Public Summary Document
Product: Dimethyl Fumarate, capsules, 120 mg and 240 mg, Tecfidera®
Sponsor: Biogen Idec Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The major submission sought an Authority required listing for the treatment of relapsing remitting multiple sclerosis.

2. Background

Dimethyl fumarate had not previously been considered by the PBAC as a treatment option for relapsing remitting multiple sclerosis.

3. Registration Status

At the time of the July 2013 consideration, dimethyl fumarate was not yet registered for patients with relapsing-remitting multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The proposed indication was subsequently registered by the TGA on 29 August 2013 as follows: Tecfidera is indicated in patients with relapsing multiple sclerosis to reduce frequency of relapse and to delay the progression of disability.

4. Listing Requested and PBAC's View

The submission requested listing on the basis of superior comparative benefit and non-inferior comparative safety over ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate), and non-inferior benefit and safety compared to fingolimod.

5. Clinical Place for the Proposed Therapy

Dimethyl fumarate (DMF) is an orally administered disease modifying therapy for relapsing multiple sclerosis.

The submission positioned dimethyl fumarate as a first-line treatment option.

6. Comparator

The submission nominated ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate) collectively as the main comparator, on the basis that these are the most widely prescribed PBS treatments for relapsing-remitting multiple sclerosis.

The submission also nominated fingolimod as a secondary comparator on the basis that it is the only oral multiple sclerosis treatment currently listed on the PBS.

The PBAC agreed that the nominated comparators were appropriate in the context of the current clinical management algorithm. Given the positioning of dimethyl fumarate as first line treatment, the PBAC considered that the comparison with the ABCR therapies was the most relevant to the requested listing.

7. Clinical Trials

The submission presented one head-to-head randomised trial comparing dimethyl fumarate vs. glatiramer acetate vs. placebo (CONFIRM). The PBAC noted that CONFIRM was powered for the comparisons of dimethyl fumarate vs. placebo, and glatiramer acetate vs. placebo, but not dimethyl fumarate vs. glatiramer acetate.

The submission also presented the following indirect comparisons:

- dimethyl fumarate (CONFIRM, DEFINE) vs. interferon beta-1a/glatiramer acetate (MSCRG, PRISMS, Co1MSSG) using placebo as the common comparator.
- dimethyl fumarate (CONFIRM, DEFINE) vs. fingolimod (FREEDOMS, TRANSFORMS) using placebo as the common comparator
- dimethyl fumarate (CONFIRM) vs. fingolimod (TRANSFORMS) using active 'common' comparators (interferon beta-1a/glatiramer acetate). The PBAC noted that this analysis relied on the assumption that interferon beta-1a and glatiramer acetate are similar enough to be treated as a single 'common comparator.'

Additional potentially relevant trials of interferon beta-1b vs. placebo (IFNB MS) and fingolimod vs. placebo (FREEDOMS II) were identified during the evaluation.

Details of these trials are shown in the table below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Dimethyl fumarate vs. glatiramer acetate vs. placebo trials		
MS-302 (CONFIRM)	Fox et al (2012). Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis	New England Journal of Medicine 367: 1087-1097
Dimethyl fumarate vs. placebo trials		
MS-301 (DEFINE)	Gold et al (2012). Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis	New England Journal of Medicine 367: 1098-1107
ABCR therapy vs. placebo trials		
NS26321-01 (MSCRG)	Jacobs et al (1996). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis	Annals of Neurology 39: 285-294
BRAVO	Vollmer et al (2011). A placebo-controlled and active comparator Phase III trial (BRAVO) for relapsing-remitting multiple sclerosis	Conference abstract 5th Joint triennial Congress of the European and Americas Committees for treatment and research in multiple sclerosis
	Carrol et al (2012). Assessing variations in transitions in employment in relapsing remitting multiple sclerosis patients treated with either laquinimod, interferon beta 1-a or placebo: Exploratory evidence from the United States substudy of BRAVO	Conference abstract Value in Health 15: A149
PRISMS	PRISMS Study Group (1998).	Lancet 352: 1498–1504

	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis	
	Li et al (1999). Magnetic resonance imaging results of the PRISMS trial: a randomised, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis	Annals of Neurology 46: 197–206
IMPROVE	De Stefano et al (2010). Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis	Multiple Sclerosis Journal16:888–892
	De Stefano et al (2012). Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study	Journal of the Neurological Sciences 312: 97–101
Co1MSSG	Johnson et al (1995). Copolymer 1 reduces relapse rate and improves disability in relapsing- remitting multiple sclerosis: Results of a phase III multicenter, double- blind, placebo-controlled trial	Neurology 45:1268– 1276
Fingolimod vs. placebo trials		
FREEDOMS	Kappos et al (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis	New England Journal of Medicine 362: 387–401

The PBAC agreed that the current Australian MS population and the populations in recent trials are becoming increasingly different from the populations in the older interferon trials, largely due to changes in the diagnosis of MS and, possibly, thresholds for treatment. This means that the interferon trials are becoming less suitable for inclusion in indirect comparisons with newer treatments, and that comparisons including these studies may be less informative to PBAC decision making than in the past, unless it can be clearly shown that the populations, and baseline event rates, are sufficiently similar for the analysis to be meaningful.

