Slides for public – Redacted

Chair's presentation

Ocrelizumab for treating primary progressive multiple sclerosis (ID938)

2nd Appraisal Committee meeting

Committee B, 2nd August 2018

Lead team: David Chandler, Richard Hoddes and Sanjeev Patel

Chair: Amanda Adler

Assessment Group: Warwick Evidence

NICE technical team: Thomas Walker, Rebecca Albrow

ACD: Preliminary recommendation

- Ocrelizumab is not recommended, within its marketing authorisation, for treating early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity in adults

- There is a large unmet need for treatment for people with primary progressive multiple sclerosis
- Ocrelizumab slows disability progression compared with placebo, although with an uncertain size and duration of the effect
- Cost-effectiveness estimates from the company's base-case model were far higher than those NICE normally considers acceptable
- Committee had several preferences for the model that differed from the company's base case and which would increase the ICER even further

Ocrelizumab (Ocrevus)

Marketing authorisation	Ocrelizumab is indicated for the treatment of adult patients with **early** primary progressive multiple sclerosis in terms of disease duration and level of disability, and with **imaging characteristic of inflammatory activity**
Mechanism	Depletes CD20+ B cells
Route and dose	Intravenous (IV) infusion • First 600 mg dose administered as two 300 mg infusions 2 weeks apart • Subsequent doses as a single 600 mg infusions every 6 months Minimum interval of 5 months between each dose
Cost	List price: £4,790 per 300 mg vial Simple discount patient access scheme (PAS) has been approved
Average cost of treatment	£19,160 per patient per year

Clinical evidence: ORATORIO trial

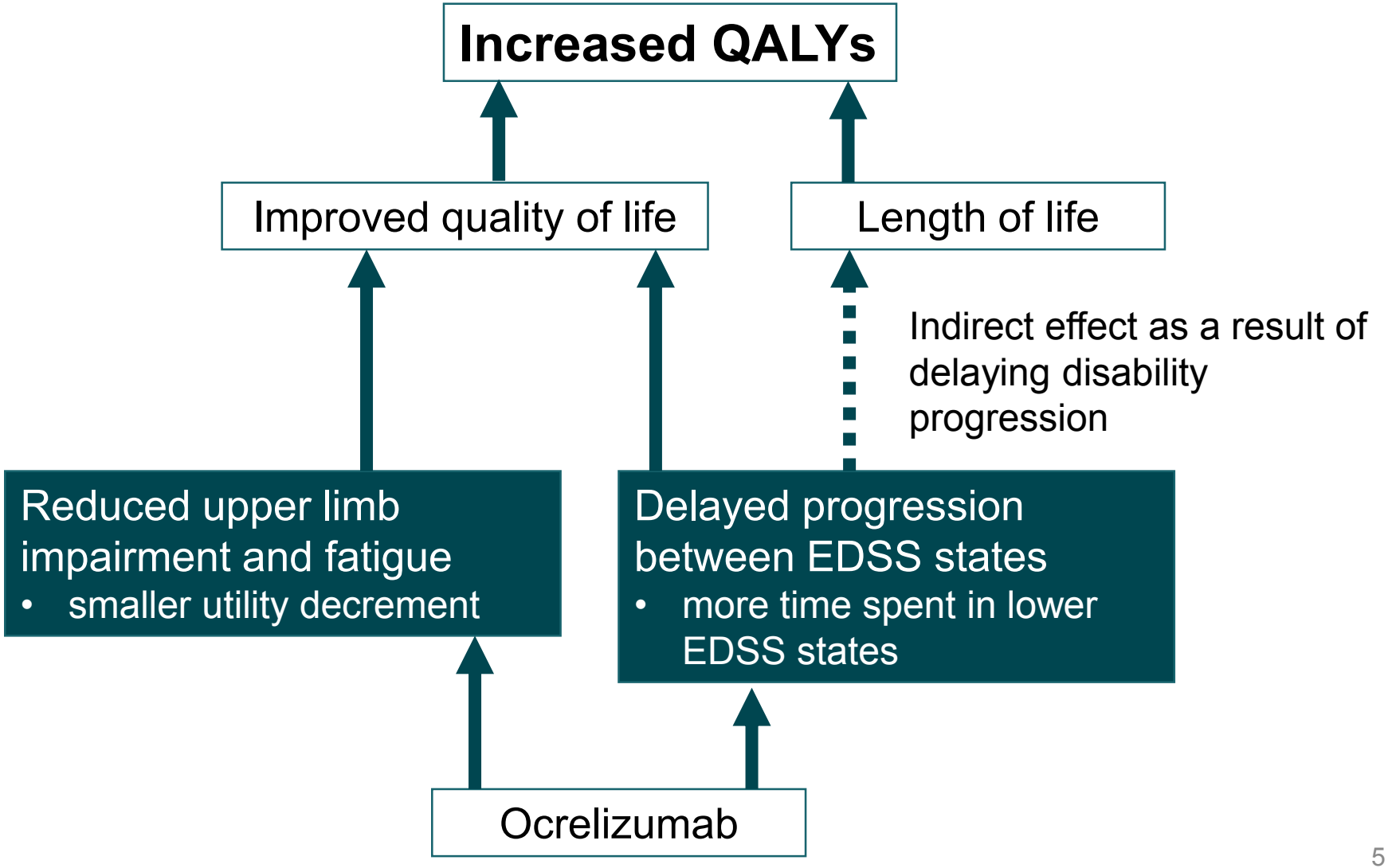
Design	Phase III, randomised, parallel-group, double-blinded, placebo
Population	• PPMS, **18 to 55** years, EDSS at screening: **3.0 to 6.5** • Disease duration of: − <15 years if EDSS at screening >5.0 − <10 years if EDSS at screening ≤5.0
Intervention	Ocrelizumab 600 mg (n=488; 24 from UK) • 2 x 300 mg infusions 14 days apart, every 6 months
Control	Placebo (n=244; 5 from UK)
Outcomes	• Confirmed disability progression (CDP): − sustained for 12 weeks (CDP-12) [1◦outcome]* − sustained for 24 weeks (CDP-24) [2◦outcome] • SF-36 physical component summary score *Exploratory* endpoints included: • Upper limb function (9 hole peg test)* • Fatigue (Modified Fatigue Impact Scale [MFIS])*
Treatment	• No stopping rule

