



Cost-effectiveness of cladribine (Mavenclad®) for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features

The NCPE has issued a recommendation regarding the cost-effectiveness of cladribine (Mavenclad®).

Following assessment of the applicant's submission, the NCPE recommends that cladribine (Mavenclad®) be considered for reimbursement.

This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Merck Serono Europe Ltd) economic dossier on the cost effectiveness of cladribine (Mavenclad®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In December 2017, Merck Serono Europe Ltd submitted a dossier of clinical, safety and economic evidence in support of cladribine (Mavenclad®) for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. This includes both relapsing remitting MS (RRMS) and secondary progressive MS (SPMS), as relapses in RRMS and SPMS are assumed to have the same underlying inflammatory pathophysiology. Reimbursement is being sought under the High Tech Drug Arrangements.

Cladribine is a nucleoside analogue of deoxyadenosine. Cladribine has been shown to exert long-lasting effects by preferentially targeting lymphocytes and the autoimmune processes involved in the pathophysiology of MS.

Cladribine is available as a 10mg tablet. The recommended cumulative dose of cladribine is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.

Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

The applicant anticipates that cladribine will be used as an alternative treatment option to natalizumab, alemtuzumab and fingolimod, in patients with highly active RRMS. Fingolimod is reimbursed via the high tech arrangements in Ireland, while alemtuzumab and natalizumab are delivered as hospital drugs.

1. Comparative effectiveness of cladribine

- The efficacy of cladribine in patients with RRMS was assessed in one main pivotal trial along with its 2-year extension study. The CLARITY study was a 96 week, Phase 3, randomized, double-blind, 3-arm, placebo-controlled, multicentre study to evaluate the safety and efficacy of 2 doses of oral cladribine (3.5 mg/kg and 5.25 mg/kg) in subjects with

RRMS. Eligible patients had definite RRMS with EDSS from 0-5. Exclusion criteria included SPMS or PPMS, disease-modifying drugs (DMD) within the last three months, failure of two or more DMDs (based on efficacy). Eligible patients were assigned in an approximate 1:1:1 ratio (433:456:437) to receive cladribine over 96 weeks or matching placebo. The 5.25 mg/kg dose evaluated in the trials is unlicensed and the conduct/results from this arm of the study are therefore not presented here. No clinical meaningful difference in efficacy between the doses was observed.

The primary endpoint was the qualifying relapse rate at 96 weeks. Secondary endpoints included: proportion of patients qualifying relapse-free at 96 weeks and disability progression at 96 weeks, among others. An assessment of patient health related quality of life (HRQL) and health care resource utilisation (HRU) were included as tertiary endpoints.

The annualized qualifying relapse rates (ARR) were 0.14 for cladribine, and 0.33 for placebo (relative risk 0.43, 95% CI 0.34, 0.54 $p < 0.001$). 79.7% of subjects in the cladribine group, and 60.9% of subjects in the placebo group remained relapse-free at Week 96 (OR 2.53, $p < 0.001$; 95% CI 1.87; 3.43). Cladribine significantly prolonged the time to both 3-month sustained change in EDSS score and 6-month sustained change in EDSS score over 96 weeks compared to placebo (HR for 3-month change was 0.67 ($p = 0.018$; 95% CI 0.48, 0.93; HR for 6-month change was 0.53 ($p = 0.0016$; 95% CI of the HR=0.36;0.79)).

Post hoc analysis was conducted in patients with high disease activity (HDA) in line with CHMP advice in 2014 to identify a target population with a more favourable benefit-risk balance. Four HDA subgroups were defined, considering number of clinical relapses in a previous year as well as number of T1 Gd+ or T2 lesions as criteria. In general, the effect of cladribine compared to placebo was larger across all HDA subgroups compared to the respective non-HDA groups. The qualifying ARRs were 0.16 for cladribine, and 0.47 for placebo (relative risk 0.33, 95% CI 0.23, 0.48 $p < 0.0001$). These findings support a trend for a greater benefit of cladribine in patients with HDA.

