Is the assumption of treatment waning applied consistently across Canada's Drug Agency reimbursement reviews? Reviewing pharmacoeconomic assessments of disease modifying therapies for the treatment of multiple sclerosis

HTA97

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SUMMARY

OBJECTIVES

- Multiple sclerosis (MS) is a chronic autoimmune disease, and the Canadian Drug Expert Committee (CDEC) has considered disease-modifying therapies (DMTs) as possibly relevant MS treatments to prevent long-term disability.
- Long-term treatment effects (TE) of interventions influence cost-effectiveness outcomes in health economic modelling; the TE waning of DMTs over model time horizons and the application of stopping rules in MS has recently been debated in technology appraisals in the UK.
- This study aimed to investigate how consistently TE waning assumptions have been applied in CDA-AMC reimbursement reviews in MS and whether there is consensus within CDEC regarding its inclusion.

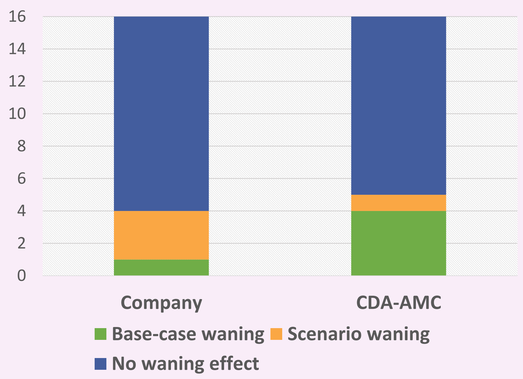
METHODS

- A document analysis following a search of the CDA-AMC website for pharmacoeconomic reports of DMTs in MS. Data concerning treatment effect waning assumptions were extracted as considered by companies, the CDA-AMC and involved clinical experts. Identified trends over time were analysed.

FINDINGS

- In total, 16 pharmacoeconomic reports that published CDEC recommendations on DMTs in MS were reviewed, of which 5 applied TE waning assumptions.
- 1 out of 5 included in the company base-case.
- 4 out of 5 included in the CDA-AMC base-case.
- 5 out of 5 used stepwise waning.

Figure 1. Treatment waning inclusion



BACKGROUND

- Multiple sclerosis (MS) is a complex, chronic autoimmune disease and is currently divided into 4 types – clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). MS affects approximately 2.3 million people worldwide and is often diagnosed between the ages of 20 and 50 years, with females experiencing it more often than males.[1] Several immunomodulatory and immunosuppressive therapeutic agents i.e., disease-modifying therapies (DMTs), are used to reduce the early clinical and subclinical disease activity that eventually contributes to long-term disability in MS.
- Long-term treatment effects (TE) of interventions i.e., attenuation of treatment effect over time, influence cost-effectiveness outcomes in health economic modelling.[2] The inclusion of and approach to modelling DMTs TE waning in cost-utility analyses and the application of stopping rules in MS has recently been debated in technology appraisals in the UK.[3]

AIMS & METHODS

- This study aimed to investigate how consistently TE waning assumptions have been applied in CDA-AMC reimbursement reviews for DMTs in MS and whether there is consensus within the CDEC regarding its inclusion.
- A targeted search of the CDA website was conducted for reimbursement reviews in MS published from inception to 23 October 2024. The retrieved records were exported into Excel and screened for indication and review relevance. The published pharmacoeconomic reports of eligible reviews of DMTs in MS were retrieved and appraised for TE waning in the economic modelling.
- Information on TE waning assumptions, methodology, and rationale was extracted into a pre-formed data extraction form, by one reviewer and crosschecked for accuracy by a second reviewer. Identified trends over time were analysed.

RESULTS

- In total, 16 of 87 screened reviews were included: these were reviews of DMTs in MS which were published with CDEC recommendations. 13 of these published recommendations for RRMS, 1 for SPMS, 1 for PPMS and 1 for CIS. Of these 16 reports, 8 reviews applied TE waning assumptions and/or stopping rules in the company or CDA base case analysis, or the scenario analysis – 6 of these were in RRMS, 1 in PPMS, and 1 in SPMS.
- Of the 5 reviews in which TE waning only was included in the appraisal, only 1 was included in the company base-case (3 included as scenarios), but 4 were included in the CDA-AMC base-case (1 included as a scenario) (see **Figure 1**).
- Of these 5 reviews, every instance used a stepwise waning effect, i.e. creating distinct stages where the treatment effect is reduced by a constant amount relative to each stage. This would indicate that when TE waning is applied, the methodology is consistent.
- However, the application of the stepwise approach varied with each submission, from a 30% reduction after 3 years, 50% after 5 years, and 70% after 9 years, to a 25% reduction after 2 years and 50% after 4 years (see **Table 1**). This doesn't necessarily indicate inconsistency as many differences in treatment could impact length of treatment waning.