Post-hoc subgroup analysis to match marketing authorisation population: ***'MRI active'***

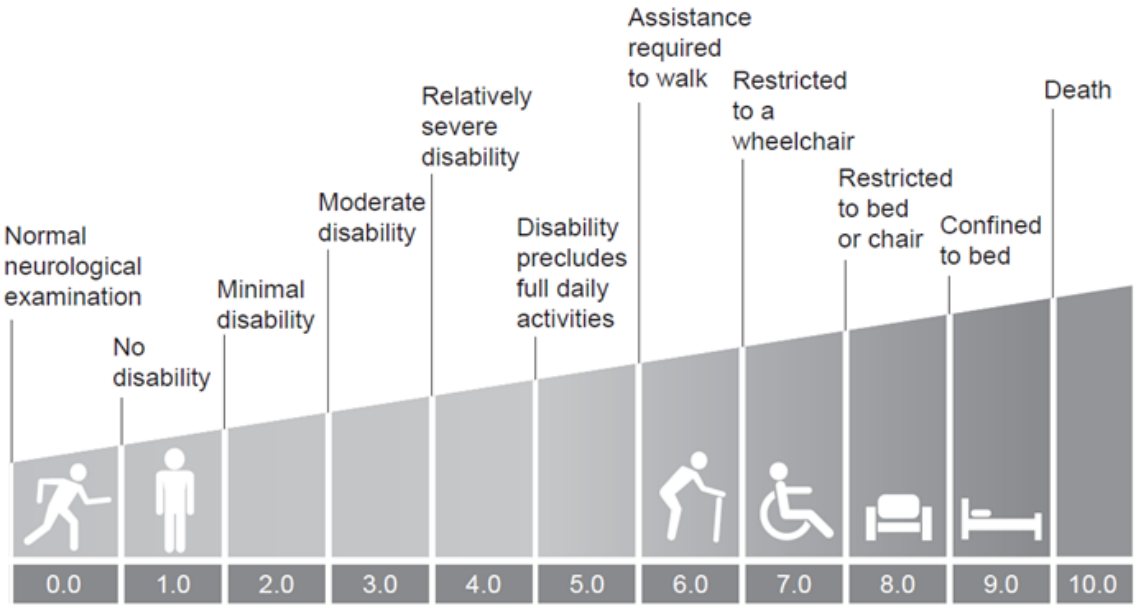
* Used in company's original economic model

