Expanded Disability Status Scale (EDSS) observed over 2 years of the trial.

EDSS scores

	INFN-1b (N=292)			Placebo (N=176)		
Observation point	**N**	**Mean (SD)**	**Median (Q1-Q3)**	**N**	**Mean (SD)**	**Median (Q1-Q3)**
Baseline	292	1.59 (0.86)	1.50 (1.0;-2.0)	176	1.49 (0.88)	1.50 (1.0;-2.0)
Month 6	253	1.30 (0.93)	1.50 (1.0;-2.0)	152	1.30 (0.90)	1.50 (1.0;-2.0)
Month 12	229	1.24 (0.89)	1.50 (1.0;-2.0)	120	1.32 (0.85)	1.50 (1.0;-2.0)
Month 18	210	1.24 (0.87)	1.0 (1.0;-2.0)	111	1.18 (0.81)	1.0 (1.0;-2.0)
Month 24	196	1.26 (0.96)	1.0 (1.0;-2.0)	91	1.18 (0.83)	1.0 (1.0;-2.0)
End of study	277	1.49 (1.05)	1.50 (1.0;-2.0)	167	1.56 (1.08)	1.50 (1.0;-2.0)

Q1–Q3 = range (1st to 3rd quartile).

9. Clinical Claim

The submission claims INFN-1b has significant advantages in effectiveness over and less (sic) toxicity than placebo in the treatment of MS when diagnosed according to the McDonald criteria.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

A series of preliminary economic evaluations were presented. The resources included were drug costs. The trial-based incremental discounted cost per extra discounted patient avoiding a diagnosis of Clinically Definite Multiple Sclerosis (CDMS) at 2 years was estimated to be in the range of $105,000 – $200,000.

Two modelled economic evaluations were presented. The PBAC noted that one model was not relevant to the current requested restriction while the other model did not provide any

estimate of incremental costs and benefits of the proposed algorithm for treating MS compared with the current algorithm.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be < 10,000 in Year 4, while the financial cost per year to the PBS was estimated to be < $10 million in Year 4.

12. Recommendation and Reasons

The PBAC noted that the submission proposed that the PBS restriction for interferon beta-1b (INFN-1b) be amended in line with current clinical practice as represented by the McDonald criteria. The PBAC acknowledged, as stated in the hearing, that the Poser criteria for diagnosing multiple sclerosis (MS) had now been superseded by the McDonald criteria using magnetic resonance imaging (MRI) and one attack of neurological dysfunction. However, there was concern about the specificity of the McDonald criteria in differentiating between MS and other neurological conditions, which could lead to inappropriate use of INFN-1b.

The PBAC indicated that to support any change to the PBS restriction to adopt the McDonald criteria, evidence would be required that the incremental efficacy gained from earlier treatment with INFN-1b, balanced by the incremental harm of exposing more patients to INFN-1b for a longer period of time than they would have been under the Poser criteria, is cost-effective.

However, the PBAC agreed that the evidence from the BENEFIT trial was not informative in relation to the question of replacing the Poser criteria with the McDonald criteria because patients were not enrolled in the trial according to either of these criteria. Patients were considered eligible for enrolment if they had symptoms suggestive of MS, in other words, at baseline (Day 1) of the trial they had "probable/possible" MS, but did not have confirmed MS using either the McDonald or Poser diagnostic criteria. Enrolled patients then followed over time to determine whether the earlier treatment with INFN-1b delays progression of disease more than would have been achieved by treating later. After 1 year (360 days of treatment) 55.6% of patients treated with INFN-1b had a MS diagnosis confirmed according to the McDonald criteria, but only 18.4% of those had the MS diagnosis also confirmed according to the Poser criteria. The only conclusion that can be drawn from these data is that treatment with INFN-1b delays the diagnosis of MS, regardless of which criteria for diagnosis of MS are used, in comparison with placebo.

The PBAC also noted that there was uncertainty whether this delay in MS diagnosis (regardless of which criteria for diagnosis are used) observed with INFN-1b translates into a slower progression of disability. At 2 years there was no statistically significant difference in EDSS scores between patients with "probable/possible" MS treated with INFN-1b in comparison with similar patients on placebo.

On the other hand, the PBAC acknowledged that the relevance of a PBS restriction based on the Poser criteria for the current clinical management of MS in Australia is likely to be eroded over time, especially given that the clinical trials of future MS drugs will likely recruit patients according to the newer McDonald criteria.

- The economic uncertainties about the submission arose from the clinical uncertainties.

The PBAC concluded that the submission's claim that it is cost-effective to initiate treatment with INFN beta-1b upon diagnosis of MS by the McDonald criteria was not adequately supported by the evidence presented. The PBAC therefore rejected the submission because of uncertain clinical benefit and uncertain cost effectiveness.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Due to the general acceptance of the McDonald criteria, for the diagnosis of multiple sclerosis, the sponsor will work with the PBAC to justify updating the wording of the authority for Betaferon to reflect current best practice in multiple sclerosis treatment.