Online submission to PBAC regarding Mavenclad® (cladribine) for Relapsing Remitting MS (RRMS)

Submissions to be lodged by 6 June at:
https://www.health.gov.au/internet/main/publishing.nsf/Content/PBAC_online_submission_form

Medicine: Mavenclad® (cladribine)

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Declaration of interest:

MS Australia is making this submission as we have an interest in the health and well-being of all people with MS. MS Australia is the national peak body for people living with MS in Australia. We work with governments at all levels, engaging on the issues that concern the lives of people living with MS, their families and carers, the community and the economy. We declare that we have received funding support from Merck and from other pharmaceutical companies with an interest in MS in the form of grants for projects. The contacts for the two consumer case-studies included in this submission were provided by Merck.

Consumer input:

MS Australia is writing to support the inclusion of the medication cladribine (marketing name Mavenclad®) to the Pharmaceutical Benefits Scheme (PBS) for people with relapsing remitting MS (RRMS). As the national peak body for people with MS we are proud to advocate on behalf of our member organisations and the MS community. One area we are particularly passionate about is the provision of more affordable and accessible treatments that can improve the lives of people with MS.

There are currently more than 25,600 people living with MS across the country and over 7.6 million Australians know or have a loved one with this potentially debilitating disease. MS can be particularly debilitating and has an unpredictable disease course. No two cases of MS are the same. There is no one-size fits all treatment for people living with MS and to date, there is no known cure.

The challenges faced by people with MS can be significant and can have a devastating impact on their families and the wider community. Relapses can result in short term or long term disability, resulting in the need for physical and/or psychological care and support, medical investigations, treatments and hospitalisation.

The symptoms of MS (such as fatigue and neuropathic pain), and/or the gradual progression of the disease through relapses, mean that the majority of people with MS are unable to retain their employment. In fact, people with MS are more likely to be unemployed than those with any other chronic disease. This contributes to an increasing economic burden of MS on the rest of society. The economic cost of MS to the Australian community has been estimated to be around $1.9 billion every year.

Being able to better manage and limit the frequency and impact of relapses can help alleviate the burden of MS on the community and the individual.

This submission is largely based on submissions provided to the PBAC in November 2017 and February 2018, when cladribine was previously submitted to the PBAC for consideration. In addition, it is worth noting that cladribine has been approved as a treatment for people with highly active relapsing MS on the NHS in England and Wales and is under consideration for reimbursement in Scotland and Ireland.

Outcomes from a focus group held by MSA of MS consumers: questions and responses

1. Do you think we need another treatment for RRMS?

Responses:

New treatments are perceived by some as being very "aggressive" and there is some concern as to what the 'active ingredients' are, and how they will affect one's body. There is also a perception that some new medicines have been developed from cancer treatments, so treatment difficulties and side effects can be considerable, therefore need to be really sure that the treatment is right for me.

There was a preference expressed for more work to de done on existing treatments, to make them more effective, "we don't need more drugs, we need better drugs".

It was agreed that more choice in treatments is good on the one hand and on the other hand makes it more difficult to choose, even with the advice of one's health team.

2. What are the main factors you consider when comparing one treatment to others? Can you rank these?

For example,

- Is the administration (oral, infusion or injection) of the treatment important e.g. for people living in rural or regional settings?
- Is ease of storage of the medicine important?
- Are related costs (and stresses) such as transport/travel, any other out-of-pocket expenses for other medications, etc important?
- Is the burden of monitoring important e.g. frequency of follow up blood tests, visits to neurologist?

Responses:

All of these factors are important considerations, especially for the newly diagnosed. Ranking them is very difficult, almost impossible, as everyone's circumstances vary. Everyone with MS experiences it differently, so each person needs to find the medication that suits them.

Oral medications for a range of diseases are well understood; it's no different for MS. If the impact of side effects is minimal, oral treatments are obviously better and easier to administer, store and monitor.

"Let's face it, most people don't want to stick a needles in themselves". Some, however are not so concerned about injections once they've been shown how to use them and they are confident to administer them correctly.

Ease of storage (of tablets) is a great benefit, but no-one in the group seems to have any problems with storage of either tablets or injections, even when travelling.

The benefits of oral medications are clearly there for people with MS living in rural and regional settings, including reduced burden of monitoring, but even if you can see your local GP for any follow up, you still have to travel to a city for neurologist appointments. Access to an MS Nurse is critical in rural and regional settings and becomes essential if availability or relationship with local GP and/or neurologist is limited or not great.

3. **Having read the MAVENCLAD® (cladribine) treatment sheet and CMI, are there any obvious pros or cons for this treatment you can suggest?**
    - For RRMS, in the clinical trials MAVENCLAD® (cladribine) has been shown to result in fewer relapses, less disease activity in the brain and less progression of disability. If this clinical trial evidence applied to you, can you suggest how this might impact on your quality of life/health/wellbeing?
    - How might this impact on your carers/family/friends?

