Application to add azathioprine to the WHO Essential List of Medicines for treatment of multiple sclerosis
General items

1. Summary statement of the proposal for inclusion

The 18th edition of WHO Model List of Essential Medicines (April 2013) includes Azathioprine under 8.1. Immunosuppressive medicines (complementary List) and under 30.2. Disease modifying agents used in rheumatoid disorders (DMARDs).

Azathioprine has long been used in many countries to treat Multiple Sclerosis (MS), an autoimmune inflammatory and neurodegenerative disease of the central nervous system (CNS) affecting more than 2.3 million people worldwide according to the Multiple Sclerosis International Federation (MSIF) (1). There is no cure for MS but disease-modifying therapies (DMTs) can reduce relapse rate although their effects in slow down disability progression in the long term is not yet clear (2). Since the approval of beta interferons (IFNs) and other newer high-priced immunomodulating drugs for Relapsing-Remitting (RR) MS azathioprine was no longer recommended as a first line therapy (3). However, recent meta-analyses, head-to-head trials and Magnetic Resonance Imaging (MRI) studies show a similar or non-inferior effect of azathioprine compared to IFNs in RRMS, supporting this treatment as an effective, less expensive and convenient alternative to IFNs (4-8).

We propose Azathioprine for the WHO list of essential medicines with the indication for MS to be prescribed by neurologists as a disease-modifying agent, taking care in the selection of eligible patients and ensuring regular medical and laboratory examinations for monitoring possible adverse effects especially leukopenia.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

None

3. Name of the organization(s) consulted and/or supporting the application

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4. International Nonproprietary Name (INN, generic name) of the medicine

Azathioprine

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)
Azathioprine: Oral tablets of 50 mg

Children, pregnant or breast-feeding women excluded

6. International availability - sources, of possible manufacturers and trade names

Azathioprine is already included in the World Health Organization’s List of Essential Medicines under 8.1. Immunosuppressive medicines (complementary List) and under 30.2. DMARDs. We propose to add the indication for Multiple Sclerosis. The generic azathioprine is produced worldwide by a considerable number of manufacturers, some of them in emerging economy countries, under different brand names.

Trade names (some):

Azathioprine
Azasan
Imuran
Azamun
Imurel
Imurek
Imazar
Azoprim
Azoran
Azapress
Immunoprin
Azaform
Azain
Azapin

Manufacturers (some):

GlaxoSmithKline
Salix
Hexal
Sofar
Sandoz

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

As an individual medicine.

8. Information supporting the public health relevance

MS is one of the world’s most common cause of non-traumatic neurologic disability in young adults (1). Worldwide prevalence estimates range from 2.1-2.2 per 100,000 in Sub-Saharan Africa and East Asia to 108 – 140 or more per 100,000 in the highest risk areas (Europe and North America), with a north-south gradient and a lower incidence closer to equator. Disease onset typically occurs between 20 and 40 years of age with relapsing-remitting symptoms and signs involving different CNS regions. During the chronic course over 30-40 years or more a high proportion of diseased people
experience progressive disability with a tremendous impact on their quality of life and major implications on social costs (1). Inequalities have been reported in the availability of and access to DMTs in the world. Of the 90 countries that provided a reason why not all people with MS are receiving treatment, affordability was ranked as the most common by 46%, which rose to 86% in the 21 low and lower-middle income countries that answered this question (2, 9).

Moreover, the costs of MS therapies are continuously increasing as newer immunomodulating drugs, mostly tested in trials sponsored by pharmaceutical companies, are incorporated into clinical practice: government funded DMTs were available in 96% of high income group countries, but in only 45% of lower middle income group countries and in none of the low income group (2). Recent reviews and comparative trials suggest that azathioprine, carefully prescribed by neurologists and monitored in time, can be an alternative to IFNs as first-line therapy in RRMS. IFNs are expensive, in many patients show no or little efficacy or are not well tolerated. Azathioprine is a low cost drug easily administered by oral route, well tolerated and with limited toxicity. Concerns over safety profile of azathioprine exists in view of potential risk of cancer due to the inhibitory effect on the immune system (4). The whole data available from MS azathioprine treated populations show a possible long-term risks related to treatment duration above ten years (cumulative doses above 600 g) (4).

