Understanding the economic sections of ASARs

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Section 4 of the ASAR

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

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AWMSG SECRETARIAT ASSESSMENT REPORT

Fingolimod (Gilenya®) 0.5 mg hard capsules

Reference number: 3135

FULL SUBMISSION

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost utility analysis (CUA) comparing oral fingolimod 0.5 mg once daily with natalizumab 300 mg intravenous infusion every four weeks and alemtuzumab 12 mg intravenous infusion once daily for 5 days, followed 12 months later by 12 mg once daily for 3 days in patients with RES RRMS[1]. The company suggests the chosen comparators are the most relevant alternative treatments for this patient group in Wales, and reflect NICE guidance and Welsh clinical expert opinion[10,13].

First paragraph describes the decision problem, the type of economic evaluation that has been conducted, and a brief clinical context of the economic evaluation

DOES THE ECONOMIC EVALUATION MATCH THE LICENSED INDICATION?

Population

- Aligned with the licensed indication?
- Representative of eligible population in Wales?
- Uncertainty due to small populations
- How does the modelled population reflect the trial population?
- Are there sub-groups that may be more relevant?

Comparator

- Have all the appropriate comparators been considered?
- Are modelled treatment pathways representative of care in Wales?
- Was clinical opinion sought?

The CUA uses two pair-wise Discrete Event Simulation (DES) models to separately compare fingolimod with each of the comparators. DES has been used to try to adequately structure the serious adverse events associated with the comparators, which have long-term sequelae. The models adopt an NHS Wales/Personal Social Services perspective and a lifetime time horizon (simulated patient age is capped at 101 years). The model structure is informed by the cohort Markov models used in previous NICE technology appraisals[28-32]. Individual patient data for 528 RES RRMS patients are derived from the pooled pivotal phase III studies for fingolimod[17-19]. This patient group is cloned to

…….

Second paragraph describes the methods: how the model was constructed, how were health states defined, what were the clinical pathways represented by the model etc. This is a factual description of the company's economic model.

DOES THE MODEL ACCURATELY REFLECT THE CLINICAL CONTEXT?

Model structure

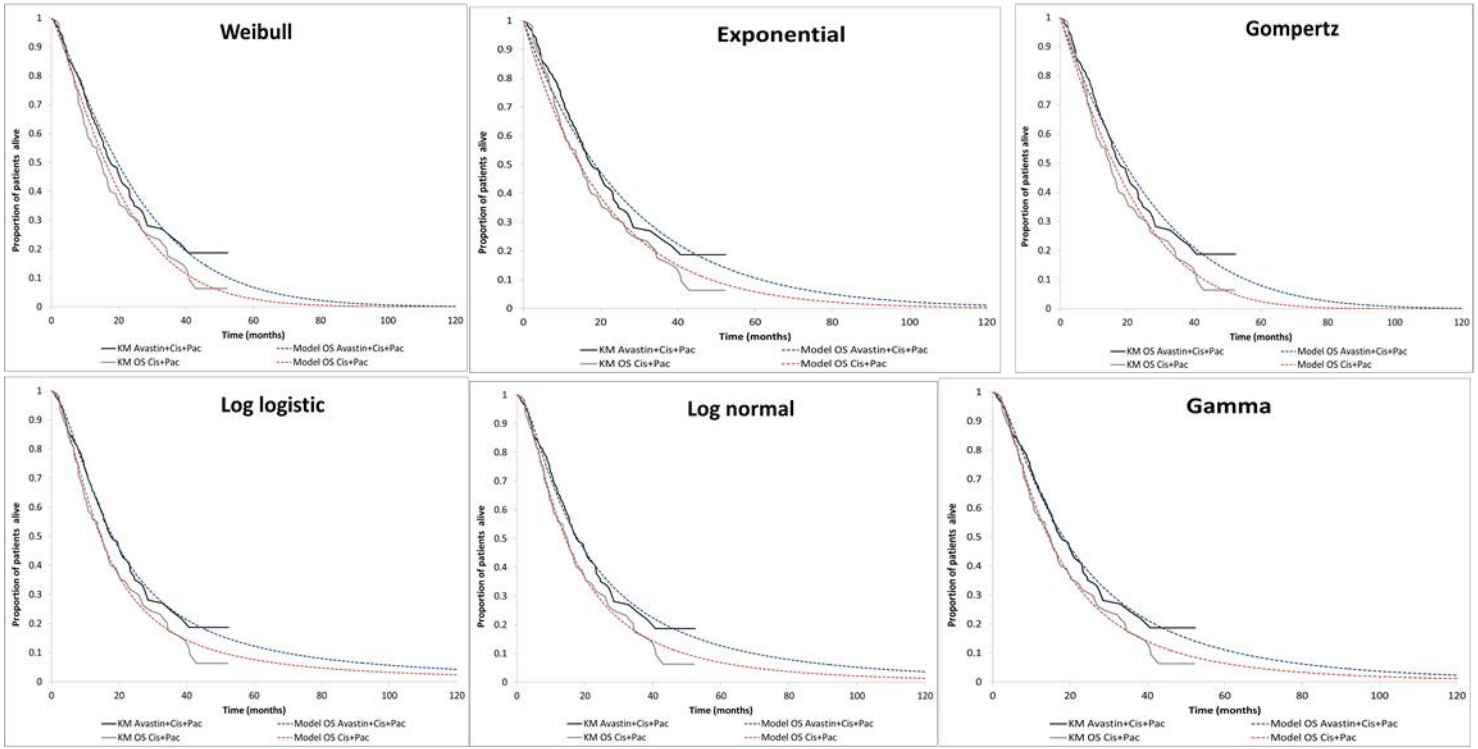
- Models for extrapolation of benefit, specification of health states etc should be transparent, validated, subjected to different scenario analyses
- Consider alternative model specifications
  - DES may be more applicable than Markov
  - Is an overly complicated model necessary (reduces transparency)?
- Impact of structural uncertainty on the ICER