Table 1. Modelled TE waning assumptions and stopping rules applied to disease-modifying therapies submitted in CDA-AMC reimbursement reviews

Population	Intervention *Year*	Waning	Company base-case	Company scenario only	CDA-AMC base-case	CDA-AMC scenario only	Company justification	Clinical expert	CDEC decision
RRMS	Ozanimod *2021*	Yes	No	**3-5 years: 75% efficacy; onward years: 50% efficacy**	3-5 years: 75% efficacy; onward years: 50% efficacy	NI	NI	CDEC clinician validation	Do not reimburse
	Ofatumumab *2021*	Yes	No	Year 3-4: 75% efficacy; onward years: 50% efficacy	Year 3-4: 75% efficacy; onward years: 50% efficacy	NI	In line with cladribine (2018) RRMS review	In line with cladribine (2018) RRMS review	Reimburse
	Cladribine *2018*	Yes	All therapies except cladribine. **Year 2-5: 75%; onward years: 50%**	NR	**Equal TE for all therapies.** Year 2-5: 75%; onward years: 50%	NI	No validation to support differential treatment waning	CDEC clinician validation	Reimburse
	Peginterferon beta-1a *2018*	Unclear	Cost comparison	NI	NI	NI	NI	NI	List
	Ocrelizumab *2018*	No	Stopping rule – EDSS 7 or transition into any SPMS state	"Waning in sensitivity analysis for modelled comparators"	No	**Stopping rule – active SPMS patient reaches EDSS 5**	NI	**Loss of efficacy is generally attributed to progression of illness**	Reimburse
	Glatiramer acetate *2016*	Unclear	Cost comparison	NI	NI	NI	NI	NI	Reimburse
	Daclizumab beta *2016*	No	Cost comparison	No	Stopping rule – active SPMS patient reaches EDSS 5 or developed SPMS	No	Stopping rule – active SPMS patient reaches EDSS 7	NI	Reimburse
	Alemtuzumab *2014*	Yes	No	Intervention group only: **Year 4-5: 70%; Year 6-9: 50%; onward years: 30%**	Both arms: Year 4-5: 70%; Year 6-9: 50%; onward years: 30%. No stopping rule after two years	NI	NI	NI	List
	Teriflunomide *2013*	No	No	No	No	No	None due to model limitations	NI	Do not list
	Dimethyl fumarate *2013*	Unclear	NI	NI	NI	NI	NI	NI	List
	Fingolimod *2011*	Unclear	NI	NI	NI	NI	Uncertainty regarding duration of intervention benefit	NI	List
	Natalizumab *2008*	Unclear	NI	NI	NI	NI	NI	NI	List
	Natalizumab *2006*	Unclear	NI	NI	NI	NI	NI	NI	Do not list
SPMS	Siponimod *2020*	Yes	No	No	No	**4-5 years: 75% efficacy; onward years: 50% efficacy**	TE waning significantly affects QALY gains	**Waning is not a common SPMS phenomenon**	Reimburse
PPMS	Ocrelizumab *2018*	No	**Stopping rule – discontinuation in EDSS 7**	No	No	No	Loss of efficacy is due to progression of illness rather than loss of effect of intervention	Stopping rule based on DMTs for RRMS, unclear if it applies to PPMS	Reimburse
CIS	Glatiramer acetate *2009*	Unclear	Cost-minimisation	NI	NI	NI	NI	NI	Do not list

References

1. *Dobson (2019). Multiple sclerosis–a review. European journal of neurology, 26(1), 27-40.*
2. *Hoyle (2014). Key drivers of cost-effectiveness of anti-cancer drugs. Annals of Oncology, 25, iv358.*
3. *Armoiry (2022). Is the assumption of waning of treatment effect applied consistently across NICE technology appraisals? A case-study focusing on disease-modifying therapies for treatment of multiple sclerosis. International Journal of Technology Assessment in Health Care, 38(1), e83.*

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