We propose to include the indication for MS besides rheumatoid disorders for azathioprine in the WHO List. This extension should provide a first-line treatment for people with MS even in low and middle income countries through the primary health care systems. The financial impact of this process should permit to make more affordable the innovative and more efficacious second-line treatments required when the disease becomes non responsive to first-line therapies.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

There are no clinical guidelines for azathioprine in MS: usually neurologists refer to the guidelines for rheumatoid arthritis (RA) (10) or other neurological autoimmune disorders such as myasthenia gravis, with changes due to the different measure of efficacy in MS (relapse frequency/new MRI lesion reduction).

Starting dose and maintenance treatment
The initial dose of azathioprine in MS, as in rheumatoid arthritis, is approximately 1 mg/kg of body weight/day, i.e. 50 to 100 mg given as a single does or twice daily. This dose can be gradually increased over 4 to 6 weeks to a maintenance dose of 2.5-3 mg/kg/day (100-150 mg/day), individually adjusted to the white cell counts. In the case of WBC < 3.5 x 10^9/l or lymphocyte count < 900 x 109/l ml a 25/50 mg dose reduction is required.
Azathioprine should be administered with food to reduce gastrointestinal disturbance. A minimum of 12 weeks is required to achieve adequate therapeutic response.

Toxicity monitoring
Full blood count and liver function tests weekly for 4 weeks then 2 weekly until dose stable, then monthly until maintenance dose is achieved, then every 3 months, with electrolytes, urea and creatinine every 6 months.
Analysis of the enzyme thiopurine S-methyltransferase (TPMT) genotype should be considered for patients who develop severe leukopenia.
In RA treatment may be continued indefinitely if patient is responding well and in absence of significant side effects (10). According to systematic reviews the duration of treatment in MS should not go beyond ten years (4).
Public health need and evidence appraisal and synthesis

10. Summary of comparative effectiveness in a variety of clinical settings

Identification of clinical evidence, available data, and estimates of comparative effectiveness:

Historical trials of azathioprine in MS were conducted in 80’s and early 90’s and suffered from methodological limitations as low power and lack of MRI evaluation (11-14). Casetta et al (2007) in a meta-analysis including five parallel group randomised placebo-controlled trials (RCTs) of at least one year duration found that in 698 involved MS patients azathioprine was associated with a statistically significant reduction in the number of patients who had relapses during the first, second, and third years of treatment (relative risk reduction 20, 23, and 18 percent, respectively (4)). Furthermore, analysing only the three small trials with available data on disability progression during the first two to three years (overall 87 patients) there was a statistically significant benefit of azathioprine (relative risk reduction 42%) (4). These results were consistent in sensitivity analyses and there was no heterogeneity among the studies. In the MRI era and after IFNs approval a few studies evaluated azathioprine efficacy in MS. Massacesi et al (2006) conducted a small open-label study of 14 RRMS patients with short disease duration and at least 3 gadolinium-enhancing brain lesions at MRI observed within 6 months before treatment, and found that Azathioprine up to 3 mg/kg daily reduced new gadolinium-enhancing brain lesions and was well tolerated (6). The relative efficacy of IFNs (IFN1a s.c., IFN1a i.m. or IFN1b s.c.) and azathioprine in 94 previously untreated RRMS patients was compared in a randomized single-blind trial of 12 months duration by Etemadifar et al (2007) (7). The mean number of relapses was lower in the azathioprine group than in the IFNs arm (0.28 vs. 0.64, P < 0.05), at one year 57.4% of IFNs arm remained relapse free compared with 76.6% of those in azathioprine, and Expanded Disability Status Scale (EDSS) was reported as decreased in both groups. Filippini et al (2013) in a recent network meta-analysis on immunomodulators and immunosuppressant for MS concluded that there are insufficient high quality data for a definitive conclusion on whether there is a favourable benefit-risk balance with azathioprine, although this drug might be effective in decreasing the odds of participants with RRMS having clinical relapses and disability progression over 24 to 36 months (15). They suggest as future research priority the direct head-to-head comparison(s) between natalizumab and IFNβ-1a or between azathioprine and IFNβ-1a.