Responses:

General anxiety was expressed about changing medications – people with MS want to be absolutely sure that symptoms and disease progression will still be addressed effectively. This is also true for people for whom medication is not working; it is scary to change to something else that might also not work.

Sometimes changes are welcome, one participant said it was "equivalent to a lottery win for me to change from daily injections to twice weekly". Similar sentiment was expressed in changing from injections to oral medications.

People with MS rely strongly on advice from their neurologist and equally, if not more importantly, the advice of an MS nurse regarding treatments, side effects and the long term impact of treatments.

The long term consequences of various MS treatments are not well understood by patients, and need to be considered alongside maintaining healthy lifestyle choices, diet, exercise, talking vitamin supplements, etc. Treatments for MS that are backed up with a solid evidence-base are always going to be preferred to those not scientifically proven such as bee-sting therapy or forms of stem cell treatment.

Some focus group members knew of some people with MS who had previously taken cladribine and said that, anecdotally, they appeared to have had great results and were generally very hopeful that this particular medicine would be a great addition to the treatments available.

There was general agreement that there are significant potential quality of life benefits of cladribine given its ease of administration and clinical trial results; being able to maintain and active social life with family and friends, continue employment and so on, and also there are obvious benefits in reducing the burden of care on family members and partners. The group seemed to feel that these benefits are self-evident to those in the MS community. Some have little or no expectation that a new treatment will improve their quality of life, health and well-being but are more concerned to

maintain their current status (especially those that have lived with MS for many years), expressing the fear that their condition may progress and symptoms will worsen at some stage, so a new treatment that will address this fear is welcome.

Details of submission previously provided in November 2017

Mavenclad® (cladribine) has been shown to result in fewer relapses, less disease activity in the brain, less progression of disability and improved quality of life, as borne out by the studies reported below:

1. De Stefano N, Giorgio A, et al 2017, *Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing MS treated with cladribine tablets,* Multiple Sclerosis Journal, 10.1177/1352458517690269

This report concluded that, "Cladribine tablets given annually for 2 years in short-duration courses in patients with RMS in the CLARITY study significantly reduced brain atrophy in comparison with placebo treatment, with residual rates in treated patients being close to physiological rates. Furthermore, the brain atrophy reduction was closely associated with a lower risk of disability progression".

2. Afolabi D, Albor C, et al 2017, *Positive impact of cladribine on quality of life in people with relapsing MS*, Multiple Sclerosis Journal, 10.1177/1352458517726380

This report concluded, "we independently analysed QoL data collected during the largest ever trial of cladribine versus placebo in pwRMS. Over and above the established efficacy of cladribine on clinical outcomes, the treatment led to significant improvements in QoL."

3. Giovannoni G, Comi G, et al 2010, *A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis*, The New England Journal of Medicine, 10.1056/NEJMoa0902533

This report concluded, "short-course treatment with cladribine tables for only 8 to 20 days per year provided a significant benefit for patients with RRMS with respect to the rate of relapse, disability progression and MRI measures of disease activity during the 96-week study period".

4. Leist T P, Comi G, et al 2014, Effect of oral claribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial, Lancet Neurol 2014; 13: 257-67

This report concluded that, "this population of patients with a first demyelinating event suggestive of MS, treatment with cladribine 5.25 mg/kg or 3.5 mg/kg over 2 years significantly delayed conversion to both clinically definite MS according to the Poser criteria and MS according to the 2005 McDonald criteria, and also significantly reduced MRI lesion counts compared with placebo."

Further material regarding clinical trial outcomes is included in the submission from MS Research Australia, which we commend to you.

Merran Boyd is a person with Relapsing Remitting Multiple Sclerosis (RRMS) who has lived with the disease since diagnosis in 1992.

Merran was a participant in a clinical trial for Cladribine in 2011 and received 2 years of dosing.

Merran says:

“Cladribine administration was extremely simple and required 5 days of oral tablet medication in one month followed one month later by another 5 days of medication and then you were complete for the year. This made compliance with adhering to the medication extremely easy and convenient.

My RRMS symptoms prior to taking Cladribine were debilitating and I was at the point of social isolation. My symptoms included constant neuropathic pain in my left leg and foot for which I was taking regular strong pain relief medications. I was unable to walk unaided and I was considering leaving my part time job as a mental health nurse. I had severe bowel incontinence issues which had confined me to the home along with constant stinging burning pain and I experienced frequent episodes of Optic Neuritis and had been told I was going to go blind as a result. I also experienced ongoing heat sensitivity and extreme fatigue. I became depressed and anxious about my future. I was unable to participate in routine tasks around the home and at work and was at the point where I had considered applying for a disability support pension. Managing my RRMS symptoms required multiple different medications to try and control symptoms as well as regular monthly visits to medical professionals to ensure I was monitored effectively. This became a constant strain on both my finances as well as impacting on the financial burden associated with subsidies of my care within the health care system.