8. Results of Trials

Direct comparison of dimethyl fumarate vs. glatiramer acetate

There was no statistically significant difference in disease relapses or disability progression between dimethyl fumarate and glatiramer acetate, although the PBAC noted that the reported relapse outcomes favoured dimethyl fumarate. Analyses were post-hoc as the

CONFIRM trial was not designed to directly compare dimethyl fumarate and glatiramer acetate and was underpowered to detect a difference between active treatments.

A summary of the direct comparison of key outcomes between dimethyl fumarate, glatiramer acetate and placebo (CONFIRM trial) are shown in the table below.

Outcome	DMF (N = 359)	GA (N = 350)	Placebo (N = 363)	DMF vs. GA (95% CI)
Annualised relapse rate (95% CI)	0.22* (0.18, 0.28)	0.27* (0.23, 0.35)	0.40 (0.33, 0.49)	Rate ratio 0.78 (0.59, 1.05)
Proportion of patients free of relapse at 2 years, n/N (%)	266/359 (74)*	246/350 (70)*	223/363 (61)	RR: 1.05 (0.96, 1.16)
Proportion of patients with disability progression sustained for 3 months, n/N (%)	40/359 (11)	48/350 (14)	52/363 (14)	RR: 0.81 (0.55, 1.20)

Indirect comparison of dimethyl fumarate vs. ABCR therapies (placebo common comparator)

The submission claimed that ABCR therapies are equivalent to each other and therefore assumes that they can be combined in a single meta-analysis. The PBAC noted that there are known differences between these treatments including; mode of action (glatiramer acetate belongs to different drug class to the interferons), dosing frequency (varying from daily to weekly), route of administration (intramuscular or subcutaneous injection) and adverse event profiles.

The results of the indirect comparison of annualised relapse rates with dimethyl fumarate vs. ABCR therapies using a placebo common comparator is shown in the table below.

Trial	Dimethyl fumarate	Placebo	ABCR therapies	Relative difference (95% CI)
Annualised relapse rate (95% CI)				Rate ratio
DEFINE (N = 818)	0.17 (0.14, 0.21)	0.36 (0.30, 0.46)	-	0.47 (0.37, 0.61)
CONFIRM (N = 1,072)	0.22 (0.18, 0.28)	0.40 (0.33, 0.49)	GA 0.29 (0.23, 0.53)	0.56 (0.42, 0.74) 0.71 (0.55, 0.93)
MSCRG (N = 301)	-	0.82	INF 1a 0.67	0.82 (0.67, 0.99)
PRISMS (N = 371)	-	1.32	INF 1a 0.88	0.67 (0.51, 0.89)
Co1MSSG (N = 251)	-	0.84	GA 0.59	0.70 (0.54, 0.91)
Meta-analysis of dimethyl fumarate trials				0.51 (0.42, 0.62)
Meta-analysis of ABCR therapy trials				0.75 (0.65, 0.86)
Indirect estimate of effect (results < 1 favour dimethyl fumarate)				0.68 (0.54, 0.86)

Sensitivity analysis (base case uses CONFIRM results for dimethyl fumarate vs. placebo comparison, sensitivity analysis uses CONFIRM results for ABCR vs. placebo)	0.64 (0.48, 0.84)
Sensitivity analysis (include preliminary results from BRAVO)	0.69 (0.55, 0.86)

Dimethyl fumarate was associated with a statistically significant reduction in annualised relapse rate compared to ABCR therapies. Other relapse outcomes (proportion of relapsed/relapse-free patients and time to relapse) also favoured dimethyl fumarate but most of these differences did not reach statistical significance.

The indirect comparison of dimethyl fumarate vs. fingolimod (placebo common comparator), showed no statistically significant difference in annualised relapse rates between dimethyl fumarate and fingolimod. There was a statistically significant difference in favour of fingolimod for the proportion of relapse-free patients at two years (in terms of relative risk but not odds ratio). Other relapse outcomes (time to relapse, proportion of patients with relapse) presented in the submission also consistently favoured fingolimod compared to dimethyl fumarate. There were no apparent differences in disability progression between treatments.

The PBAC considered that the results of the indirect comparison of dimethyl fumarate vs. fingolimod (ABCR common comparator) were difficult to interpret given that two different drugs (glatiramer acetate and interferon beta-1a) were being used as the 'common' comparator.

The indirect comparison of annualised relapse rate favoured fingolimod compared to dimethyl fumarate but the difference did not reach statistical significance. There was a statistically significant difference in favour of fingolimod for the proportion of relapse-free patients at one year (in terms of relative risk but not odds ratio). Other relapse outcomes also favoured fingolimod. There were no apparent differences in disability progression between treatments.

With regard to comparative harms, treatment with dimethyl fumarate was associated with a higher incidence of flushing events, gastrointestinal side effects (diarrhoea, nausea, vomiting, upper abdominal pain, abdominal pain) and skin reactions (rash, pruritus) compared to placebo and glatiramer acetate. A similar pattern of adverse events emerged when dimethyl fumarate was more broadly compared against other disease-modifying therapies for multiple sclerosis.