Two recent reviews on disease-modifying drugs in MS did not include azathioprine (Zintzara et al, 2012, Smith et al, 2010) (16, 17).

Massacesi et al (2014) conducted an independent multicenter RCT to evaluate the non-inferiority of azathioprine efficacy vs. IFNs on clinical and MRI measures of disease activity in RRMS (8). Annualized relapse rate (primary outcome) was 0.26 (95% Confidence Interval, CI, 0.19–0.37) in the azathioprine and 0.39 (95% CI 0.30–0.51) in the interferon group. Non-inferiority analysis showed that azathioprine was at least as effective as b interferons (relapse RRAZA/IFN 0.67, one-sided 95% CI 0.96; p <0.01). No significant difference was noted between azathioprine and IFNs for MRI secondary outcome: the annualized new T2 lesion rate was 0.69 (95% CI, 0.54–0.88) in the IFNs and 0.76 (95% CI, 0.61–0.95) in the azathioprine patients (p =0.75). This trial was limited by the small sample size and the single-blind design. However, in a previous systematic review of IFNs in RRMS by Rice et al (2003) the authors argued that due to the well documented side effects of IFN injection, mainly injection-site reactions and influenza-like symptoms, many, if not most, treated patients became aware of the treatment they were receiving and these trials should be regarded as single-blind (18). Massacesi et al (2014) concluded that the results of their non-inferiority trial are robust, clinically meaningful and relevant for clinical practice, supporting azathioprine as a rational and effective
alternative to IFNs in RRMS, considering also the convenience of oral administration, the tolerability and the cost, lower than the other available treatments (8).

11. Summary of comparative evidence on safety:

Azathioprine is the oldest immunosuppressive drug used for the treatment of organ transplantation and autoimmune disorders, such as rheumatoid arthritis, Crohn’s disease, and MS. It is a pro-drug, converted in the body to the active metabolite 6-mercaptopurine and acting through the inhibition of purine synthesis necessary for the proliferation of cells, especially leukocytes and lymphocytes. Azathioprine was synthesized in late 50’ and at first used in chemotherapy. Then its remarkable immunosuppressive activity was discovered.

Its most severe side effect is bone marrow suppression and close hematologic monitoring for leukopenia and lymphopenia is needed. The enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine: about 11% of the population has reduced TPMT activity and in 0.3% TPMT deficiency is inherited as an autosomal recessive trait. In these patients, active 6-mercaptopurine accumulates, and a larger proportion of 6-mercaptopurine is converted to the cytotoxic 6-thioguanine nucleotide analogues, which can lead to bone marrow toxicity and myelosuppression. The concomitant administration of purine analogues such as allopurinol is contraindicated.

It is not possible to estimate the global number of patients exposed to azathioprine: in Europe is still used in MS treatment while in U.S.A. it has been almost abandoned since IFNs approval. Given the long duration of presence of the medicine in the market, the list of possible adverse effects reported so far is well known.

Adverse effects (in MS) (4)

According to a systematic review on azathioprine treatment in MS, gastrointestinal disturbances, bone marrow suppression and hepatic toxicity were greater in the azathioprine group rather than in the placebo group (4). However, they were anticipated, and, by monitoring and dosage adjustment, were easily managed. Withdrawals due to adverse effects were few, occurring mostly during the first year of azathioprine treatment and mainly due to gastrointestinal intolerance (5%).

Most common side effects

Nausea, vomiting, anorexia, gastric or abdominal pain
Depression of bone marrow function, leukopenia, thrombocytopenia, macrocytic anemia
Mild elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases
Alopecia

Less common side effect

Pancreatitis
Interstitial pneumonia
Cutaneous rash
Infections

Oncological adverse effects

Myelodysplastic syndrome, lymphoma
Skin malignancies

Practical issues (10)

TPMT Deficiency
TPMT deficiency (heterozygous state) may be associated with delayed (up to 6 months after starting azathioprine) hematological toxicity including bone marrow toxicity. Azathioprine can be fatal in homozygous TPMT states and is contraindicated.