As soon as I was commenced on the Cladribine trial within one month I was aware of symptoms dissipating. At the 3 month mark after initial dosing I had a MRI which showed reversal of disease progression with significantly less active lesions within my brain than in the past. I started to notice normal feeling return to my left leg and foot. I could walk unaided and I was not fatigued. I had energy again and I also regained normal sensation in my bowels and was able to regulate this normally. Pain started to disappear and for the first time since my RRMS diagnosis I felt normal again.

I was able to apply for a promotion at work and became the Manager of a 51 bed private mental health unit working full time once again. Cladribine gave me my life back!

For 4 years after receiving 2 years of treatment on Cladribine I was able to live and work normally without any further RRMS symptoms. The only side effect I had was a short period of leukopenia after initial dosing. My blood results returned to normal within 3 months.

Currently I am taking Fingolimod to assist with symptom management as all my previous symptoms began to reappear after the 4 year mark from my initial dose of Cladribine. It is not effective as I have all my symptoms back and they are worsening day by day. I have had to reduce my hours to part time again at work and am struggling once more with extreme fatigue, heat sensitivity and pain. I am constantly leukopenic whilst on Fingolimod and have to avoid any situation which may expose me to infection. As I am JCV+ I am also at great risk of Progressive Multifocal Leukoencephalopathy (PML) due to this which is fatal.

If I were to stay on my current treatment Fingolimod I am at risk of further RRMS episodes and I liken it to the equivalent of currently treading water waiting for the next wave. As my RRMS symptoms progress, the ability to stay productive in the workforce is slowly being eroded and the possibility of me having to rely on welfare/NDIS support becomes a much greater possibility.

From an economic point of view the ability to adhere to Cladribine is of great advantage as it has reduced administration requirements. This medication reduces patient symptoms and provides greater certainty of positive outcomes to the health professional. It also increases the physician’s ability to provide a greater range of services to others given the reduced focus on medication usage for symptom management as well as the reduction in relapses for patients. This will free up beds in

the hospital system and reduce treatment costs. Secondary factors also need to be taken into consideration as when the patient with RRMS has a better outcome with symptom and disease management they are then able to contribute to the workforce and reduce the impact and burden on the NDIS, welfare systems and subsidy costs to the current health care system.

From a health management and economic perspective treating RRMS patients with Cladribine will create a situation whereby Neurologists will be able to see more patients as those being treated with Cladribine will require less frequent visits to hospital with active relapses, if any at all.

When considering the economic considerations to the patient, Cladribine provides the best balance for both patient workforce output and opportunity, it provides the ability for the person with RRMS to stay active in the workforce providing income tax and GST to the Federal/State Governments and reduces the need to access funds from strained welfare budgets in the form of transfer payments and services. It unlocks economies of scales for both the government and the health professional.

Ultimately, Cladribine is good for the patients health, good for the health professional in application, regulation and patient compliance and great for the government in economic benefits and reduced strain on health/welfare budgets.

There is absolutely no question in my mind that Cladribine should be available to patients with RRMS as my experience is that it is an effective treatment to not only halt disease progression but also to improve current symptoms."

Stuart Allen was diagnosed with MS in 2008.

Stuart's story:

"Originally I was part of the PFP (Patient Familiarisation Program, which happens after a drug is approved but before it is subsidised by the government). It was approved by Australia and Russia in 2010 before the FDA said they wanted more data and Merck pulled it off the market. I have been told that I was the first commercial patient to be prescribed Cladribine in the world. This was in late 2010.

I also know three patients who were part of the original trial, and one other who was on the PFP like me. Although I have heard about many others.

Firstly, the MS nurses in Australia seem to have quite strongly positive opinions about it. One of them (not my nurse) recently said that the day Merck pulled Cladribine was like the day Princess Diana died; everyone (the nurses) remembers where they were when they got the news.

My wife (who is actually my nurse, and a Clinical Nurse Specialist in MS) said that one of the patients had a car accident when they called her to say that Cladribine had been withdrawn. She was so in shock she reversed into a brick wall.

When I was told it was withdrawn I didn't initially feel that angry, because I thought that there were plenty of other drugs on the horizon that would be just as good. But as time went on, when each new drug had side effects, and most didn't stop my relapses, I really began to hate the fact that it was gone. Cladribine for me was life changing. It stopped my relapses, it had no side effects, and you only took it yearly (sort-of). While on it I forgot I had MS. I don't say this lightly. I have been on seven different medications and changed nine times (I've been on two drugs twice Avonex and Cladribine).