How QALYs accrue

Company's original base case



Expanded Disability Status Scale (EDSS) to measure disability progression

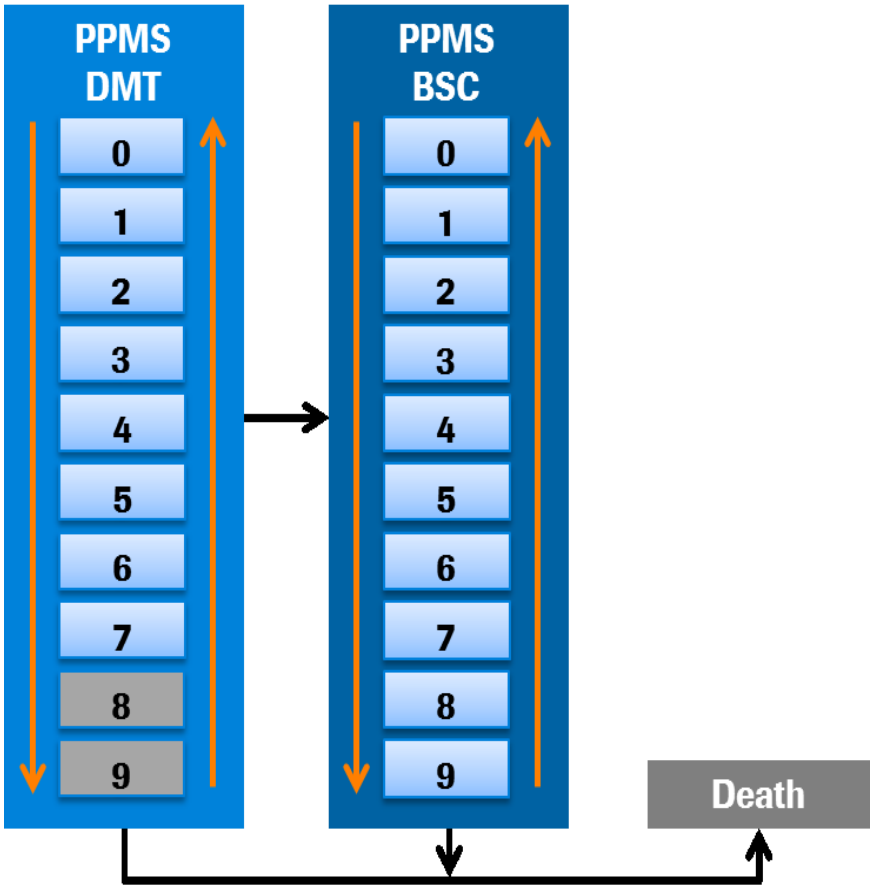


- Per MS Trust EDSS
- **7.0** Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
- **8.0** Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms

https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss

Company's model

- Cohort Markov model, 1 year cycle length
- **Base case population**: 'MRI active'
- Health states defined by EDSS
- Patients transition between EDSS states and can withdraw from active treatment (to best supportive care)
- Treat to EDSS 8 then stop (original base case)
  - RRMS treat to EDSS 7
- Transition probabilities between EDSS states from natural history data (MSBase registry)
  - Patients can improve



DMT: disease modifying therapy
BSC: best supportive care

ACD consultation responses

- Consultees
  - Association of British Neurologists
  - MS Society
  - MS Trust
  - Patient expert
  - Roche
- 52 web comments
- Company submitted new evidence
  - Further evidence: Open label extension of the ORATORIO study
  - Revised base case economic model with updated assumptions

Committee's conclusions (1)

Issue (section of ACD)	Committee's conclusion	Company adjustment	Match committee's preference?
Modelled treatment effect on disease progression (3.7)	Confirmed disability progression CDP-24 preferred to CDP-12	CDP-24 used; but treatment effect from new data (open label extension)	Partially
Relapses (3.8)	Include costs, disutilities and a treatment effect associated with relapses	Included	Yes
Progressive multifocal leukoencephalopathy (3.9)	PML a possible adverse event and should be modelled	PML included in model	Yes
Treatment effect waning (3.11)	True waning effect is likely between company (no waning) and ERG (50% after 5 years)	50% treatment waning effect after 10 years	Partially

