National Essential Medicine List
Tertiary Level Medication Review Process
Component: Medication for use in Neurology

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: September 2019
Medicine (INN): Interferon Beta or teriflunomide
Medicine (ATC): L03AB07/L03AB08; L04AA31
Indication (ICD10 code): Multiple Sclerosis (ICD -10: G35)
Patient population: Relapsing remitting multiple sclerosis
Prevalence of condition: 5-30 per 100 000. Two hundred cases in public sector.
Level of Care: Tertiary
Prescriber Level: Specialist neurologist
Current standard of Care: Supportive care
Efficacy estimates:[1]

NNT to prevent one relapse per year:

IFN Beta 1a	11
Teriflunomide 7mg	8
IFN Beta 1a	8
IFN Beta 1b	6
IFN Beta 1a	6
Teriflunomide 14mg	6

*assuming background relapse rate of 0.5622 relapses per year

NNT to prevent one disability progression:

IFN Beta 1a	24
Teriflunomide 14mg	20
IFN Beta 1a	19
IFN Beta 1b	16

*assuming background risk for disability progression of 0.176

Note: Due to a lack of randomized controlled comparison data, these NNTs were derived from a Health Technology Assessment performed by the California technology Assessment Forum.[1]

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3. **Author affiliation and conflict of interest details:** Prof Moodley is the Head of Neurology at the University of the Free State. Dr Mametja is the Head of Knowledge Management at the South African Medical Association. No conflicts declared

4. **Introduction/ Background**

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. Although there is little published epidemiological information available on the disease in South Africa[2], the Multiple Sclerosis Society of South Africa estimated in 2008 that there were 5000 MS sufferers in the country, and that South Africa fell in the countries of "medium frequency" prevalence i.e. 5 to 30 cases per 100 000 population. [3]

The cause of MS remains unknown[4] however, inflammation, demyelination, and axonal degeneration are the major pathologic mechanisms that cause the clinical manifestations.[5, 6] The most widely accepted theory is that MS begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes. Later, the disease is dominated by microglial activation and chronic neurodegeneration. [3]

Several MS phenotypes are recognized, although relapsing remitting MS (RRMS) characterises 85 to 90% of cases[7]. These phenotypes include

- Radiologically isolated syndrome (RIS): Patient is asymptomatic but active disease is noticed on magnetic resonance imaging (MRI)
- Clinically isolated syndrome (CIS): Patient has experienced a first demyelinating attack, usually mono-symptomatic
- Clinically Definite MS (CDMS): Two episodes disseminated in time and space
- RRMS: patients experience attacks (relapses) of neurological deficits with full or near recovery initially, but incomplete recovery later in the course of disease
- Secondary Progressive MS (SPMS): Steady progressive neurological decline with or without superimposed relapses. RRMS patients tend to develop SPMS after a period of 10 to 12 years.
- Primary Progressive MS (PPMS): Affects approximately 15% of patients and is characterised by progressive disease without relapses.

The presentation of the disease may be mono- or multifocal and usually targets the optic nerve (25% of cases), brainstem (15%) or spinal cord (50%). In a 10-year follow-up of clinically isolated syndrome (CIS) in patients with an abnormal MRI, over 80% converted to CDMS, while only 11% with a normal MRI progressed to CDMS. Fifty percent of patient are wheelchair-bound within 15 years and dementia occurs in 50% of patients and may be of earlier onset than previously recognised. However, some observational studies have suggested that the use of Disease Modifying Therapies (DMTs) for patients with MS is associated with a lower long-term risk of disease progression. [8, 9]

MS is a disabling disorder with considerable personal, social and economic consequences. People with MS live for many years after diagnosis with significant impact on their ability to work, as well as an adverse and often debilitating effects on their and their family's quality of life. Relapses are resource intensive requiring admission by specialist neurologists in the Tertiary/Quaternary setting, requiring access to at least one DMT.