**Photosensitivity**
Patients should be advised to use a sunscreen with a high protection factor and protective clothing to reduce sunlight exposure.

**Pregnancy, Breast Feeding and Contraception**
Azathioprine is not recommended in pregnancy. Men and women Considering family planning should be referred to their neurologists. Women treated with azathioprine must not breast feed.

**Vaccinations**
Patients must not receive immunisations with live vaccines such as oral Polio, MMR, BCG or Yellow fever. Seasonal and pandemic influenza vaccination are safe and recommended. If patient is non-immune (i.e. VZV IgG not detected), patients exposed to chickenpox/shingles should receive passive immunisation with VZIG (varicella-zoster immunglobulin).

**Clinically Significant Drug Interactions**
- **Allopurinol** – enhanced effects and increased toxicity of allopurinol - reduce azathioprine dose to 25% of the original dose
- **Warfarin** – reduced anticoagulant effect, monitor INR closely and increase maintenance dose if necessary
- **Co-trimoxazole, trimethoprim, sulfamethoxazole** – avoid, increased risk of hematological toxicity

Azathioprine is also listed by the International Agency for Research on Cancer as a group 1 carcinogen (carcinogenic to humans).

12. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:**

**Summary of comparative safety against comparators**

- **Side effects of IFNs**
  IFNs side effects are frequent (30-60%): flu-like syndrome, fever, local and systemic reactions, fatigue and spasticity increasing
  Azathioprine side effects are commonly nausea, vomiting, abnormal blood count

In the head-to-head comparative trial of azathioprine vs. IFNs no unknown adverse events (AE) occurred and similar number of patients developed at least one AE in the two group (8). Leuko/lymphopenia (azathioprine group) was not associated with a higher incidence of infections. Treatment discontinuations after AEs were significantly higher in azathioprine treated group, mainly occurring during the first months of therapy, while most IFNs patients dropped the therapy in the second year, confirming the different temporal AE profile of each treatment (8).

- **Range of costs of the proposed medicine**

According to the *International Drug Price Indicator Guide* (2013) the unit price of azathioprine is $0.1696/tablet (DURBIN), lowest price $0.1233/tab-cap (SAFRICA) – highest price $0.2300/tab-cap (NAMIBIA), with a median price of $0.1671/tab-cap
resource use and comparative cost-effectiveness presented as range of cost per routine outcome

The cost of treatment of a person suffering from Multiple Sclerosis using azathioprine is around $16 per month.
The cost of treatment of a person suffering from Multiple Sclerosis using IFNs is around $1000 per month.

The cost-effectiveness comparison between IFNs and azathioprine is in favour of azathioprine.


Regulatory information
13. Summary of regulatory status of the medicine (in various countries)

In the United States, 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 multiple sclerosis (MS), usually if they have problems with standard FDA-approved medications for their MS, or if they are unable to tolerate injection.
In Europe azathioprine is still widely used for patients with RRMS who do not respond to IFNs or in the eastern countries where the market availability of IFNs is limited. In many countries azathioprine is approved for autoimmune diseases, but is off-label for MS.


British Pharmacopoeia, Yes
International Pharmacopoeia, Yes
European Pharmacopoeia, Yes
United States Pharmacopoeia, Yes

15. Proposed (new/adapted) text that could be included in a revised WHO Model Formulary

The same used for RA.

Recent meta-analyses, head-to-head trials and Magnetic Resonance Imaging (MRI) studies show a similar or non-inferior effect of azathioprine compared to beta interferons (IFNs) in Relapsing-Remitting Multiple Sclerosis, supporting this treatment as an effective, less expensive and convenient alternative to IFNs as a first-line therapy.
We propose Azathioprine for the WHO list of essential medicines with the indication for MS to be prescribed by neurologists as a disease-modifying agent, taking care in the selection of eligible patients and ensuring regular medical and laboratory examinations for monitoring possible adverse effects especially leukopenia.
References


10. GSTFT Drug and Therapeutics Committee Reference Shared Care Prescribing Guideline - Azathioprine in adult patients with rheumatoid arthritis. Review June 2012


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For further information, please refer to:
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