Committee's conclusions (2)

Issue (section of ACD)	Committee's conclusion	Company adjustment	Match committee's preference?
Stopping treatment (3.12)	Uncertain how long people take ocrelizumab	50% increase in stopping rate after 5 years (per ERG)	Partially
Stopping rule (3.13)	Considerable uncertainty. Would welcome comments on an acceptable stopping rule during consultation	Treatment stops at EDSS 7.0 as with RRMS (rather than 8.0)	Partially
Utilities for EDSS states (3.14)	Use utility values from Orme et al. (2007) for all EDSS states	Mixture of utilities from ORATORIO and Orme	No
Utility decrement for fatigue (3.15)	Do not include disutility for fatigue separately in model	Removed	Yes
Utility decrement for upper limb dysfunction (3.15)	Do not include disutility for upper limb dysfunction separately in model	Included	No

Consultation comments
Unmet need for treatment (1)

Committee discussion

- PPMS has a substantial effect on the lives of people with the condition and their families. Large unmet need for treatment.
- Slowing disability progression and preserving upper limb function allow people to work, engage in everyday activities and self-care

Association of British Neurologists / MS Society / Multiple Sclerosis Trust / Public

- Huge unmet need for treatment, unlike relapsing remitting MS (RRMS)
- It is “discriminatory” to recommend ocrelizumab for RRMS and not PPMS
- Being diagnosed with untreatable progressive condition has a big effect on mental health; should consider that ocrelizumab provides hope
- Slowing disease progression will reduce costs, reduce need for support from family/friends, maintain independence for longer and allow people to stay in work

Consultation comments
Unmet need for treatment (2)

- Significant differences between PPMS and RRMS
  - PPMS is diagnosed later in life
  - more complications with comorbidities
  - symptoms are harder to manage
- Modelling may not reflect people's experience of 'best supportive care'
  - variable levels of care currently available (for example, physiotherapy)
  - people often have to pay privately for treatment/therapy
- Introducing a treatment for PPMS would "…result in a greater focus on services for progressive MS and a more pro-active approach to managing PPMS which would ultimately benefit a much wider group of people with PPMS than just those who might be eligible for ocrelizumab"

Consultation comments
Increase in MRI scans

Committee discussion
- Identifying patients for ocrelizumab likely to increase MRI scans
- Cost of MRI scans included in modelling

Association of British Neurologists

- Although defining 'active' disease may increase need for MRI "…practical definitions and use of other sequences such as diffusion weighted change may mitigate this burden"

Patient expert

- Identifying people may not increase demand for MRI scans if ORATORIO trial criteria are used to determine eligibility for ocrelizumab

Public

- It is "…discriminatory to suggest that PPMS patients are less-entitled to a possible increase in their MRIs.." and should therefore not have access to an effective treatment
- Regular MRI scans part of best supportive care, so MRI scans should not be considered an additional cost

Background to upper limb dysfunction
ORATORIO 2∘ and exploratory endpoints

Upper limb dysfunction treatment effect based on 20% increase in time to complete 9-hole peg test (9-HPT)

2 ∘ endpoints

- Time to CDP-24
- Change in timed 25-foot walk
- Change in total volume of T2 lesions on MRI scans (week 0 to 120)
- To evaluate the safety of ocrelizumab

Exploratory endpoints

- Change in EDSS score
- Change in Multiple Sclerosis Functional Composite scale (MSFCS)
- **Time to sustained 20 percent increase in timed 25 foot walk and 9-HPT**
- **Proportion of patients with (i) a 20% increase in timed 25 foot walk time, (ii) a 20% increase in 9-HPT**
- **Time to sustained disability progression over the treatment period (EDSS or 25 foot walk time or 9-HPT)**
- Change from baseline in total volume of T2 lesions
- Change in the total number of new or newly enlarging T2 lesions
- Change from baseline in total non-enhancing T1 lesion volume
- Total gadolinium-enhancing T1 lesion count
- Change in brain volume on MRI scans
- Change in cortical gray matter volume
- Change in SF-36 and EQ-5D
- Change in fatigue as measured by the Modified Fatigue Impact Scale (MFIS)

