ID64 STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Confidential until published

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A MEMBER OF THE RUSSELL GROUP

The company identified 9 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here. Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Text deleted completely (as opposed to being reworded) is blacked out (for example, [redacted]).

symptoms are mild or disappear altogether) followed by relapses (which may or may not result in residual disability). Some people with RRMS can progress to develop secondary progressive multiple sclerosis (SPMS).

2.2 Critique of company's overview of current service provision

The company presents a brief overview of the clinical care pathway in Sections B.1.3.2 and B.1.3.3 of the CS and provides details of the McDonald diagnostic criteria for MS in Table 5 of the CS.[11] The ERG considers that the overview of the clinical care pathway in the CS is largely accurate.

The ERG notes that there is no current cure for MS and that RRMS is managed using disease-modifying therapies (DMTs). The aim of treatment with DMTs is to reduce the frequency / severity of relapses and delay progression of the disease.

The company reports that the Association of British Neurologists (ABN)[12] classifies DMTs into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles). The DMTs in each category are listed in the CS (CS, Figure 6), and reproduced here in Figure 1. The company does not know whether the ABN will designate cladribine tablets as a Category 1 or Category 2 DMT. The company suggests that a new category might be needed (CS, p24). Clinical advice to the ERG is that cladribine tablets are likely to be considered as a Category 2 drug. Cladribine tablets would be the only Category 2 drug that is administered orally and the only oral drug available as a treatment option for rapidly-evolving severe RRMS (RES-RRMS).

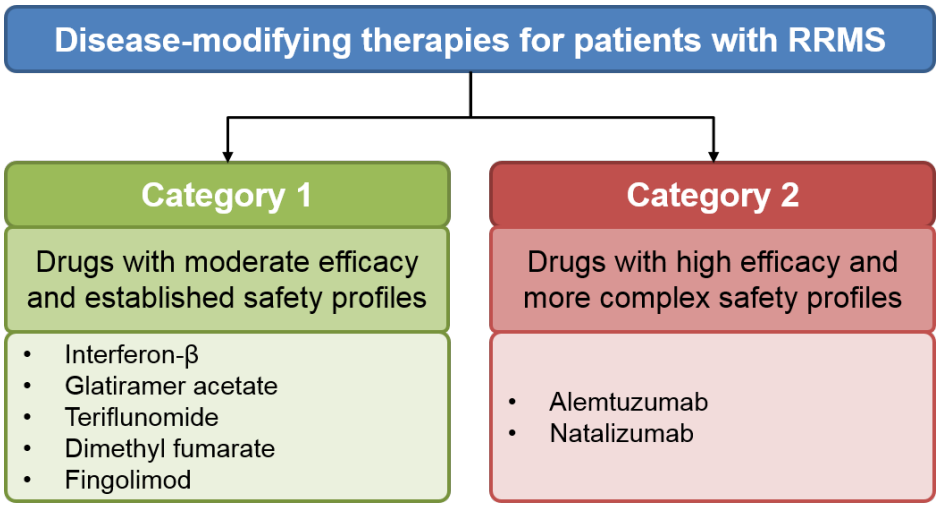

Figure 1 Categorisation of disease-modifying therapies according to the ABN guidelines

Source: CS, Figure 6

2.3 Indication / market authorisation

The company received a negative opinion in response to its 2009 marketing authorisation application to the European Medicines Agency (EMA)[13] for the treatment of people with RRMS and to a subsequent application for conditional approval for the treatment of people with high disease activity RRMS (HDA-RRMS) in 2010 (CS, pp18-20). The company states that the Committee for Medicinal Products for Human Use (CHMP) acknowledged the efficacy benefits of treatment with cladribine tablets, but raised concerns about the safety profile (CS, p19). The company reports that the Food and Drug Administration (FDA) issued a complete response letter following the company's request in 2010 for conditional approval of the use of cladribine tablets to treat people with MS in the USA with HDA-RRMS.

A new marketing authorisation application was submitted to the EMA in June 2016 following the availability of new data (i.e. from the integrated safety analysis performed on combined data from the CLARITY, CLARITY-EXT and ORACLE trials, and the PREMIERE registry), which the company states 'has substantiated the positive clinical efficacy of cladribine tablets while also mitigating safety concerns previously identified by the CHMP' (CS, p20).

At the time the CS was submitted to NICE (26th June 2017), cladribine tablets did not have a marketing authorisation in Europe. The company had anticipated that the marketing authorisation for cladribine tablets would be for adults with HDA-RRMS (CS, p11). However, on the 22nd June 2017, the CHMP of the EMA[14] issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features. The company states throughout the CS that they were assuming that the marketing authorisation granted by the EMA would be for the HDA-RRMS population, which includes people with [redacted]RES-RRMS and people with RRMS sub-optimal therapy (SOT-RRMS). The HDA-RRMS is a narrower population than the highly active relapsing MS population.

2.4 Summary of relevant clinical guidance and guidelines

The CS does not include details of relevant published guidance and treatment guidelines for MS. A summary of the available NICE guidance for technologies included as comparators in the final scope issued by NICE is provided in Table 1.

The ERG notes that although beta interferon and glatiramer acetate are not currently recommended by NICE for the treatment of people with MS, these therapies are available in the NHS through a risk sharing scheme arranged by the Department of Health.[10] Beta interferon and glatiramer acetate are being assessed as part of an ongoing multiple technology appraisal (TA32).[15]

5.3.1 NICE reference case checklist

Table 1 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	[redacted] Cost effectiveness results were only generated for two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS)
Comparator(s)	As listed in the scope developed by NICE	[redacted] Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS subgroups
Perspective costs	NHS and PSS	Partial. The ERG considers the inclusion of informal care costs was inappropriate and outside of the NICE reference case
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial. The ERG considers the inclusion of carer disutility was inappropriate and outside of the NICE Reference Case
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Trial data as well as data from the company's NMAs and meta-regression were used to populate the company model
Outcome measure	Health effects should be expressed in QALYs.	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=Personal Social Services

6.1 Conclusions of the cost effectiveness section

The ERG considers that the economic model submitted by the company is well designed and commends the company on the efforts that they have made to identify data with which to populate it.

However, the ERG considers that the usefulness of the model to decision makers is limited. The two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets versus placebo and versus other DMTs, and (ii) the inclusion of costs and benefits that are outwith the NICE reference case.[31] Whilst changes to the model can address the latter of these issues, no data are available to address the clinical evidence related issues.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence using data from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 19 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively. This means that the samples have low power to detect statistically significant changes in outcomes.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model). This means that any model results, for patients in the SOT-RRMS subgroup, showing that treatment with cladribine tablets is cost effective compared with any comparator should be viewed with caution.
- Evidence allowing the clinical effectiveness of cladribine tablets to be compared with other DMTs has been drawn from a set of NMAs and a meta-regression. The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS (see Section 4.7).