Extrapolation

- Did they choose a function based on one that makes ICER look lowest!
- Different parametric functions
  - Diagnostics, visual inspection
  - Based on fit to the observed data
- Duration of treatment benefit in extrapolated phase
  - Nil
  - Same as treatment phase and continues at the same level
  - Diminishes in the long term
- Plausibility
  - 12 week trial => lifetime benefit?
  - Expert clinical opinion on plausibility

Visual fits of the data

Parametric functions for OS compared with observations in the clinical study



Clinical inputs for natalizumab and fingolimod are derived from *post-hoc* subgroup analysis of RES RRMS patients from the pivotal studies[17-19,36]. Given the lack of appropriate data for alemtuzumab, its efficacy is assumed to be equivalent to natalizumab, reflecting the approach taken in the alemtuzumab NICE submission[30]. Two …….

Third paragraph describes the clinical inputs: which data did the company use to estimate the medicine's effectiveness and adverse effects?

WERE APPROPRIATE ESTIMATES OF EFFICACY USED IN THE MODEL? DID THEY MATCH THE CLINICAL EFFECTIVENES SECTION OF THE ASAR? USE OF INDIRECT TREATMENT COMPARISONS

Effectiveness

- Non-inferiority ≠ equivalence
- Indirect treatment comparisons should *only* be conducted if there are no direct trials of the relevant comparator
  - Informed by a systematic review of the evidence
  - Full details of SR, reasons for inclusion/exclusion, tests for heterogeneity, (in)consistency, etc should have been reported

The model incorporates costs associated with: disease status (EDSS score); relapse; treatment acquisition, administration and monitoring; and adverse events. Costs included for disease status are derived from a previous NICE submission for fingolimod[8], which were based on a 2005 UK MS survey[37], and have been inflated to reflect 2014/2015 .....

Next paragraph describes resource use and costs, how they relate to health states, how they were estimated and valued

WERE COSTS BASED ON RELIABLE DATA, OR OPINION?

The model incorporates utility values for EDSS score, carer disutility, relapse disutility, adverse event disutility, and utility adjustments associated with year since diagnosis and gender. Utility values associated with EDSS and time since diagnosis and gender, and disutility associated with relapse, are based on a UK study[44] which assessed …….

How did utilities relate to the modelled health states? How were they estimated? Which methods were used to map from clinical measures? Were externally sourced utilities used in preference to those measured directly in the clinical trials?

HOW RELIABLE AND PLAUSIBLE ARE THE UTILITIES? HOW DO PATIENTS' QUALITY OF LIFE SCORES COMPARE WITH THE GENERAL POPULATION?

Utilities

- EQ-5D is the preferred measure of HRQL in adults, other methods accepted
  - EQ-5D-5L, CHU9D, disease-specific utilities etc.
- Primary QoL data from trial should be used where available
  - Avoid unnecessary mapping
- Separate TTO study acceptable if there are no utility data whatsoever

Univariate sensitivity and scenario analyses test the influence of the uncertainty of individual parameters and structural assumptions on the robustness of the base case results. Sensitivity analyses explore the impact of varying all parameters, to reflect lower and upper bounds of 95% confidence intervals (where available), or to measure the effects of a 20% change in either direction. Scenario analyses additionally test the impact of altering: incidence of all adverse events to zero; the probability of treatment withdrawal and efficacy of the comparators being set equal to fingolimod; and altering the discount rate.

Final paragraph of the methods section concerns the approach taken to consider uncertainty in the analysis. This includes sensitivity analysis, probabilistic sensitivity analysis and scenario analysis

WAS AN APPROPRIATE AND COMPREHENSIVE APPROACH TAKEN FOR THE CONSIDERATION OF PARAMETER (AND STRUCTURAL) UNCERTAINTY?