From Montalban et al. (2017)

Consultation comments
Upper limb dysfunction

Committee discussion
- Preserving upper limb function important for all forms of MS
- Not appropriate to model additional utility decrements

Roche
- Excluding utility decrements consistent with RRMS appraisals
- "Whilst we agree that maintaining upper limb function is important for both people with RRMS and those with PPMS, it is more ***relevant*** for people with PPMS"
- EDSS scale is less sensitive to increasing disability at later stages
- Upper limb function affects quality of life ***independent*** of EDSS state in ORATORIO

MS Society / Multiple Sclerosis Trust / Public
- Growing recognition of importance of upper limb function – should use new ways to assess quality of life (beyond EDSS)
- Clinical experts would likely consider that greater importance should be placed on upper limb function in all types of MS

Upper limb dysfunction
ERG's comments

- Company has not provided any further valid reason to support inclusion of utility decrements related to upper limb impairment
- ERG retains concerns about inclusion of utility decrements for upper limb dysfunction
  - Measured as an exploratory outcome in ORATORIO
  - Potential for double counting by including utility decrements for upper limb impairment in addition to utility values for each EDSS level
  - Not included in previous MS appraisals
- ERG's revised base-case still excludes utility decrements related to upper limb dysfunction

⊙ *Does the committee wish to change its conclusion that it is inappropriate to include (model) additional (separate) disutility for upper limb dysfunction?*

Background to discussion on utility
ORATORIO vs Orme et al.

- For base case, company used trial-based EQ-5D and literature-based values (Orme et al.)
- Utility values from ORATORIO higher than those in 2 other identified studies
  - Suggested to be because of lower age in ORATORIO

EDSS	Utility values ORATORIO	Utility values Orme et al.	Carer disutility
0	See ORME	0.837	0.000
1	See ORME	0.766	-0.001
2	0.791	0.672	-0.003
3	0.738	0.541	-0.009
4	0.678	0.577	-0.009
5	0.665	0.485	-0.020
6	0.605	0.425	-0.027
7	0.428	0.264	-0.053
8	See ORME	-0.082	-0.107
9	See ORME	-0.228	-0.140

Consultation comments
Health state utility values for EDSS states

Committee discussion

Use utility values from Orme et al. (2007) for all EDSS states

- ORATORIO utility values higher than Orme; potentially because of lower age of participants in ORATORIO (<55 years)
- Preferred a single source for utility values

Roche

- Few people over 55 years expected to be eligible for treatment with ocrelizumab (reduced inflammatory activity with age)
- Values in Orme from people with PPMS, not specifically early disease *with inflammatory activity*
  - Higher age in Orme suggests few people had inflammatory activity
- Previous RRMS appraisals have used utility values from trials supplemented with Orme et al.
  - Although not ideal to mix utility sources, trial data is best available data for the eligible population

Multiple Sclerosis Trust

- Utility values are lower for people with progressive MS than RRMS; do the utility values from Orme reflect PPMS (rather than MS in general)?

⊙ *Does the committee still prefer Orme et al. to be used for all EDSS states?*

Background to discussion on treatment effect / adjusting for cross over

- Data from **open label extension (OLE)** of ORATORIO provided at consultation (not presented in original submission)
- Original submission had data from double blind controlled period and data from this period plus an 'extended controlled treatment period' (patients remained blinded and on-treatment)
- People completing ORATORIO could enter the OLE; people previously receiving placebo were switched to ocrelizumab
- Company used the Rank Preserving Structural Failure Time (RPSFT) method to adjust for crossover
  - Assumes common treatment effect; company's clinical experts considered this assumption is valid
  - Robustness of adjustment method assessed in sensitivity analysis
  - Alternative method - inverse probability of censoring weighted (IPCW) – was not used because required data on longitudinal data on covariates and patient characteristics was not collected in the OLE

