Ocrelizumab is a second generation, fully humanised anti-CD20 monoclonal antibody. The antibody is designed to selectively target the CD20 surface antigen on B-cells; once bound to the target antigen, ocrelizumab recruits the immune system to attack and destroy marked B-cells. Ocrelizumab is intended for the treatment of relapsing-remitting multiple sclerosis (RRMS). It is administered via intravenous (IV) infusion at 600mg every 24 weeks on a continuing basis (dual infusions of 300mg on day 1 and 15 of cycle 1, followed by single infusions of 600mg on day 1 of each subsequent cycle). Ocrelizumab has the potential to reduce relapse rate, and disease activity as measured by brain lesions and clinical disease activity, defined by absence of both EDSS disability progression and clinical relapse and if licenced will offer an alternative treatment option for patients with RRMS.

MS is a chronic immune-mediated condition of the central nervous system characterised by demyelination and axonal degeneration. Resultant damage leads to a wide spectrum of symptoms and signs, potentially including difficulties with weakness, sensory disturbance balance and vision. In MS, the immune system damages the myelin sheath, which is formed of outgrowths of glial cells insulating the axons of neurones, thus allowing rapid conduction of electrical signals. Damage to the myelin sheath disrupts the transfer of these nerve signals leading to MS related symptoms. Relapsing-remitting MS describes the clinical situation where a patient experiences neurological events (relapses), representing bouts of central nervous system inflammation, which are typically followed by periods of recovery and relative neurological stability (remissions). The prevalence of MS in England is approximately 0.16%, equivalent to approximately 85,600 affected people in England. Approximately 35.5% of patients have relapsing-remitting disease.

Ocrelizumab is currently undergoing two phase III clinical trials evaluating its effect on clinical relapse rate compared to interferon beta-1a. These trials are both expected to be complete by January 2020. A phase II clinical trial evaluating the effect of ocrelizumab on disease activity as measured by brain lesions compared with interferon beta-1a was published in 2011.
TARGET GROUP

- Multiple sclerosis (MS): relapsing-remitting (RRMS).

TECHNOLOGY

DESCRIPTION

Ocrelizumab (2H7v114; 2H7v16; PRO 70769; RG1594; R 1594; rhuMab 2H7) is a second generation, fully humanised anti-CD20 monoclonal antibody. The antibody is designed to selectively target the CD20 surface antigen on B-cells; once bound to the target antigen, ocrelizumab recruits the immune system to attack and destroy marked B-cells. Ocrelizumab is intended for the treatment of RRMS. It is administered via intravenous (IV) infusion at 600mg every 24 weeks on a continuing basis (dual infusions of 300mg on day 1 and 15 of cycle 1, followed by single infusions of 600mg on day 1 of each subsequent cycle).

Ocrelizumab does not currently have Marketing Authorisation in the EU for any indication.

Ocrelizumab is also currently in phase III clinical trials for primary progressive MS.

INNOVATION and/or ADVANTAGES

If licensed, ocrelizumab will offer an additional treatment option for patients with RRMS. The company state that ocrelizumab has the potential to reduce relapse rate, and disease activity as measured by brain lesions and clinical disease activity, defined by absence of both EDSS disability progression and clinical relapse.

DEVELOPER

Roche Products Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

MS is a chronic immune-mediated condition of the central nervous system characterised by demyelination and axonal degeneration\(^1\). Resultant damage leads to a wide spectrum of symptoms and signs, potentially including difficulties with weakness, sensory disturbance balance and vision\(^a\). In MS, the immune system damages the myelin sheath, which is formed from outgrowths of glial cells which insulate the neuronal axons, thus allowing rapid conduction of electrical signals\(^a\). Damage to the myelin sheath disrupts the transfer of these nerve signals leading to MS related symptoms\(^2,3\). Relapsing-remitting MS describes the clinical situation where a patient experiences neurological events (relapses), representing bouts of central nervous system inflammation, which are typically followed by periods of

\(^a\) Expert personal communication.
recovery and relative neurological stability (remissions). Although there is no typical frequency, an average patient might have a relapse every year or so, with good or complete remission in between\(^b\). After two decades of relapsing remitting disease, a significant proportion of patients (>50%) enter a secondary progressive phase, during which relapses cease or become less frequent, but the patient instead notes a slow progressive increase in their disability\(^4,b\).

### NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


### CLINICAL NEED and BURDEN OF DISEASE

MS is usually diagnosed between the ages of 20 and 40 years\(^5\) with a relatively low incidence but high prevalence\(^6\). The prevalence of MS in England is approximately 0.16%, equivalent to approximately 85,600 affected people in England. Approximately 35.5% of patients have relapsing-remitting disease, equating to around 30,388 people in England and an estimated 38.75% (11,775) of these will be eligible for drug treatment with disease modifying treatments (DMTs)\(^7\). The incident population starting treatment for MS each year in England is approximately 1,600 people.

MS has limited impact on longevity; however it causes considerable disability and impacts on employment and quality of life, with walking impairment being the most prominent disability, affecting up to 85% of people with MS\(^8\). Numbness of the face, body, or extremities is also common, and is often the first symptom experienced prior to diagnosis\(^9\), and around 80% will experience tremor or ataxia at some point during their illness. Fatigue and bladder dysfunction are also common, affecting approximately 75% of people with MS\(^10\). Cognitive impairment occurs in up to 65% of patients at any stage of the disease and is usually irreversible\(^11,12\). Bowel dysfunction, including constipation or loss of bowel control, affects up to 50% of patients\(^13\).

In 2012-13 there were 38,080 admissions for MS in England, resulting in 58,892 bed days and 40,418 finished consultant episodes\(^14\). In England and Wales, 1,218 deaths due to MS were registered in 2012\(^15\) (ICD10 G35).

\(^b\) Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Alemtuzumab for treating relapsing-remitting multiple sclerosis (TA 312). May 2014\(^{16}\).
- NICE technology appraisal. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). January 2014\(^{17}\).
- NICE technology appraisal. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (TA127). August 2007\(^{19}\).

Other Guidance

- Gilhus NE, Barnes MP and Brainin M. Acute Relapses of Multiple Sclerosis. 2010\(^{22}\).
- Royal College of Physicians, National Council for Palliative Care, British Society of Rehabilitation Medicine. Long-term neurological conditions: management at the interface between neurology, rehabilitation and palliative care. 2008\(^{24}\).

CURRENT TREATMENT OPTIONS

Current approaches to the management of MS include\(^{16,17,18,19,20,21,25}\):

- Reduction of disease activity (particularly relapse rates) through the use of immunomodulators or DMTs:
  - Alemtuzumab (Lemtrada) – for adults with active relapsing–remitting MS.
  - Teriflunomide (Aubagio) – for active relapsing–remitting MS only if they do not have highly active or rapidly evolving severe disease.
  - Interferon beta-1a (Rebif, Avonex) and interferon beta-1b (Betaferon, Extavia) (not recommended by NICE).
Fingolimod (Gilenya) – for highly active MS or patients who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.

Glatiramer acetate (Copaxone) (not recommended by NICE).

Natalizumab (Tysabri) – for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

Dimethyl fumarate (Tecfidera) – for adults with relapsing-remitting MS (NICE technology appraisal expected August 2014).

Mitoxantrone (unlicensed for this indication) – occasionally used in patients with rapidly progressive disease.

Unlicensed immunosuppressants are sometimes also used, including methotrexate, cyclophosphamide and azathioprine.

