Document Control

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1. Introduction

1.1. Multiple sclerosis (MS) is a progressive neurological condition. 80-90% of people are diagnosed with relapsing remitting MS, their disease trajectory is categorised by periods of relapse and remission. Others experience a non- relapsing progressive disease, primary progressive MS (PPMS).

1.2. Disease modifying drugs (DMD) are treatments predominately for people with relapsing remitting MS with the aim to reduce the number of relapses. Ocrelizumab is the first DMD licenced by NICE (National Institute for Clinical Excellence) for PPMS.

2. Background

2.1. This is a new guideline following the licensing of Ocrelizumab in 2018. Ocrelizumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

In addition Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

2.2. The Roche trade name for their product is Ocrevus® throughout this document Ocrelizumab will be used for consistency.

2.3. Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The precise mechanism through which Ocrelizumab exerts its therapeutic clinical effects in MS is not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B cells. The capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

OCRELIZUMAB IN ADULT MULTIPLE SCLEROSIS

3. Education

4. Issues to consider when assessing eligibility and to discuss with the person pre-treatment:

4.1. Treatment Indication and Purpose

The key evidence for the clinical effectiveness of Ocrelizumab compared with interferon beta-1a came from 2 trials, OPERA I (n=821) and OPERA II (n=835). These were phase III randomised controlled trials in adults with relapsing multiple sclerosis, with 2 or more relapses in the last 2 years or with 1 relapse in the last year. The trial included people 55 years or younger. The committee heard from clinical experts that this is common across similar trials and that only a few people over 55 years would likely have Ocrelizumab. The

NICE Panel concluded that the results of the clinical trials were generalisable to NHS clinical practice.

Ocrelizumab reduces relapses and slows disability progression compared with interferon beta-1a.

Open-label extension data show sustained efficacy of Ocrelizumab over 4 years.

Outcome	Ocrelizumab (600 mg)	Interferon beta-1a (44 micrograms)
Annualised relapse rate at week 96 (OPERA I)	0.16 (95% CI 0.12 to 0.20)	0.29 (95% CI 0.24 to 0.36)
Annualised relapse rate at week 96 (OPERA II)	0.16 (95% CI 0.12 to 0.20)	0.29 (95% CI 0.23 to 0.36)
Confirmed disability progression at 3 months* (pooled analysis OPERA I and OPERA II)	9.8 (95% CI 7.6 to 11.9)	15.2 (95% CI 12.6 to 17.8)
Confirmed disability progression at 6 months* (pooled analysis OPERA I and OPERA II)	7.6 (95% CI 5.7 to 9.5)	12.0 (95% CI 9.6 to 14.4)
Abbreviations: CI, confidence interval.		
*Kaplan–Meier estimate for the proportion of patients with the outcomes specified in the table, 96 weeks from the start of trial.		

Table 1 OPERA I and II annualised relapse rate and confirmed disability progression.

Ocrelizumab is dosed every 6 months with **no routine testing between dosing**.

4.2. Fertility, Pregnancy and Breast Feeding

Women of childbearing potential should use contraception while receiving Ocrelizumab and for 12 months after the last infusion.

Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Women should be advised to discontinue breast-feeding during Ocrelizumab therapy.

4.3. Vaccinations

The safety of immunisation with live or live-attenuated viral vaccines, following Ocrelizumab therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and not until B cell repletion. Patients who require vaccinations should complete their immunisation at least 6 weeks prior to initiation of Ocrelizumab.

4.4. Exposure in utero to Ocrelizumab and Vaccination of Infants:

Infants of mothers who have been exposed to Ocrelizumab during pregnancy should be monitored for B-cell depletion and vaccinations with live and live attenuated vaccines should be postponed until the infant's B-cell count has recovered. The safety and timing of vaccination should be discussed with the infant's physician.

5. Warning and Precautions

5.1. Contraindications

Hypersensitivity to the active substance or to any of the excipients (Sodium Acetate Trihydrate, Glacial Acetic Acid, Trehalose Dihydrate, Polysorbate 20, Water for Injection)

5.2. Infection

Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved. It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients (e.g. patients with lymphopenia, neutropenia, hypogammaglobulinemia) should not be treated.

5.3. Progressive Multifocal Leukoencephalopathy (PML)

No cases of PML were identified in Ocrelizumab clinical trials. A risk of PML cannot be ruled out since PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies.

Cases of carry over PML have been reported in patients treated with other MS therapies prior to starting Ocrelizumab.

No routine JCV (John Cunningham Virus) is required.