Company new evidence
Open label extension (OLE) of ORATORIO

- Most recent data-cut: nearly 6.5 years follow-up

		'MRI active' subgroup		
		CDP-12	CDP-24	9-hole peg test
Original submission				
Double-blind		0.68 (0.46 to 0.99)	0.71 (0.47 to 1.06)	0.52 (0.32 to 0.85)
New data (submitted at consultation)				
Double-blind + OLE	Unadjusted	[redacted]	[redacted]	[redacted]
	Adjusted (RPSFT)	[redacted]	[redacted]	[redacted]

Treatment effect applied in company's original base case, ERG's base case (committee preferred), company's revised base case

- Increase in risk reduction of CDP over time ('lag time' before reaching maximal effect); crossover-adjusted effect size is robust to different analysis methods and assumptions

Company new evidence
ERG's comments

- OLE based estimates use more mature data than double-blind period only, but at much higher risk of bias:
  - Performance bias – participants are aware of treatment allocation
  - Detection bias – assessors are aware of treatment allocation
- Unclear if analyses were pre-specified because statistical analysis plan for OLE not available
- ERG didn't have individual patient data to validate estimated cross-over effect; but estimated values seem plausible compared to unadjusted ones

⊙ *Which CDP-24 treatment effect does the committee prefer?*

Consultation comments

Treatment waning, treatment duration and stopping rule (1)

Committee discussion

- **Treatment efficacy** may wane over time with ocrelizumab, but the absolute rate of waning is uncertain
  - True waning of treatment effect is likely to lie between company's (no waning) and ERG's (50% after 5 years) approaches
- Considerable uncertainty about how long people would continue to take ocrelizumab
- Considerable uncertainty about an appropriate **stopping rule** for disease-modifying therapies for PPMS

Roche

- ORATORIO OLE data shows sustained effect over 6.5 years of follow-up (see previous slide)
- Negligible proportion of patients develop neutralising antibodies
- In the RRMS appraisal for ocrelizumab, stopping rates were used as a proxy for treatment waning; this should be relevant to PPMS as well
- Disagree that including both waning and stopping rates may have overestimated the rate of stopping

Consultation comments

Treatment waning, treatment duration and stopping rule (2)

- Roche's revised base-case includes:
  - a waning effect of 50% after 10 years (based on recent NICE appraisal of beta-interferons and glatiramer acetate)
  - an increased stopping rates after 5 years (ERG's approach)
  - treatment stopped at EDSS 7.0

Patient expert

- Stopping rule could be: "when there has been no evidence of disease progression i.e. assessed symptom deterioration and /or EDSS score increase, during a preceding 12 month time period."

MS Society

- Use of EDSS 7.0 as a stopping criteria reflects the undue prominence given to mobility over upper limb function in clinical trials
- Treatment should be continued to EDSS 8.0 (or potentially 8.5)

Multiple Sclerosis Trust

- No clinical evidence for treatment waning

Treatment waning, treatment duration and stopping rule ERG's comments

- No apparent sign of effect waning up to the end of observation period of the OLE study (6 ½ years)
  - Reasonable evidence to support absence of waning effect from 5 years as in ERG's original base-case
  - But still considerable uncertainty about longer term treatment waning
  - ERG's revised base-case assumes treatment waning from 7 years
- Company's inclusion of a waning effect from 10 years and increased rate of treatment discontinuation from 5 years is inconsistent and does **not** match the ERG's approach (time of waning and treatment discontinuation linked)
  - Company have used different annual discontinuation rates to ERG
- Use of **stopping rule** at EDSS 7.0 (rather than 8.0 in original submission) is reasonable

- *Does the committee have a preferred approach to modelling treatment waning, treatment discontinuation and a stopping rule for treatment?*
  - *Should treatment waning start at 5, 7 or 10 years? Or be excluded?*
  - *Should waning and treatment discontinuation be linked in the model, or modelled independently?*
  - *When should treatment be stopped?*

Consultation comments

Probabilities for baseline transitions between EDSS states

Committee discussion

Concerns about using the MSBase registry data to inform baseline transitions between EDSS states - use causes uncertainty in model results

- Not restricted to people with MRI scans showing inflammation
- Data largely from Eastern Europe

Roche

- MSBase cohort used matches ORATORIO inclusion criteria (early PPMS)
- Canada, Spain, Italy, Netherlands and Australia accounts for 80% of data
  - Adhere to similar definitions of PPMS diagnosis and treatment as UK
- MSBase registry currently represents the best available evidence
- Placebo arm of ORATORIO has fewer data so more uncertainty
- Registry data preferred to trial data for deriving long-term natural history in previous NICE RRMS appraisals

Patient expert

- Has the **MS Register** been considered as a data source?