The PBAC noted that three instances of progressive multifocal leukoencephalopathy (PML) associated with fumarate/fumaric acid esters have recently been described in patients treated for psoriasis. No cases of PML have been reported during the clinical development program with Tecfidera.

The submission acknowledged that there are limited long-term safety data for dimethyl fumarate and the sponsor will continue to monitor potential safety concerns in post-marketing surveillance programs.

9. Clinical Claim

The submission described dimethyl fumarate as superior in terms of efficacy compared to ABCR therapies. The PBAC considered that the claim of superiority was not sufficiently supported given the limitations of the indirect comparison, and given that the direct comparison between dimethyl fumarate and glatiramer acetate did not show a difference. The Committee agreed that a claim of non-inferiority of dimethyl fumarate to the ABCR therapies was more appropriate.

The submission described dimethyl fumarate as non-inferior in terms of efficacy compared to fingolimod. The PBAC considered that the claim of equivalent effectiveness and equivalent safety was not strongly supported given the indirect nature of the comparison, and given that the relapse outcomes reported in the indirect analyses consistently favour fingolimod.

The submission described dimethyl fumarate as non-inferior in terms of safety compared to ABCR therapies and fingolimod. The submission also claimed that dimethyl fumarate has a more convenient mode of administration and less injection site reactions than ABCR therapies. Overall, the PBAC considered that the claim of non-inferior safety was reasonable.

10. Economic Analysis

The submission presented a modelled cost effectiveness analysis of dimethyl fumarate, ABCR therapies and fingolimod. For the purpose of the economic analysis the submission assumed that dimethyl fumarate is inferior to fingolimod, and presented the results in terms of savings per QALY forgone (rather than cost per QALY gained).

Given that the PBAC did not accept the submission's claim of superiority over the ABCR therapies, the cost-effectiveness approach presented is not supported. The PBAC considered that a cost-minimisation analysis against the ABCR therapies would be appropriate.

11. Estimated PBS Usage and Financial Implications

The submission estimated that a total of 1,004 patient years of therapy would be accounted for by the PBS-subsidised use of DMF, increasing to 2,906 years by the fifth year of listing. The PBAC considered this to be an underestimate.

The PBAC notedthat the patient-years, prescriptions and costs should be re-estimated on the basis of the recalculation of fingolimod growth rates in the commentary. The submission stated that it is difficult to determine the likely extent of substitution. The submission assumes that 75% of substitution comes from ABCR, and 25% from fingolimod.

The PBAC noted that the distribution of substitutions between ABCR therapies and fingolimod in clinical practice will have implications for the actual cost to the PBS because fingolimod is substantially more expensive than the ABCR therapies.

12. Recommendation and Reasons

The PBAC rejected the listing of dimethyl fumarate at the price requested in the submission, on the grounds that the claims of superior efficacy over the ABCR therapies and non-inferior efficacy compared to fingolimod were not adequately supported by the evidence presented.

The Committee noted the heterogeneity between the ABCR trial populations and the dimethyl fumarate trial population, and considered that this made the indirect comparison difficult to interpret.

The PBAC considered that the most reliable analysis was the direct comparison between dimethyl fumarate and glatiramer acetate based on the head-to-head trial, notwithstanding that the trial was not powered to detect a difference between the active products.

The PBAC considered that the claim of equivalent effectiveness of dimethyl fumarate and fingolimod was not adequately supported given the indirect nature of the comparison, and given that the relapse outcomes reported in the indirect analyses consistently favour fingolimod.

The PBAC considered that the appropriate clinical claim based on the data provided was that dimethyl fumarate is non-inferior to the ABCR therapies in terms of efficacy and safety. Therefore, the Committee recommended the listing of dimethyl fumarate on a cost-minimisation basis with the ABCR therapies.

The PBAC recommended that, consistent with the current PBS listing for fingolimod and ABCR therapies, dimethyl fumarate is not suitable for prescribing by nurse practitioners.

The PBAC advised under Section 101(3BA) that it did not consider there were any other PBS listed drugs that are interchangeable with dimethyl fumarate on an individual patient basis.

Recommendation
Recommended

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
DIMETHYL FUMARATE				
Capsules 120 mg	14	0	Tecfidera	Biogen Idec Australia Pty Ltd

Condition/Indication:	Multiple sclerosis
Treatment Phase:	Initial treatment
Restriction:	Authority required TO BE FINALISED

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
DIMETHYL FUMARATE				
Capsules 120 mg	14	0	Tecfidera	Biogen Idec Australia Pty Ltd
Capsules 240 mg	56	5	Tecfidera	Biogen Idec Australia Pty Ltd

Condition/Indication:	Multiple sclerosis
Treatment Phase:	Continuing treatment

Restriction:	Authority required TO BE FINALISED

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

Biogen Idec appreciates the PBAC's review and the opportunity to engage in dialogue regarding the submission. The company will continue to evaluate opportunities to present additional analyses that demonstrate the full clinical merit of Tecfidera in Australians living with multiple sclerosis.