In a chronic, progressive neurological disorder, this review seeks to assess the evidence associated with these DMTs with the view to facilitating access to at least one appropriate agent on the Tertiary/Quaternary Essential Medicines List (EML). The review focuses on Interferon beta as an injectable as well as teriflunamide as an oral alternative. Interferon beta products are currently available on National Contract, and thus being used by some provinces for this indication. There was thus a need for the evidence based evaluation by the EML to decide whether this is the most

appropriate and cost effective option. Teriflunomide was included in the review as it is an oral agent (simplifying administration for these patients), and has had significant price reductions in the last year.

MEDICATION:

Several treatment options are available in South Africa for the treatment of relapsing remitting multiple sclerosis, and some newer treatments are not yet registered or available in the country:

Injectable Disease Modifying therapies (DMTs):

- Interferon beta-1a INFB-1a
- Interferon beta-1b IFNB-1b
- Glatiramer acetate
- Mitoxantrone HCl *(significant haematological and cardiac toxicity)*

Oral Disease Modifying therapies:

- Fingolimod
- Teriflunomide

Conventional immunosuppressants:

- Corticosteroids (relapse management)
- Azathioprine
- Methotrexate
- Cyclophosphamide
- Cyclosporine

Primary Outcomes to be included for this review:

Relapses: proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study. A relapse is defined as newly developed or recently worsened symptoms of neurologic dysfunction that last for at least 24 hours, occurring in the absence of fever or other acute diseases and separated in time from any previous episode by more than 30 days.

Disability worsening: proportion of participants who experience disability worsening over 24 or 36 months after randomisation or at the end of the study. Worsening is defined as at least a 1-point Expanded Disability Status Scale (EDSS) increase or a 0.5-point increase if the baseline EDSS was greater than or equal to 5.5, confirmed during two subsequent neurological examinations separated by at least a six-month interval free of attacks.

While there are a number of other secondary measures and surrogate outcomes which have been included in trials, relapse rates and disability progression are the most clinically relevant outcomes and will form the basis of this review.

5. Purpose/Objective i.e. PICO question

- **P** Participants 18 years of age or older with a diagnosis of RRMS according to McDonald diagnostic criteria. Include all participants regardless of sex, degree of disability, and disease duration.
- **I** Interferon beta (all 1a and 1b and all doses), teriflunomide
- **C** Placebo or active comparator
- **O** Relapse rates at 12, 24 and 36 months (as reported); disability progression as measured by EDSS.

6. Methods:

a. Data sources Medline, PUBMED and Cochrane Library

b. **Search strategy** Medline, PUBMED and Cochrane Library were searched from inception until May 2019 with no limitations of language. We looked at published systematic reviews and meta-analyses based on combinations of medical subject headings and keywords. PICO uses to identify search terms has proven difficult given the very wide scope of medicines and possible outcomes for this review, however.

Six meta-analyses/systematic reviews were found to be suitable for this review.

1. Cochrane review of 2001 by GB Rice et al.[10] IFN
2. Systematic review by Fillipini et al in 2003 published in Lancet.[11] IFN
3. Meta-analysis in Clinical Therapeutics by Nikfar et al, 2010. [12] IFN
4. Meta-analysis and review by Oliver et al in Journal of neurological sciences in 2011. [13] IFN
5. Cochrane review of He D et al. 2016.[14] Teriflunomide

c. Excluded studies:

(i) combination treatments; (ii) trials in which a drug regimen was compared with a different regimen of the same drug without another active agent or placebo as a control arm; (iii) treatments not yet registered in South Africa ; (iv) all non-pharmacological treatments, and treatments considered to be "complementary" and not registered with the Medicines Control Council, (v) Trials in other variants of Multiple sclerosis (CIS, PPMS, SPMS), vi) treatment of specific symptoms accompanying RRMS e.g. depression, spasticity. Cost effectiveness analyses were also excluded, although have been recorded to inform analyses going forward.

d. Evidence synthesis

CLINICAL EVIDENCE FOR DMTs (IFN BETA, TERIFLUNOMIDE) FOR RRMS

Historically, the establishment of the "best" first line treatment for RRMS has proven difficult. Uncertain outcomes measurements, lack of head to head trials against active comparators and large dropout rates characterised the early trials of disease modifying agents, including interferon beta.