⊙ *Have the company's clarifications of the population in the MSBase cohort addressed any of committees uncertainties with its use?*

Cost effectiveness results
Company's proposed pricing

- At the last meeting:
  - List price – not shown
  - Patient access scheme (PAS discount) price currently available for ocrelizumab in RRMS was considered
  - Company also proposed 'Managed access' arrangement – collection of further evidence alongside a commercial offer. Committee concluded
    - further evidence would not address relevant uncertainties
    - proposed commercial offer was not cost effective
- Proposed new commercial offer:
  - Different discounts for RRMS and PPMS
  - Not approved by NHS England; can only consider these types of arrangements in specified circumstances:
    - Products entering CDF
    - Products evaluated through HST Programme
    - Legacy CDF
- **Reminder:** Beyond the remit of NICE to negotiate price – can only consider prices agreed with NHSE (*4.6 TA process guide*)
- **Reminder:** Complex PASs may be specific to one or more indications; but a PAS should only modify the cost of a single product. NHS E unlikely to agree to more than one PAS per medicine (*5.34 PPRS 2014*)

Cost effectiveness results
Company's revised base case

- Company states that its revised base case incorporates committee preferences, ***except***:
  1. CDP-24 treatment effect now from crossover adjusted OLE data
  2. Uses ORATORIO data and Orme et al. for EDSS state utilities (rather than Orme for all states)
  3. Includes separate utility decrement for upper limb function

- In addition, company now uses the UK MS Survey as the source of EDSS costs (to match approach used for RRMS appraisal)

ERG: Welcomed this change

Company's revised model results with patient access scheme discount (PAS)

Base case analysis

Population	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
MRI active	£62,766	£67,336

ICER = incremental cost effectiveness ratio

Selected scenario analyses

Scenario	ICER (£/QALY) (*Deterministic*)
CDP-24 (double blind period only) used for treatment effect	£92,331
No treatment waning	£59,079
Stopping rule set to EDSS 8.0	£63,592
Utility decrement for upper limb impairment ***excluded***	£69,282
EDSS state utilities from Orme et al.	£69,318

- Lowest ICER in scenario analyses is £50,396 per QALY gained (assuming only progression between EDSS states allowed)

ERG's scenario analyses in company's model

Scenario	ICER (£/QALY) (*Deterministic*)
• Treatment waning: 50% decrease in treatment effect from year **7**, and • Increase in rate of people stopping treatment (year **7**+)	£67,400
Included non-medical direct costs	£60,300

- 2 additional ERG scenario analyses replicate those done by company

ERG's revised base case

	Company's base case	ERG's base case
Treatment effect	CDP-24: OLE data	CDP-24: Double-blinded controlled period data
Treatment waning effect	50% reduction in treatment effect from year **10** onwards	50% reduction in treatment effect from year **7** onwards
Stopping treatment – extrapolating beyond trial	Gompertz: increase in annual discontinuation rate from year 5	Gompertz: increase in annual discontinuation rate from year 5 – **but** annual discontinuation rates calculated differently
EDSS utility values	From ORATORIO and Orme et al. (2007)	From Orme et al. (2007)
Stopping rule	At EDSS 7.0	At EDSS 7.0
Utility decrement for upper limb impairment	Included	Excluded
Non-medical direct costs	Excluded	Included

ERG's revised model results with patient access scheme discount (PAS)

Base case analysis

Population	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
MRI active	£130,300	£136,500

ERG's scenario analyses

Scenario	ICER (£/QALY) (*Deterministic*)
Efficacy set to CDP-24 (OLE data)	£88,900
• Treatment waning: 50% decrease in treatment effect from year **5**, and • Increase in rate of people stopping treatment (year **5**+)	£141,200
Including EDSS utility values from ORATORIO	£116,300
Including utility decrements for upper limb dysfunction	£113,700
Stopping rule set to EDSS 8.0	£135,500