Multiple Sclerosis and Related Disorders 25 (2018) 144–149

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Key considerations in reimbursement decision-making for multiple sclerosis drugs in Australia

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ARTICLE INFO

Keywords:
Multiple sclerosis
Pharmaceutical reimbursement, Decision-making

ABSTRACT

Background: : In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) advises on the reimbursement of drugs to be subsidised through the Pharmaceutical Benefits Scheme (PBS). This study aims to provide insights into the PBAC process and key considerations regarding the reimbursement of MS drugs in Australia.

Methods: : The factors considered by the PBAC and its advice on whether to reimburse a drug are documented in public summary documents (PSDs). Qualitative content analysis of PSDs was conducted for all MS drugs considered by the PBAC between January 2006 and January 2018. Key issues identified by the PBAC were extracted and categorised. Common issues were identified and compared between drugs indicated for MS.

Results: : A total of 23 submissions were evaluated relating to 13 MS drugs. Eight were recommended for reimbursement; an approval rate of 35% per submission and 62% per drug. Approval rates were higher for disease modifying treatments (73% per drug) than for symptomatic drugs (0% for nabiximols and fampridine submissions). The most frequently discussed issues in PSDs, irrespective of PBAC decision, were: (1) the validity of the indirect comparisons formed (n = 11); (2) the validity of the approach to obtain utilities (n = 6); (3) the lack of appropriate/long-term safety data (n = 8); and (4) the time horizon used in the economic models (n = 3).

Conclusion: : A small but important number of issues have been consistently identified by the PBAC in relation to submissions for reimbursement of MS drugs. Drug developers and clinical trial investigators who are aware of these issues will be able to anticipate data requirements for reimbursement decision-making and thus potentially improve the evidence submitted for listing of MS drugs in Australia.

1. Introduction

In the past two decades, remarkable advances have been made in treatment options for multiple sclerosis (MS) (Wingerchuk and Carter, 2014). These advances have been made hand-in-hand with considerable increases in spending on MS treatments by patients, healthcare payers and society as a whole (Palmer et al., 2013). For example, in Australia, the number of patients accessing government-subsidised drug treatment for relapsing-remitting MS (RRMS) increased from 8,630 in 2006 to 15,704 in 2014 (DUSC 2015). Based on the published prices for RRMS therapies, this resulted in an increase in the net cost to the Australian Commonwealth from AUD$91 m in 2006 to over AUD$288 m in 2014 (DUSC, 2015).

In Australia, drug reimbursement is provided through the Pharmaceutical Benefit Scheme (PBS), a scheme which aims to provide universal, affordable access to prescription medicines. Before drugs can be listed on the PBS, they must be assessed by the Pharmaceutical Benefits Advisory Committee (PBAC), an expert advisory committee which evaluates pharmaceuticals for their comparative clinical effectiveness, safety, and cost-effectiveness. Under Australian legislation, the PBAC is responsible for assessing requests to list new drugs, as well as significant changes to currently listed drugs on the PBS (Wonder and Dunlop, 2015; Henry et al., 2005). PBAC recommendations enable the Australian Government to determine which drug technologies provide good value for money and should therefore be publicly subsidised (DoH, 2017a).

Abbreviations: CHMP, committee for medicinal for human use; ICER, incremental cost-effectiveness ratio; MCID, minimal clinically important difference; MS, multiple sclerosis; PBAC, pharmaceutical benefits advisory committee; PBS, pharmaceutical benefits scheme; PSD, public summary document; QALY, quality-adjusted life year; RPBS, repatriation pharmaceutical benefits scheme; RRMS, relapsing-remitting multiple sclerosis; RSA, risk-sharing arrangement

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https://doi.org/10.1016/j.msard.2018.07.020
Received 11 May 2018; Received in revised form 25 June 2018; Accepted 5 July 2018

The PBAC's recommendations are made transparent to the public by publishing them online as public summary documents (PSDs). The purpose of the PSDs is to provide contextual information pertaining to each recommendation. Albeit they are limited in terms of the amount and depth of information published, PSDs provide insight into the factors and trade-offs the PBAC noted in arriving at its recommendations. They therefore represent a valuable source of information, allowing various stakeholders to learn about the issues of importance during the PBAC process (Chim et al., 2010; DoH, 2017b).

Given the rapid pace of advancement in MS treatments, it is worth studying the issues PBAC considered in arriving at recommendations regarding MS drug reimbursement. Internationally, MS patients and their health care professionals have expressed concern about unmet needs in MS management, and barriers to personalised medicine due to current reimbursement policies (Rieckmann et al., 2018). While the PBAC's recommendations impact which drugs will get reimbursed, not much is known about the key hurdles within the PBAC processes for MS drugs to be listed speedily for access by the Australian public.

This study provides a review and descriptive analysis of PSD's for MS treatments. The project aims to provide insights into the reimbursement process and key considerations by the PBAC regarding MS drugs. The results may facilitate understanding by clinicians, drug manufacturers and other stakeholders regarding the factors that influence reimbursement approval for MS drugs in Australia.