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Interferon-beta							
Rice GP. et al (2001) Cochrane database of systematic reviews[10]	Systematic review and Meta-analysis of randomised trials	8 trials 1301 patients 919 contributed to relapse and disability data at 2 years	Pts with relapsing remitting MS	Placebo	Relapses and progression after 2 years	Interferon beta significantly reduced the occurrence of exacerbations (Relative risk [RR] 0.80, 95% confidence interval [CI] 0.73 to 0.88, p < 0.001) and progression of the disease (RR 0.69, 95% CI 0.55 to 0.87, p = 0.002) two years after randomisation	Moderate reduction in recurrences and disability. No quantitative MRI results
Fillipini et. al Lancet. 2003 [11]	Systematic review of placebo-controlled randomized trials	7 trials 1215 patients	Pts with relapsing remitting MS	Placebo	Relapses at 1 and 2 years	Interferon beta reduced the number of patients who had exacerbations during the first year of treatment (relative risk 0.73, 95% CI 0.54-0.99)	Moderate reduction in relapses at 1 year. Results at 2 years was not robust due to high dropout rate from AE
Nikfar et al Clinical Therapeutics. 2010 [12]	Meta-analysis of placebo controlled randomized trials	9 trials 3980 pts 359 RMS 932 RRMS	Pts with RRMS, Primary progressive MS, secondary progressive MS	Placebo	Number of patients with 1 relapse and mean change in EDSS score Number of pts discontinued due to adverse events, number of deaths, completed and attempted suicide	RR for 1 relapse in 2 years was 0.77 (95% CI, 0.57 to 1.05) for all types of IFN-beta in relapsing-remitting MS. Mean EDSS change was –1.71 (95% CI, –4.70 to 1.28) for the 22-µg dose and -1.71 (95% CI, –4.70 to 1.27) for the 44-µg dose RRs were 2.76 (95% CI, 1.97 to 3.89; *P* < 0.001) for	Subgroup analysis showed Beta 1b was more effective in reducing relapses than Beta 1a Durelli et al also found that 51% of patients treated with IFN-beta-1b remained relapse free over 2 years, compared

						discontinuation due to adverse events (9 trials), 1.53 (95% CI, 0.45 to 5.15) for death (3 trials), and 0.86 (95% CI, 0.41 to 1.79) for completed suicides and suicide attempts (5 trials)	with 36% of those treated with IFN-beta-1a (RR for relapse = 0.76; 95% CI, 0.59–0.90; P = 0.03).
Oliver BJ, et al Journal of neurological sciences 2011[13]	Meta-analysis and systematic review	7 trials Low dose 1a 747 High dose 1a 569 High dose 1b 290 Low dose 1 a (Avonex 30µg, Rebif 22µg) High dose 1a (Rebif 44µg) High dose 1b (Betaseron250µg)	Pts with relapsing remitting MS	LD1a vs HD1a LD1a vs HD1b HD1a vs HD1b	1.Proportion relapse free 2.Proportion progression free (EDSS stability) 3. MRI stability At 6 to 24 months	1. Relapse outcome (LD1a vs Total HD) RR = 0.86 (95% CI 0.79 – 0.95). Favours HD 2. EDSS outcome (LD1a vs HD1a) RR = 0.99 (95% CI 0.93 – 1.06) 3. MR outcome (LD1a vs Total HD) RR = 0.61 (95% CI 0.53 – 0.71)	3/7 studies showed HD IFN beta superior to LD IFN beta. Four studies showed no superiority 70% of studies were funded by drug companies Author conclusion: High dose treatment is superior in relapse control and MRI stability not in EDSS outcome
Teriflunomide							
He D, et. al. Cochrane 2016[14]	Systematic review of randomized, controlled, parallel-group trials	5 trials, 3231 patients Terifluonmide 7mg or 14 mg versus placebo or interferon beta-1a	Adults with relapsing forms of MS	Placebo or interferon beta-1a	Number of participants with at least 1 relapse over one year/two years Disability progression	**<u>Versus placebo:</u>** Reduction in the number of participants with at least one relapse over one year <u>Teriflunomide 7mg:</u> risk ratio (RR) 0.72, 95% confidence interval (CI) 0.59 to 0.87, P value = 0.001. <u>Teriflunomide 14mg:</u> RR 0.60, 95% CI 0.48 to 0.75, P value < 0.00001) Reduction in the number of participants with at least one relapse over two year <u>Teriflunomide 7mg:</u> RR 0.85, 95% CI 0.74 to 0.98, P value = 0.03 <u>Teriflunomide 14mg:</u>	Low quality evidence The quality of available data was too low to evaluate the benefit of teriflunomide as monotherapy versus IFN-1a or as combination therapy with IFN

