**Title**: Benefit-risk assessment of cladribine tablets using Multi-Criteria Decision Analysis (MCDA) for patients with relapsing multiple sclerosis demonstrating high disease activity.

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**Background**: Relapsing multiple sclerosis (RMS) with frequent relapses is described as high disease activity (HDA). Benefit-risk assessment of disease modifying drugs (DMDs) for patients with HDA is important. Increasingly, decisions about treatments with multiple criteria employ Multi-Criteria Decision Analysis (MCDA).

**Objective**: Apply MCDA to a structured benefit-risk assessment of cladribine tablets (CT) and newer DMDs for patients with HDA.

**Methods**: Decision conferencing with expert physicians created an MCDA model incorporating available evidence and clinical decisions. Workshops followed the PrOACT-URL (**Pr**oblem formulation, **O**bjectives, **A**lternatives, **C**onsequences, **T**rade-offs, **U**ncertainties, **R**isk attitude, and **L**inked decisions) framework. Benefit-risk assessments were conducted for DMDs in patients with RMS and HDA (≥2 relapses in the previous year). Experts identified 7 favourable and 11 unfavourable effects and a preference value for DMDs using hypothetical treatment effect data. Preference values were 'swing-weighted' by the experts (blinded to the specific DMDs) to represent trade-offs between favourable and unfavourable effects. DMDs included in the model were CT, alemtuzumab, natalizumab, fingolimod, dimethyl fumarate and teriflunomide. Overall weighted preference values were calculated for each DMD. Sensitivity analyses involved changing the swing-weights for unfavourable effects. Benefit-risk profiles of CT and other DMDs were also compared.

**Results**: CT had the highest overall weighted preference value for patients with HDA (confirmed in sensitivity analyses), followed by alemtuzumab and natalizumab. Comparisons of risk-benefit profiles with weighted differences favoured CT for severe lymphopenia, autoimmune disease, herpetic infections, infections, gastrointestinal effects and ease of use, and favoured alemtuzumab for T2 lesions and T1 Gd+ lesions. Differences favoured CT for progressive multifocal leukoencephalopathy,

durability of effect and 3-month and 6-month confirmed disability progression and favoured natalizumab for relapse rate, T2 lesions and T1 Gd+ lesions.

**Conclusions**: Using MCDA with decisions from blinded expert physicians, the benefit-risk profile of CT in HDA patients was favourable compared to the other DMDs included.

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