OCRELIZUMAB (Ocrevus®) PROTOCOL FOR THE TREATMENT OF RELAPSING MULTIPLE SCLEROSIS (RMS)

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Ocrelizumab Therapy for Relapsing Multiple Sclerosis (RMS)

INDICATIONS FOR USE:

*INDICATION	ICD10	Protocol Code
Ocrelizumab (Ocrevus®) is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	G35	MS102

**Ocrelizumab (Ocrevus®) is also licensed for primary progressive MS (PPMS); this protocol is for the RMS indication only.*

Treatment with ocrelizumab (Ocrevus®) should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions.

ELIGIBILTY:

- Indication as above.
- Adult patients aged 18 years or older.
- The prescribing consultant has received approval for use from the HSE Corporate Pharmaceutical Unit.
- The company provides ocrelizumab according to any commercial in confidence arrangements agreed with the HSE.

CONTRAINDICATIONS:

- Hypersensitivity to ocrelizumab or to any of the excipients.
- Current active infection until resolution.
- Active hepatitis B viral infection. Hepatitis B virus (HBV) screening should be performed in all patients prior to initiation of treatment with ocrelizumab as per local guidelines. See **ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS** Section for further information.
- Patients in a severely immunocompromised state. Concomitant use of immunosuppressants is not recommended with ocrelizumab except corticosteroids for symptomatic treatment of relapses.
- Known active malignancies.
- Progressive Multifocal Leukoencephalopathy (PML).

PREGNANCY AND BREASTFEEDING:

- Pregnancy: ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Refer to **ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS** section for recommendations relating to vaccinations in infants of mothers who have been exposed to ocrelizumab during pregnancy.

- Women of child bearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion.
- Breastfeeding: women should be advised to discontinue breast-feeding during ocrelizumab therapy.

See the Summary of Product Characteristics for Ocrevus® for full prescribing information; available from: https://www.medicines.ie/medicines/ocrevus-300-mg-concentrate-for-solution-for-infusion-33182/smpc .

TESTS:

Baseline Measures:

MRI within 3 months prior to treatment, to serve as baseline.

Baseline tests:

- Full Blood Count (FBC)
- Neutrophil, IgG, IgA, and IgM titres
- Liver Funtion Tests (LFTs)
- Urea & Electrolytes (U&Es)
- Serum creatinine (SrCr)
- John Cunningham Virus (JCV) serology – if JCV antibody positive and switching from natalizumab assess for evidence of PML (cerebrospinal fluid JCV PCR and recent MRI review)
- HIV serology
- Hepatitis B virus serology: anti-Hepatitis B core Antibody, Hepatitis B Surface Antigen and anti-Hepatits B Surface Antibody
- Hepatitis C virus serology
- Varicella Zoster Virus (VZV) Serology - VZV vaccination of antibody-negative patients should be considered. VZV vaccination should be administered at least 6 weeks in advance of treatment.
- Evaluation for active or latent TB as per local guidelines
- Discuss vaccination status with the patient, as appropriate. All vaccinations must be completed at least 6 weeks prior to treatment initiation.
- Serum pregnancy test if female of childbearing potential
- Standard breast cancer screening as per local guidelines – see **ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS** section for further information relating to malignancies.

Regular tests:

- FBC, Neutrophil, IgG, IgA, and IgM titres in advance (within 4 weeks) of each planned infusion date. Monitoring should continue for the duration of treatment.
- Annual MRI
- Monitoring for malignancy via national screening programs – including standard breast cancer screening

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test(s) as directed by the supervising Consultant. An annual MRI scan for disease activity should be carried out. An EDSS score should be included prior to each treatment or change to treatment.

TREATMENT:
Ocrelizumab is administered by intravenous infusion. The initial 600mg dose is administered as two separate 300 mg intravenous infusions given 2 weeks apart; subsequent doses are administered as a single 600 mg intravenous infusion every 6 months. There should be a minimum interval of 5 months between each subsequent dose.

PREMEDICATIONS:
The following two medicines **must** be administered prior to each ocrelizumab infusion to reduce the frequency and severity of infusion related reactions (IRRs):

- 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion
- Antihistamine approximately 30-60 minutes prior to each infusion

In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each infusion.

Dose	Day	Drug	Dose	Route	Diluent	Rate
1 *(administered as two separate infusions 14days apart)*	0 (Infusion1)	Ocrelizumab	300mg	Intravenous infusion	250mL of 0.9% Sodium Chloride	Initiate the infusion at a rate of 30 mL/hour for 30 minutes. The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. Each infusion should be given over approximately 2.5 hours.
	14 (Infusion 2)	Ocrelizumab	300mg	Intravenous infusion	250mL of 0.9% Sodium Chloride	
6 months after initial dose						
Subsequent Doses	at 6 month intervals	Ocrelizumab	600mg	Intravenous infusion	500mL of 0.9% Sodium Chloride	Initiate the infusion at a rate of 40 mL/hour for 30 minutes. The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour. Each infusion should be given over approximately 3.5 hours.
Patients should be monitored during the infusion and for at least one hour after the completion of the infusion. Resources for the management of anaphylaxis or serious infusion related reactions should be available.						

If an infusion of ocrelizumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) should be maintained between doses.

Infusion adjustments in case of infusion related reactions (IRRs)

Life-threatening IRR:
If there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome, the infusion must be stopped immediately and the patient should receive appropriate treatment.
Ocrelizumab must be permanently discontinued in these patients.

Severe IRR
If a patient experiences a severe IRR (such as dyspnoea) or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Mild to Moderate IRR
If a patient experiences a mild to moderate IRR (e.g. headache) the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

DOSE MODIFICATIONS:

No dose reductions are recommended with ocrelizumab.