Uncertainty

- “...medicines with presented ICERs less than £20,000 per QALY gained may not be recommended if AWMSG are not persuaded by the **plausibility** of the inputs to the economic modelling and/or the **certainty** around the estimated ICER”
- “Above a most **plausible** ICER of £20,000 per QALY gained, judgements about the acceptability of the medicine as an effective use of NHS resources will specifically take account of ...the degree of **certainty** surrounding the calculation of ICERs...”

Uncertainty

- Structural uncertainty
  - Scenario analyses
  - Committee members should decide which scenario they consider to be most plausible
- Parameter uncertainty
  - Sensitivity analyses reveal how sensitive the ICER is to changes in inputs
  - Probabilistic Sensitivity Analysis gives the probability of being cost-effective at thresholds of £20k and £30k per QALY
    - Not helpful if only applied to a base-case which is not considered most plausible

4.1.2 Results

The results of the base case pair-wise comparisons are detailed in Table 2. When fingolimod is compared with both natalizumab and alemtuzumab, the base case point estimates fall in the south-west quadrant of the cost-effectiveness plane. This reveals how fingolimod is comparatively less effective, with fewer quality-adjusted life years (QALYs) …….

The principal findings of the company base case analysis are presented in the next section

HOW PLAUSIBLE ARE THE ASSUMPTIONS RELATING THE TO COMPANY'S CHOSEN BASE-CASE?

	Fingolimod	Comparator treatment	Difference	NMB valuing a QALY £20,000†	NMB valuing a QALY £30,000†
Fingolimod versus natalizumab					
Total costs*	¶¶	¶¶	¶¶	¶¶	¶¶
Total QALYs*	¶¶	¶¶	¶¶		
ICER (£/QALY forgone)		¶¶			
Fingolimod versus alemtuzumab					
Total costs*	¶¶	¶¶	¶¶	¶¶	¶¶
Total QALYs*	¶¶	¶¶	¶¶		
ICER (£/QALY forgone)		¶¶			

The principal findings of the company base case analysis are always tabulated, separating QALYs from costs and LYG where possible

REMEMBER THESE RESULTS RELATE TO THE COMPANY'S CHOSEN BASE-CASE (MIGHT NOT BE YOUR PREFERRED SET OF ASSUMPTIONS). ARE THE LY/QALY GAINS CREDBLE?

The univariate analyses comparing fingolimod and alemtuzumab also revealed how the NMBs produced are most sensitive to relative risk of progression and costs of treatment, in addition to the cost discount rate. In all of these cases, the NMB was negative. While it can be argued that uncertainty surrounding cost and discount rate can be ruled out, given that these are known and fixed, the same cannot be said for the uncertainty surrounding efficacy.

The results of the sensitivity analyses are described next (and tabulated).

HOW PLAUSIBLE ARE THE ASSUMPTIONS RELATING THE TO COMPANY'S CHOSEN BASE-CASE?

Scenario	ICER (£ saved/QALY forgone)	Plausibility
Set incidence of all adverse events in the model to zero: a) fingolimod versus natalizumab b) fingolimod versus alemtuzumab	¶¶ ¶¶	These scenarios provide added insight. However, they do not offer plausible alternatives to the base case, given that all treatments considered are associated with adverse events.
Probability of treatment withdrawal for comparator set equal to fingolimod: a) fingolimod versus natalizumab b) fingolimod versus alemtuzumab	¶¶ ¶¶	Withdrawal rates have been shown to differ in the pivotal studies included in the model. Therefore, these scenarios are unlikely to be plausible alternatives.

.....

The results of the scenario analyses are important.

THERE IS OFTEN A SCENARIO (OR SET OF INPUTS) WHICH IS MORE APPROPRIATE THAN THE COMPANY'S CHOSEN BASE CASE

4.1.3 AWTTC critique

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.

Limitations:

- Due to the *post-hoc* definition of RES RRMS during the licensing process, the intention-to-treat population of the pivotal clinical studies (including comparator studies) included a broader set of RRMS patients than those targeted in this

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AWTTC's balanced critique of the company submission gives a summary of the key problems, and their potential influence on the ICER.

TO WHAT EXTENT IS THE ICER RELIABLE? UNCERTAINTY IS NOT A GOOD THING!

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any cost-effectiveness studies focused on the treatment comparisons included in this submission for the subpopulation of interest.

Sometimes AWTTC are able to find published economic evaluations. These are often for different countries (and so costs are not generalisable) but QALY estimates may still be relevant.

HOW COMPARABLE ARE THE RESULTS TO THE COMPANY'S SUBMISSION?

Diolch yn fawr - Thank you

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PAMS Patient Access to Medicines Service
WNPU Welsh National Poisons Unit
WeMeReC Welsh Medicines Resource Centre
Yellowcard Centre Wales
WAPSU Welsh Analytical Prescribing Support Unit