The CLARITY extension study (CLARITY EXT) was a double-blind, randomized, placebo-controlled, multicentre, parallel-group 96 week extension trial to CLARITY to evaluate the safety, tolerability and efficacy of oral cladribine for up to 4 years (192 weeks, including the 96 weeks of CLARITY) in subjects with RRMS. The trial included two further blinded 48-week treatment periods, and a 24-week supplemental follow-up phase during which subjects did not receive treatment, for a total of 216 weeks of observation (including CLARITY). Subjects

randomized to placebo during CLARITY were assigned to cladribine and subjects randomized to oral cladribine during CLARITY were re-randomized in a 2:1 allocation ratio to receive either low-dose oral cladribine or placebo. Cladribine and matching placebo were administered as 2 treatment courses separated by 1 year. Efficacy endpoints were exploratory in the CLARITY EXT study. The majority of clinical efficacy results suggested that there was no relevant added benefit of additional treatment courses beyond year 2 and that the treatment effect obtained in CLARITY was maintained.

The results of the ONWARD study (a phase II study of combination cladribine/IFN β treatment) were consistent with the CLARITY study. The ONWARD study included a low number of SPMS patients with superimposed relapses. Subgroup analyses indicate a similar treatment effect in terms of relapse reduction with cladribine in both RRMS and SPMS patients with superimposed relapses. Analysis of the combined CLARITY + ONWARD patient population using baseline EDSS ≥ 3.5 as a proxy for SPMS (or high risk of transitioning to SPMS) was performed to strengthen this finding. This supported the definition of the target population as patients with highly active RMS instead of RRMS, as it is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology.

A network meta-analysis was undertaken by the applicant to assess the relative efficacy, safety and tolerability of cladribine versus relevant comparators; reporting a finding of comparable efficacy for cladribine compared with alemtuzumab, fingolimod and natalizumab, in the HDA-RRMS population. The following three outcomes were included in the economic evaluation: ARR, CDP3M and CDP6M. There was a numerical tendency in favour of natalizumab and alemtuzumab compared with cladribine (where information was available) in the RES-RRMS subgroup while this trend was reversed in the HDA-RRMS subgroup. Overall, there were no significant differences between cladribine and any of the other DMTs evaluated in the subgroups of interest. Results in different subgroup and for different clinical outcomes are somewhat contradictory, and reflective of the lack of direct comparative evidence between the comparators of interest, and the paucity of evidence in the subgroups overall.

2. Safety of cladribine

- The most clinically relevant adverse reactions reported in MS patients who received cladribine at the recommended dose in clinical studies were lymphopenia (grade 3 or 4 occurring in 20% to 25% of patients, the largest proportion seen 2 months after the first dose in each year) and herpes zoster. To decrease the risk for severe lymphopenia, lymphocyte counts must be determined before, during and after cladribine treatment and strict criteria for initiating and continuing cladribine treatment must be followed. The incidence of herpes zoster was higher during the period of grade 3 or 4 Lymphopenia. If lymphocyte counts drop below 200 cells/mm³, anti-herpes prophylaxis according to local standard practice should be considered during the time of grade 4 lymphopenia. In clinical studies, events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo (0.29 events per 100 patient-years compared with 0.15 events per 100 patient-years). An individual benefit-risk evaluation should be performed before initiating cladribine in patients with prior malignancy.

2. Cost effectiveness of cladribine

Methods

- A cohort-based multi-state Markov state transition model was used, in line with previous submissions for DMT for RRMS. An annual cycle length was adopted with outcomes evaluated over a time horizon of 50 years. Cost-effectiveness was assessed in terms of the cost per Quality Adjusted-Life Years (QALY) gained and the perspective of the Irish Health Services Executive was adopted, as per national guidelines.
- This structure comprises 10 health states representing disability status according to the EDSS scale, and a single state for death from all causes. The EDSS is a 10-point instrument that measures different areas of functional disability ranging from normal neurological examination at EDSS 0 to “confined to bed” at EDSS 9. At model entry, the cohort was proportionally assigned to the 10 EDSS states according to the baseline EDSS distribution in the CLARITY study population. Over yearly cycle periods, the cohort was at risk of: (1) experiencing disability progression (move to a higher EDSS state), (2) improving in disability status (move to a lower EDSS state), (3) remaining at their current level of disability (remain in their current EDSS state), or death. The cohort was also at