5.4. Hepatitis B Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with anti-CD20 antibodies. HBV screening should be performed in all patients before initiation of treatment with Ocrelizumab.

Patients with active HBV (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with Ocrelizumab.

Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody (HBcAb +); carriers of HBV (positive for surface antigen, HBsAg+) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

5.5. Malignancies

An increased number of malignancies (including breast cancers) have been observed in clinical trials in patients treated with Ocrelizumab compared to control groups. However, the incidence was within the background rate expected for an MS population. Individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients should follow standard breast cancer screening as per local guidelines.

5.6. Severely Immunocompromised Patients

In other auto-immune conditions, the use of Ocrelizumab concomitantly with immunosuppressive medications resulted in an increase of serious infections, including opportunistic infections. It is not recommended to use other immunosuppressants concomitantly with Ocrelizumab except corticosteroids for symptomatic treatment of relapses.

When initiating Ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after Ocrelizumab, the potential for overlapping pharmacodynamic effects should be taken into consideration.

6. Screening Tests to Be Done Prior To Starting Therapy

- Full Blood count
- Hepatitis B and C
- HIV (Human Immunodeficiency Virus)
- Liver Function Tests
- Renal Function Test
- Varicella zoster virus antibody
- Measles serology
- Mumps serology
- Rubella serology
- Quantiferon Test

6.1. Radiology

- Chest X-ray
- MRI reviewed within last 12 months

7. Funding Approval

Ocrelizumab must have funding approval made each year of treatment via the Blueteq online system. This will ensure NHS England funding can be claimed for the treatment

8. Referral to Ms Specialist Nurse

Neurologist refers to MS specialist nurse for further education and if patient meets above criteria.

MS Specialist Nurse:

- Continues education and provides written information.
- Informs neurologist if there are any outstanding screening tests.
- Advises neurologist if person happy to proceed.
- Arranges appointment with Seamoor Unit.

9. Treatment

9.1. Storage

An unopened vial (300 mg) has a shelf life of 18 months and must be stored in a refrigerator (2°C – 8°C). Vials should be kept in the original packaging to protect from light. Do not freeze the vial.

9.2. Preparation

Ocrelizumab should be prepared by an appropriately qualified person using aseptic technique. Ocrelizumab must be diluted and should not be administered as an intravenous push or bolus. Do not shake the vial. Do not use the product if discoloured or if it contains foreign particles.

Once reconstituted Ocrelizumab should be administered immediately to minimise risk of microbial contamination. Only in exceptional circumstances (seek advice from pharmacist) should it be stored between 2^{o}C to 8^{o}C protected from light and discarded if not used after 8 hours.

(See 9.4. for dosing and administration)

9.3. Prior to Administration

Premedication must be administered prior to each Ocrelizumab infusion to reduce the frequency and severity of infusion-related reactions (IRR):

- 125 mg intravenous methylprednisolone (or an equivalent) 30 minutes prior to each Ocrelizumab infusion,
- Oral antihistamine 30-60 minutes prior to each Ocrelizumab infusion.
- An antipyretic (e.g paracetamol) may also be considered 30-60 minutes prior to each Ocrelizumab infusion.

9.4. Dosing and Administration

Dose 1:

Is divided into two doses given on Day 1 and Day 15

300 mg of Ocrelizumab (1 vial) is diluted into 250mls of sterile isotonic 0.9% NaCl solution (300 mg/250 mL)

Subsequent Doses:

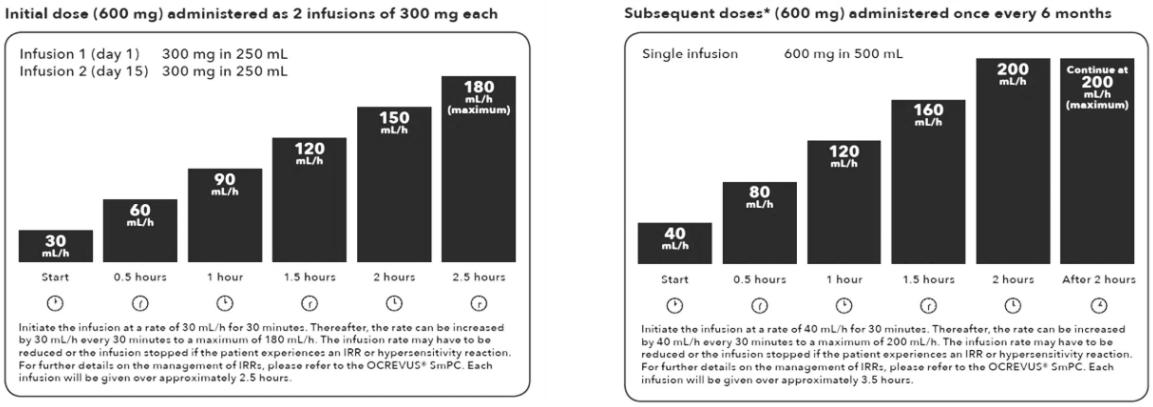
600 mg of Ocrelizumab (2 vials) is diluted into 500mls of sterile isotonic 0.9% NaCl solution (600 mg/500 mL)