2. Methods

Current pharmacological treatment options for MS drugs were identified through the Australian Medicines Handbook 2017, the Australian Therapeutic Guidelines and the MS Australia website (https://www.msaustralia.org.au/about-ms/medications-treatments). PSDs of the identified drugs were obtained via the PBS Department of Health website under the heading “Public Summary Documents by Product”, accessed in March 2017 and updated in March 2018.

Inclusion criteria were that the drug needed to have been considered by the PBAC between January 2006 and January 2018 and explicitly requested PBS listing as a treatment for MS (any stage). Treatments used for MS patients but where the submission to the PBAC did not specifically request MS as the indication (e.g. botulinum toxin type A, Botox®) were excluded. All relevant PSDs for MS drugs were selected, independent of whether they were a major or a minor submission.[2]

A range of information items was extracted from each selected PSD (see Table 1). For each item, the following was extracted: (1) what was included in the sponsor's[3] submission (e.g. which comparators were proposed in the submission), (2) did the PSD cite any issues raised by the PBAC related to this item, and (3) where issues were raised, what were the particular matters of concern for the PBAC as cited in the PSD. For each of the information items, key issues were extracted and categorised into themes. Differences and similarities between drugs in how those themes emerged were explored. Extracted information was first recorded in Microsoft Word 2016 and later tabulated in Microsoft Excel 2016.

[2] According to the procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme, major submissions generally relate to requests for the listing of a new medicine or vaccine, a new indication for a currently listed medicine, or to make material changes to a currently listed indication where an economic model is required to support a claim of cost-effectiveness, cost-utility or cost-minimisation. Minor submissions generally relate to requests to change existing listings that do not change the population or cost-effectiveness of the treatment, or the listing of a new form or strength of an already-listed medicine that has a bioequivalence or equivalence statement from the Therapeutic Goods Administration.

[3] The “sponsor” of a submission can be a pharmaceutical company or another organisation or individual supporting the preparation of the submission.

The main issues identified by the PBAC were described and summarised per variable according to the themes that emerged. Data extraction and coding was performed by YHLP and cross-checked by NvdL to ensure completeness and consistency. Discrepancies were revisited by YHLP and re-checked by NvdL to confirm their resolution.

3. Results

Since 2006, a total of 23 submissions, covering 13 drugs, were considered by the PBAC for the treatment of MS in Australia. Seventeen submissions sought listing (or changes to the listing) for treatment of RRMS. Six submissions sought listings in other MS settings; one (glatiramer acetate) for the treatment of patients with a demyelinating event indicative of MS, one for primary progressive MS, and one submission (interferon beta – 1b) requested a review of the eligibility criteria of drugs for the treatment of MS to allow for the use of the McDonald criteria as opposed to the Poser criteria to determine patient eligibility to access treatment. Three submissions sought listing for MS-related symptoms: one (nabiximols) for the treatment of moderate to severe spasticity due to MS, and two (both for fampridine) for the symptomatic improvement of walking ability in ambulatory MS patients.

Fig. 1 shows a timeline for the consideration of MS drugs over the last eleven years. Before 2006, the PBAC had already funded access to three beta-interferons (Avonex, Betaferon and Rebif) and to daily injections of Copaxone. From 2006 onwards, eight more drugs were recommended for listing. Thirteen submissions were rejected; for two drugs (fingolimod and daclizumab), the decision was deferred. The resulting approval rates were 35% per submission and 62% per drug. The mean number of submissions per drug was 1.8. Teriflunomide had the highest number of submissions ($n = 3$).

Approval rates were higher for disease modifying treatments (DMTs) than for symptomatic drugs. For the latter, none of the three submissions (one for nabiximols, two for fampridine) resulted in a recommendation for reimbursement: a 0% approval rate. For the DMTs, approval rates were 40% per submission and 73% per drug.

While daclizumab was considered by the PBAC (July and November 2016), marketing authorisation for this product was recently withdrawn worldwide, following safety issues (MS_Research_Australia, 2017). Cladribine, previously approved for marketing in Australia but rejected for reimbursement in March 2011, has been subsequently withdrawn. Recently, it has been reintroduced but was rejected for reimbursement in November 2017 (Biogen, 2018).

In the PSDs of 22 of 23 submissions, the PBAC indicated issues with one or more of the following: the main comparator, secondary comparator(s), type of studies performed, key endpoints, the MCID, the clinical claim with respect to effectiveness and safety, the economic evaluation, the estimated ICER, number and type of health states, key data used, the proposed risk-sharing agreement and/or the financial estimations. For one submission (glatiramer acetate, March 2015), no issues were identified in the PSD. This was a minor submission requesting listing for an additional strength of the drug.

The issues raised by the PBAC were categorised and four themes of common clinical and economic issues emerged: the validity of the indirect comparison, the validity of the approach used to determine quality of life (including the claim that disutility is associated with injectable drugs), the lack of appropriate safety data and the time horizon used in the economic model. Each of these themes is discussed below.

3.1. Indirect comparisons

The PBAC addressed issues regarding the validity of the indirect comparison in eleven submissions: two for natalizumab (November 2006 and November 2007), one for fingolimod (March 2011), two for cladribine (March 2011 and July 2017), one for dimethyl fumarate