- Treatment of acute exacerbations with corticosteroids.
- Treatment of chronic symptomatology through pharmacological approaches alongside physiotherapy, speech and language therapy and occupational therapy and occasionally surgery.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>OPERA I, NCT01247324; ocrelizumab vs interferon beta-1a; phase III.</th>
<th>OPERA II, NCT01412333; ocrelizumab vs interferon beta-1a; phase III.</th>
<th>NCT00676715; ocrelizumab vs interferon beta-1a vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
<td>Publication, trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=821 (planned); aged 18-55 years; MS; ≥2 clinical attacks within 2 years of screening or one clinical attack in the year prior to screening (but ≥30 days prior to screening); neurological stability ≥30 days; Expanded Disability Status Scale (EDSS) 0-5.5 inclusive; disease duration of &lt;10 years in patients with EDSS score ≤2.0 at screening; no contraindications for MRI.</td>
<td>n=835 (planned); aged 18-55 years; MS; ≥2 clinical attacks within 2 years of screening or one clinical attack in the year prior to screening (but ≥30 days prior to screening); neurological stability ≥30 days; Expanded Disability Status Scale (EDSS) 0-5.5 inclusive; disease duration of &lt;10 years in patients with EDSS score ≤2.0 at screening; no contraindications for MRI.</td>
<td>n=220; MS; relapsing-remitting; no secondary or primary progressive disease; no previous treatment with rituximab or lymphocyte-depleting therapies; no use of lymphocyte trafficking blockers ≥ 24 weeks; no use of β interferons, glatiramer acetate, IV immunoglobulin, plasmapheresis, or immunosuppressive treatments ≥12 weeks or use of systemic glucocorticoids ≥4 weeks.</td>
</tr>
</tbody>
</table>

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*Expert personal communication.*
<table>
<thead>
<tr>
<th>Schedule</th>
<th>Randomised to ocrelizumab 600mg IV every 24 weeks (dual infusions of 300 mg on day 1 and 15 of cycle 1, single infusion of 600 mg on day 1 of each subsequent cycle) in combination with placebo SC 3 times weekly; or interferon beta-1a (Rebif) SC (8.8µg on weeks 1 and 2; 22µg on weeks 3 and 4; 44µg on week 5 and subsequent weeks) 3 times weekly in combination with placebo IV every 24 weeks (dual infusions on day 1 and 15 of cycle 1; single infusion on day 1 of each subsequent cycle).</th>
<th>Randomised to ocrelizumab 600mg IV every 24 weeks (dual infusions of 300 mg on day 1 and 15 of cycle 1, single infusion of 600 mg on day 1 of each subsequent cycle) in combination with placebo SC 3 times weekly; or interferon beta-1a (Rebif) SC (8.8µg on weeks 1 and 2; 22µg on weeks 3 and 4; 44µg on week 5 and subsequent weeks) 3 times weekly in combination with placebo IV every 24 weeks (dual infusions on day 1 and 15 of cycle 1; single infusion on day 1 of each subsequent cycle).</th>
<th>Randomised to ocrelizumab 600mg IV (dual infusions of 300 mg on day 1 and 15 of cycle 1, single infusion of 600 mg on day 1 of subsequent 24 week cycles) in combination with placebo IV; or ocrelizumab 2,000mg IV (dual infusions of 1,000 mg on day 1 and 15 of a 24 week cycle followed by 1,000mg IV for the subsequent treatment cycles); or interferon beta-1a 30µg once weekly for one 24 week cycle; or placebo IV on day 1 and day 15 of a 24 week cycle. Patients in the placebo group and interferon beta-1a groups switched to ocrelizumab 600mg IV (dual infusions of 300 mg on day 1 and 15 of cycle 1, single infusion of 600 mg on day 1 of subsequent 24 week cycles). Patients receiving ocrelizumab or placebo received methylprednisolone 100mg IV to reduce potential infusion-related reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Active treatment for 96 weeks.</td>
<td>Active treatment for 96 weeks.</td>
<td>Active treatment for 72 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Annualised protocol-defined 2 year relapse rate at 96 weeks.</td>
<td>Annualised protocol-defined 2 year relapse rate at 96 weeks.</td>
<td>Number of gadolinium-enhancing T1 lesions observed on brain MRI scans at weeks 12, 16, 20, and 24.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Time to onset of sustained disability progression of at least 12 weeks; time to onset of sustained disability progression of at least 24 weeks; proportion of relapse-free patients; change in total T2 lesion volume as detected by brain MRI; total number of new, and/or enlarging T2 hyperintense lesions as observed on brain MRI.</td>
<td>Time to onset of sustained disability progression of at least 12 weeks; time to onset of sustained disability progression of at least 24 weeks; proportion of relapse-free patients; change in total T2 lesion volume as detected by brain MRI; total number of new, and/or enlarging T2 hyperintense lesions as observed on brain MRI.</td>
<td>Annualised protocol-defined relapse rate; proportion of relapse-free patients; total number of gadolinium-enhancing T1 lesions to week 24; change in total volume of T2 lesions from baseline to week 24; safety and tolerability of two dose regimen; safety up to 96 weeks. No quality of life</td>
</tr>
<tr>
<td>Key results</td>
<td>Adverse events (AEs)</td>
<td></td>
<td></td>
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<tr>
<td>Results are expected in Q3-4 2015.</td>
<td>For ocrelizumab 600mg, ocrelizumab 2,000mg, interferon beta-1a, and placebo respectively: AEs to week 24, 62%, 66%, 56% and 70%. Serious infections occurred at similar rates in ocrelizumab and placebo patients. One patient in the 2000mg group died in week 14. At first infusion, more patients given 600mg 35% (95% CI, 22–47) and 2,000 mg, 44% (95% CI, 31–57) ocrelizumab had</td>
<td></td>
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</table>
infusion-related adverse events than did those in the placebo group 9%, (95% CI, 2–17).