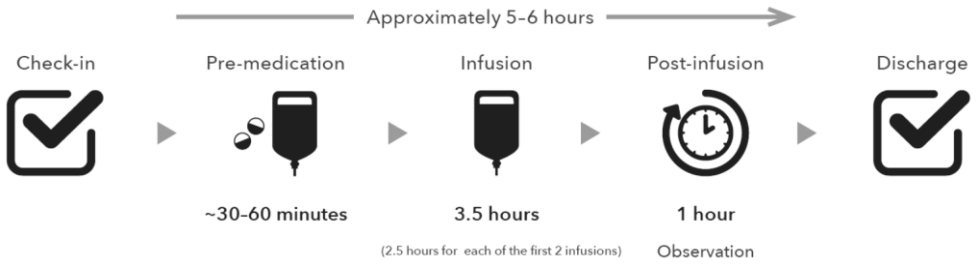
The diluted solution must be administered using an infusion set with a 0.2 or 0.22 micron in-line filter. Prior to the start of the intravenous infusion, the content of the infusion bag must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Dose 2:

The second dose should be administered 6 months after the first infusion of the initial dose. If a planned Ocrelizumab infusion is missed, patients should not wait until the next planned dose and Ocrelizumab should be administered as soon as possible.

The infusion rate should increase incrementally to monitor and respond to identified Infusion Related Reactions (IRR) :





9.5. Infusion Related Reactions

The most important and frequently reported adverse drug reactions were IRR and infections.

IRR were most common on the first infusion, rates of IRR decreased with subsequent doses. There were no fatal IRR.

IRR in the Ocrelizumab clinical studies included, but were not limited to:

pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea, tachycardia.

Infusion adjustments in the instance of IRR:

Mild to moderate[1]

e.g headache or other mild to moderate IRR

Reduce infusion rate to half that at the onset of the event and maintain for **at least 30 minutes**

If tolerated, increase the infusion rate according to the initial schedule

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Severe[1]

e.g. dyspnea or a complex of flushing, fever, and throat pain symptoms or similar IRR

Interrupt the infusion immediately and provide symptomatic treatment

Restart the infusion **after all symptoms have resolved** at half the rate of that at the time of IRR onset

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Life-threatening[1]

e.g. acute hypersensitivity, acute respiratory distress syndrome or similar IRR

Immediately stop the infusion and provide appropriate treatment

Ocrelizumab should be **permanently discontinued**

Patients treated with Ocrelizumab should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR. Clinicians should alert patients that an IRR can occur within 24 hours of infusion.

Hypotension may occur during the infusion. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each Ocrelizumab infusion. If this is indicated it will be recorded in the Treatment Record.

9.6. Records

A summary of each infusion is written in the Treatment Record and Prescription Chart.

9.7. Testing and Monitoring

The patients will be neurologically reviewed regularly either at the infusion appointment or in clinic by the consultant neurologist and / or MS nurse.

There is no routine testing recommended between dosing however it is recommended to verify the patients' immune status before dosing since immunocompromised patients' should not be treated.

Clinicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms, as these can be similar to MS disease.

9.8. Adverse Events

ADRs Reported with Ocrelizumab (in RMS)

ADR (MedDRA) System Organ Class	Very Common (≥10%)	Common (≥1% - <10%)
Infections and infestations	Upper respiratory tract infection, nasopharyngitis, influenza	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis
Respiratory, thoracic and mediastinal disorders		Cough, catarrh
Investigations	Blood immunoglobulin M decreased	Blood immunoglobulin G decreased
Blood and lymphatic system disorders		Neutropenia
Injury, poisoning and procedural complications	Infusion-related reactions	

10. Monitoring Compliance with This Guideline

Review of medical, therapy and nursing documentation by Clinical Audit and Post Marketing Surveillance programs

11. References

- Ocrelizumab / Ocrevus® Patient information leaflet
- Ocrelizumab / Ocrevus® Summary of product characteristics