risk of experiencing one or more acute relapse events during each cycle. These events were modelled separately to EDSS-related disability progression and were calculated by applying an annualised relapse rate to the number of patients alive in the model. A gender-averaged all-cause mortality rate was derived from all-cause mortality data for the Irish population, inflated for the excess mortality risk for MS. The treatment-adjusted model incorporates relapse rate ratios and hazard ratios of disability progression for each DMT versus placebo obtained from the NMA.

- Health state utilities and disutilities related to relapses and “serious but rare ‘one-off’ events ((progressive multifocal leukoencephalopathy [PML]), macular oedema, hypersensitivity, autoimmune thyroid-related events, immune thrombocytopenic purpura (alemtuzumab only), and “ongoing” events related to infusion and injection site reactions were included. A systematic literature review was conducted to identify published HRQoL studies in RRMS including studies that reported health state utilities by EDSS and for relapse. EDSS health state utility values were based on baseline EQ-5D-3L questionnaires from patients enrolled in CLARITY and CLARITY-EXT. Utility values were pooled across treatment and patient subgroups as there was no evidence of a meaningful difference across subgroups. Costs included drug acquisition, administration and monitoring costs, direct medical and non-medical costs related to EDSS health state, relapse and adverse event related costs. Relevant cost and health resource use data were identified from various sources including published costing studies, CaseMix Ready Reckoner, and the summary of product characteristics for comparators. After year 2, it was assumed that a proportion of patients will require re-initiation of cladribine. Re-initiation of cladribine was modelled on the expected proportion of patients who experience their first relapse between years 2 and 6, estimated from data on the time to first relapse in CLARITY and CLARITY EXT. After year 6, no further re-initiation was assumed given uncertainty over the rate of relapse beyond this time period

Results

- A deterministic incremental analysis of costs and benefits was presented by the applicant. The results of probabilistic analysis are most appropriate, in order to reflect the implications for decision uncertainty from all of the parameters in the model, however a probabilistic analysis was not submitted as part of the applicant’s final

submission.

- In the deterministic analysis of incremental cost per QALY (incremental cost-effectiveness ratio (ICER)), cladribine was found to be dominant (i.e. less costly and more effective) versus all alternative therapies in the pairwise comparisons, and the dominant strategy in the fully incremental analyses. Cladribine was cost saving versus all alternative strategies with incremental costs ranging from -€60,604 (alemtuzumab) to -€176,902 (natalizumab). Incremental QALYs ranged from 0.963 (alemtuzumab) to 1.664 (fingolimod).

3. Budget impact of cladribine

- Cladribine is submitted for reimbursement under the High-tech drug arrangement. The proposed price to wholesaler of cladribine 10mg x 1 tablet €2,204.72. The annual cost per patient per year is estimated to be €28,893 and €57,786 for the entire two year treatment-course. The drug-acquisition cost of cladribine is comparable to alemtuzumab and lower than other comparators over a four-year period. It was assumed that 9.3% and 4.2% of cladribine patients would require re-initiation of treatment in years 3 and 4 post initiation respectively.
- Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €5.69 million. The uptake of cladribine is assumed to displace the use of alemtuzumab, fingolimod and natalizumab, resulting in net savings over five years. It is also anticipated that cladribine will be associated with further savings versus alemtuzumab and natalizumab as it does not require hospital admission or infusion.

4. A patient submission was received from Multiple Sclerosis Ireland.

5. Conclusion

- Following NCPE assessment of the company submission, cladribine (Mavenclad®) is considered cost-effective for the treatment of adult patients with highly active relapsing MS as defined by clinical or imaging features and therefore is recommended for reimbursement.