						RR 0.80, 95% CI 0.69 to 0.93, P value = 0.004. Disability progression Teriflunomide 14 mg: at one year RR 0.55, 95% CI 0.36 to 0.84, P value = 0.006) or two years (RR 0.74, 95% CI 0.56 to 0.96, P value = 0.02). **Versus interferon beta-1a** Reduction in the number of participants with at least one relapse over one year Teriflunomide 14 mg: had a similar efficacy to IFN_beta -1a in (RR 1.52, 95% CI 0.87 to 2.67, P value = 0.14 Teriflunomide 7 mg was inferior to IFN-beta-1a: RR 2.74, 95% CI 1.66 to 4.53, P value < 0.0001	

e. **Evidence quality:** There is moderate evidence that interferon beta reduces relapse rate and prevents disability progression in Multiple Sclerosis. Comparative data on teriflunomide is very low quality compared to IFN beta 1a.

f. *NNT to prevent one relapse per year:*[1]

IFN Beta 1a	11
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7. Costs:

Interferon beta 1a and 1b are currently on national contract. A public price offer for teriflunomide was received from the company and was used in the cost comparison below:

	Strength	Unit	Dosage Form	Pack Size	SEP	Contract Price	State price offer	Cost per month	Cost per year
Teriflunomide	14	mg	Tablet	28			R4,400.00	R4,400.00	R52,800.00
Interferon beta-1a	6	MU/ml	Injection	4		R4,547.54 (4)		R4,547.54	R54,570.48
Interferon beta-1b	8	MU/ml	Injection	15		R418.64		R6,279.60	R75,355.20

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [X] Not confident [ ] Uncertain [ ]</td><td>Relapse reduction is significant. NNTs are low</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>Adverse effects include skin rash, injection site reaction (5.3% HD1a and 1% for LD1a) and flu-like symptoms which are transient.
Depression and suicidal ideation are infrequent and manageable
Teriflunomide A/E include hair loss, abnormal LFTs</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td>Specialist neurologists require at least one DMT on the EML.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]

Most affordable agent to be used.</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Interferon Beta-1a (Avonex®)</td><td>R4 547.54per month*</td></tr><tr><td>Interferon Beta-1a (Rebif 22®)</td><td>R6 859.67 per month**</td></tr><tr><td>Interferon Beta-1a (Rebif 44®)</td><td>R7 641.67 per month**</td></tr><tr><td>Interferon Beta-1B (Betaferon®)</td><td>R6 279.60 per month*</td></tr><tr><td>Teriflunomide</td><td>R4 400 per month***</td></tr></table>*Contract Price as of November 2019
**SEP as of October 2019
*** Proposed state offer</td></tr>
</table>

		Additional resources: Injection training and monitoring is offered by the drug company.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☒ X	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes ☒ X No ☐ Uncertain ☐	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒ X	☐	☐

Recommendation:	It is recommended that interferon beta 1a and/or 1b be included on the Essential Medicines List for the specialist management of patients with relapsing remitting multiple sclerosis, to prevent further relapses and secondary progression. **NEMLC RECOMMENDATION (March 2020):** **Provided offered price for teriflunomide prevails, it should be used as first line for relapsing remitting multiple sclerosis, with beta-interferon used as an alternative agent.**
Rationale	Teriflunomide is an oral produce with a comparable price to beta-interferon.
Review indicator	Alternative agents with superior efficacy, comparable costs, and good safety profiles.
Monitoring and evaluation considerations	• Monitoring of full blood count and liver function tests. Regular evaluation for injection site reactions and depression. Neutralising antibody production is very uncommon but non response suggests the likelihood.
Research priorities	Registry of all patients

References:

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