My MS history itself is the biggest ad for Claribine:

First episode 2006. Diagnosed 2008 - same year as my first massive relapse.

2008 Avonex - 14 months. Changed due to various side effects.
2009 Copaxone - 3 or 4 weeks, skin reactions.
2009 Betaferon - 2 months, same side effects as Avonex but worse.
All that time had regular very minor relapses.

2009 Avonex - 16 months, went back to what I knew.
First big relapse while on the injectables + MRI activity.

I had to get on something more effective as soon as possible, enter Claribine.

2010 Cladribine - 18 months (at least). Totally free from MS, no relapses, no MRI activity, no side effects.
Cladribine withdrawn.

2012 Gilenya - 3 weeks. I couldn't tolerate it. Extreme flu like symptoms and depression. My wife later found *some* other patients reacted the same way. In some people it's quite benign, for others like me it reacts quite badly.
2012 Aubagio - Nearly 2 years. Sudden hair loss. And once Cladribine wore off (2 years) relapses came back with a vengeance. It was like it didn't actually prevent any. I felt like it just didn't work. MRI activity.
2014 (december) Tecfidera - 1.5 years. A treasure trove of well known side effects, plus it didn't work very well. Many minor relapses. First trip to hospital due to a major relapse. MRI activity. I hated it that drug.
Those few years were horrible.

2015 Tysabri - 22 months. OMG finally a drug that worked besides Claribine. We were avoiding it because I was JCV+ but I just had to take the risk. We stretched it out as far as we could, until the risks became too great.

I did not want to risk Lemtrada. My wife shared too many stories that scared me. So I was in a bit of trouble because except for Tysabri (which I could no longer take) and Cladribine (which was not longer available) none of the other drugs seemed to work for me.

I got fed-up of waiting for Merck to bring Cladribine back. So I told my wife to call around and find a Neurologist / Hospital that would prescribe Cladribine off-label. She eventually found ONE, only one, in the whole country that would do it. The hospital was far away (10 hours drive) and we had to pay for the drug ourselves (Cladribine as subcut injection called LITAK).

2016 LITAK (Cladribine) - Bliss :-)

It's been even better than I remembered. I have even had some ongoing symptoms disappear (really!). I am again free of side effects and my MS feels like it has gone away. While on other drugs my MS was always constantly at me, even if the relapses were only small. But on Cladribine all that MS/relapse background noise has gone. I would pay for it myself again if I had to. It just works.

You simply must advocate for this drug being available as best you can. I get upset thinking about how it was taken away from me in Australia. It has made such a huge difference to my life, I could not possibly convey how much."

Overall, MS Australia believes cladribine provides a viable treatment option for people with RRMS that will help to reduce the burden for many people with MS and its potential effectiveness at reducing the progress of MS could allow people with MS to maintain parts of their lifestyle for longer, such as employment, physical activity and exercise, as well as travel and socialising with friends.

Whilst these elements may not seem particularly significant, together they provide a person with MS purpose, focus, independence and drive which can be very useful in maintaining a high quality of life and staying on top of their symptoms. More broadly, it can ultimately mean less time in hospital, reducing the drain on valuable medical and disability resources, a lower cost for at home modifications and support, and prolonged employment, which helps to reduce the economic impact of MS on society. For example, early indications of the value of NDIS plans for people with MS average around $60,000 per year, with some individual plans reaching well over $100,000.

The fact that cladribine is provided in tablet form is considered to be an advantage by some members of the MS community. In his article "Pills, Shots or Infusions for Your MS" (multiple sclerosisnewstoday.com, 24 January 2017), Ed Tobias suggests that "Oral multiple sclerosis meds appear, more and more, to be the first choice of patients who are just beginning to receive an MS treatment. A recent report by the independent marketing research firm Spherix Global Insights, shows that oral disease-modifying therapies captured a significantly higher share of the market at the end of 2016, compared to 2015…".

The introduction of the oral route for MS treatments in recent years, clearly promotes patient satisfaction and increases therapeutic compliance. Oral medications for MS are also of great benefit for people living with MS in rural and regional settings where the need for hospital and clinic visits can be minimised or not needed at all.

This medication will make a valuable addition to the repertoire of medications available to people with MS and their neurologists. It will allow for an appropriate treatment choice to be made according to the efficacy and possible side-effects in relation to an individual's circumstances and will help to alleviate the economic cost of MS to individuals, their families and the broader community.

We appreciate you considering this treatment for inclusion on the PBS.

How did you learn about this consumer submission process?

From PBAC web-site.

SUBMIT (BUTTON)