From 24–48 weeks there was no imbalance in AEs for the treatment groups, and serious AEs were similar.

No opportunistic infections or clinically relevant abnormal laboratory changes were recorded.

### ESTIMATED COST and IMPACT

#### COST

The cost of ocrelizumab is not yet known.

The cost of selected comparator treatments are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost[^10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a (Rebif)</td>
<td>44mg, SC, 3 times weekly.</td>
<td>£8,942[^31,32]</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex)</td>
<td>30mg, IM, once weekly.</td>
<td>£8,502</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>500mg daily.</td>
<td>£19,110</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300mg, IV, 4 weekly.</td>
<td>£14,690</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>20mg daily.</td>
<td>£5,823[^1,35]</td>
</tr>
<tr>
<td>Alemtuzumab (Lemtrada)</td>
<td>5 daily consecutive 12mg doses in year 1, followed by 3 daily consecutive 12mg doses 12 months later in year 2.</td>
<td>Yr 1 cost: £35,225 Yr 2 cost: £21,135[^34]</td>
</tr>
<tr>
<td>Dimethyl Fumarate (Tecfidera)</td>
<td>120mg oral twice daily; increased to 240mg oral twice daily after 7 days.</td>
<td>£18,192</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>14mg once daily.</td>
<td>£13,492</td>
</tr>
</tbody>
</table>

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability: potential for increased periods of clinical remission.

- Other:
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services:
- Decreased use of existing services: potential for delayed progression of disease.
- Re-organisation of existing services
- Need for new services
- None identified
- Other: as things stand, delivery should be relatively straightforward. All neuroscience centres should be equipped to provide natalizumab and adapting the equipment and personnel to ocrelizumab would not be an issue.

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs: potential for increased periods of clinical remission.
- None identified
- Other: increase or reduction in drug treatment costs depending on comparator.

Other Issues

- Clinical uncertainty or other research question identified: expert opinion suggests that the place of ocrelizumab in the treatment pathway will depend upon the results of the phase III clinical trials which will need to be balanced against short and long term side effect profiles and tolerability as none of the comparator treatments provide an optimal balance of therapeutic efficacy versus side effects.

However, it is likely that ocrelizumab will be targeted for second line use, as a potential alternative for alemtuzumab, fingolimod and/or natalizumab. All of these have superior efficacy to first line agents, but have disadvantages: alemtuzumab requires an involved monitoring protocol, fingolimod requires inpatient hospitalisation for cardiac monitoring at the point of initiation, and natalizumab has a well-recognised risk of progressive multifocal leukoencephalopathy. Should ocrelizumab prove at least equally effective to these agents (preferably as effective as alemtuzumab) but have a superior safety profile and convenient dosing regimen (infusions every 24 weeks), this could be a significant advance. This latter aspect could be particularly important – e.g. natalizumab requires infusions every 4 weeks.

Expert also states that there are no particular issues of clinical uncertainty at present, as the trial protocols are well described and uncontroversial.

- None identified

* Expert personal communication.
REFERENCES

8 Harris Interactive. Experiences with Multiple Sclerosis (MS): Perspectives of People with MS and MS Care Partners. Poll commissioned by: Acorda Therapeutics Inc and the National MS Society. March 2008.
27 ClinicalTrials.gov. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis.