Azathioprine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.1. Immunomodulators for non-malignant disease

ATC codes: L04AX01

Indication	Relapsing-remitting multiple sclerosis ICD11 code: 8A40.0
INN	Azathioprine
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid > tablet: 50 mg (scored)
EML status history	Application rejected in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Azathioprine
DrugBank	Azathioprine

Summary of evidence and Expert Committee recommendations

An application was submitted by neurologists Dr Maria Donata Benedetti, Azienda Ospedaliera Universitaria Integrata, Verona; Dr Luca Massaces, Azienda Ospedaliero-Universitaria Careggi, Florence; and Dr Graziella Filippini Fondazione IRCCS Instituto Neurologico Carlo Besta, Milan, for the inclusion of azathioprine on the Model List for the treatment of multiple sclerosis. Azathioprine is already included for other indications: in Section 8.1, Immunosuppressive medicines (complementary list), and in Section 30.2, Disease-modifying agents used in rheumatoid disorders (DMARDs). Expert reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to this application. Multiple sclerosis (MS) is one of the world's most common causes of non-traumatic neurological disability in young adults. Worldwide, prevalence estimates range from 2.1–2.2 per 100 000 in sub-Saharan Africa and east Asia to 108–140 per 100 000 in the highest risk areas (Europe and North America), with a north–south gradient; incidence is lower closer to the Equator and in men (1,2). Disease onset is typically between 20 and 40 years of age, with relapsing–remitting symptoms and signs involving different regions of the central nervous system. During the chronic course, over 30 years or more, a high proportion of affected individuals experience progressive disability; this has a huge impact on their quality of life and major implications for social costs (1). The Expert Committee acknowledged that: ■ The costs of multiple sclerosis therapies are continuously increasing as newer, patented, immunomodulating medicines are incorporated into clinical practice. ■ Inequalities have been reported in the availability of and access to disease-modifying therapies in the world: government-funded disease-modifying therapies were available in 96% of high-income countries but in only 45% of lower-middle-income countries and in none of the countries of the low-income group (1). ■ Affordability has been ranked by many countries, especially low- and lower-middle-income countries, as the most common reason why not all people with multiple sclerosis are receiving treatment (1). ■ Patients with a definite diagnosis of multiple sclerosis might benefit from early disease-modifying therapy although the impact of such treatment on the progression of brain lesions is still unclear. Trials of azathioprine in MS that were conducted in the 1980s and early 1990s (3-6) suffered from methodological limitations such as low

power and lack of magnetic resonance imaging (MRI) evaluation. However, a more recent meta-analysis, including five parallel-group, randomized, placebocontrolled trials, found that, in 698 patients, azathioprine was associated with a relevant reduction in the number of patients with relapses and disability progression during the first three years of treatment (relative risk reduction approximately 20% for relapse and 42% for disability progression) (7). Since the advent of MRI, few studies have evaluated azathioprine efficacy in MS. In a small, open-label, before and after study of patients with short disease duration and at least three gadolinium-enhancing brain lesions at MRI, azathioprine up to 3 mg/kg daily reduced new gadolinium-enhancing brain lesions and was well tolerated (8). The relative efficacy of interferon beta (IFN) products and azathioprine was compared in two small randomized trials (9, 10). In the first, a single-blind trial, the mean number of relapses was lower in the azathioprine than in the IFN arm, and more patients in the azathioprine arm remained relapse-free (76.6% versus 57.4%) (9). The second, an independent, multicentre, non-inferiority trial found that azathioprine was at least as effective as IFNs for relapse rate and new lesions (10). A recent network metaanalysis on immunomodulators and immunosuppressants for MS showed that azathioprine was apparently effective in reducing clinical relapses at 36 months and is likely to reduce disability to a relevant extent (11). Azathioprine is well tolerated and is associated with limited toxicity. In the meta-analysis by Casetta et al (7), gastrointestinal disturbances, bone marrow suppression and hepatic toxicity were greater in the azathioprine group than in the placebo group. However, these adverse events were anticipated and were managed with monitoring and dosage adjustment. Withdrawals due to adverse effects, mainly gastrointestinal intolerance (5%), were few and occurred mostly during the first year of azathioprine treatment. In view of the potential risk of cancer, due to the inhibitory effect on the immune system, there are concerns about the safety profile of azathioprine. However, conflicting conclusions on cancer risk – including results from sources other than clinical trials – have been reported; an overview of the data shows long-term risks, if any, to be related to treatment duration in excess of ten years (cumulative doses above 600 g) (7). Azathioprine is not recommended in pregnancy. According to the International Drug Price Indicator Guide 2013, the median price of azathioprine was US$ 0.1671/tab-cap (lowest price US$ 0.1233/ tab-cap (South Africa); highest price US$ 0.2300/tab-cap (Namibia)) (12). The cost of treating a person with MS using azathioprine is around US$ 16 per month; by comparison, the cost of treatment using IFNs is around US$ 1000 per month. The Expert Committee noted that use of azathioprine for treatment of MS is off-label in many countries. In the USA, azathioprine is currently approved by the Food and Drug Administration (FDA) for use in kidney transplantation from human donors, and for rheumatoid arthritis. The drug has been used in some patients with MS, usually if they have problems with standard FDA-approved medications or if they are unable to tolerate injection. Azathioprine is still widely used in Europe for patients with relapsing–remitting MS who do not respond to IFNs, and in countries where market availability of IFNs is limited. The Expert Committee acknowledged the significant public health burden of multiple sclerosis and noted the availability of a number of new immunomodulating medicines for this condition. The Committee therefore recommended that a comprehensive review be undertaken of all medicines used for the management of relapsing–remitting and other forms of multiple sclerosis for consideration at its next meeting. This recommendation was supported by the WHO Department of Mental Health and Substance Abuse. The Expert Committee did not recommend extending the availability of azathioprine on the EML to include use in the treatment of multiple sclerosis at this time. References: 1. Atlas of MS 2013: mapping multiple sclerosis around the world. London: Multiple Sclerosis International Federation; 2013. Available from: http://www.msif.org/about-us/advocacy/reportsand-resources/. 2. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008;71(2):129-35. 3. Double-masked trial of azathioprine in multiple sclerosis. British and Dutch Multiple Sclerosis Azathioprine Trial Group. Lancet. 1988;2(8604):179-83. 4. 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