Renal and Hepatic impairment:
The safety and efficacy of ocrelizumab has not been formally studied in patients with renal or hepatic impairment; based on drug pharmacokinetics no dose adjustment is expected to be required.

SUPPORTIVE CARE:

For pre-medications please see **TREATMENT** section above.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions; further information on reporting adverse reactions can be found at www.hpra.ie .

In order to improve traceability of biological medicinal products the name and batch number if the administered product should be clearly recorded.

Infusion-Related Reactions (IRRs) Ocrelizumab is associated with IRRs, which may be related to cytokine release and/or other chemical mediators. Symptoms of IRRs may occur during any infusion, but have been more frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion. Reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea and tachycardia.

Before the infusion:

- Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available.
- Hypotension may occur during infusions of ocrelizumab as an IRR symptom therefore withholding of antihypertensive treatments should be considered for 12 hours prior to and during each infusion. Patients with a history of congestive heart failure (New York Heart Association III & IV) were not studied.
- Patients must receive premedication to reduce the frequency and severity of IRRs.

During the infusion:

- Patients who experience severe pulmonary symptoms, such as bronchospasm or asthma exacerbation must have their infusion interrupted immediately and permanently.
- Symptomatic treatment must be administered and the patient monitored until pulmonary symptoms have resolved because initial improvement of clinical symptoms could be followed by deterioration.
- Hypersensitivity may be difficult to distinguish from an IRR in terms of symptoms. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently (see 'Hypersensitivity Reactions' below).

After the infusion:

- Patients should be monitored for at least one hour after the completion of the infusion for any symptom of IRR.
- Patients should be informed that an IRR can occur within 24 hours of infusion.

Hypersensitivity Reactions

Type 1 acute hypersensitivity reactions (IgE-mediated) may be clinically indistinguishable from IRR symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously

experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known IgE mediated hypersensitivity to ocrelizumab must not be treated.

Infection

Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved. It is recommended to check immune status before dosing since severely immunocompromised patients (e.g. with lymphopenia, neutropenia, hypogammaglobulinemia) should not be treated. Patients with swallowing difficulties are at a higher risk of aspiration pneumonia and ocrelizumab treatment may further increase the risk of severe pneumonia in these patients; physicians should take prompt action for patients presenting with pneumonia.

A risk of PML (progressive multifocal leukoencephalopathy) cannot be ruled-out since John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies, and associated risk factors (e.g. patient population, polytherapy with immunosuppressants).

Physicians 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. If PML is suspected, dosing must be withheld. Evaluation including Magnetic Resonance Imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for JCV and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B reactivation Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients treated with other anti-CD20 antibodies. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before starting treatment and should be monitored and managed following local medical standards to prevent HBV reactivation.

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 risk should be assessed in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients with a known active malignancy should not be treated with ocrelizumab. Patients should follow standard breast cancer screening per local guidelines.

In the controlled period of the clinical trials, the incidence of non-melanoma skin cancers was low and there was no imbalance between treatment groups. An increase in incidence was observed between years 3 and 4 of treatment due to basal cell carcinoma, which was not observed in subsequent years. The incidence remains within the background rate expected for an MS population.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves. In other auto-immune conditions, use of ocrelizumab concomitantly with immunosuppressive medications (e.g. chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increased risk of serious infections, including opportunistic infections. Infections included and were not limited to atypical pneumonia and *pneumocystis jirovecii* pneumonia, varicella pneumonia, tuberculosis, histoplasmosis. In rare cases, some of these infections were fatal.

An exploratory analysis identified the following factors associated with risk of serious infections: higher doses of ocrelizumab than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids. It is not recommended to use other immunosuppressives concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses. Knowledge is limited as to whether concomitant steroid use for symptomatic treatment of relapses is associated with an increased risk of infections in clinical practice. In the ocrelizumab MS pivotal studies the administration of corticosteroids for the treatment of relapse was not associated with an increased risk of serious infection.

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. Caution should be exercised when prescribing ocrelizumab taking into consideration the pharmacodynamics of other disease modifying MS therapies.

Vaccinations

Vaccination with live-attenuated or live vaccines is not recommended during treatment with ocreliuzmab and not until B-cell repletion (in clinical trials, the median time for B-cell repletion was 72 weeks).

In a randomized open-label study, relapsing MS patients were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. It is recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunisation status of patients being considered for treatment with ocrelizumab; patients who require vaccination should complete their immunisation at least 6 weeks prior to initiation of treatment.

Due to the potential depletion of B cells in infants of mothers who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered. Measuring CD19-positive B-cell levels, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunisation schedule and measurement of vaccine-induced response titres should be considered to

check whether individuals have mounted a protective immune response because the efficacy of the vaccination may be decreased. The safety and timing of vaccination should be discussed with the infant's physician.

DRUG INTERACTIONS:
No formal drug interaction studies have been performed.

See **ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS** section for information on vaccinations and concomitant immunosuppressants (it is not recommended to use concomitant immunosuppressants with ocrelizumab except corticosteroids for symptomatic treatment of relapses).

SUPPORT RESOURCES:
The Summary of Product Characteristics is available from: https://backend-lb.medicines.ie/uploads/files/uk-ie-mt-spc-Ocrevus-clean_1561714860.pdf

ATC CODE:
Ocrelizumab L04AA36

REIMBURSEMENT CATEGORY:
National Drugs Management Scheme (NDMS)

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Neurologist experienced in the treatment of MS.

REFERENCES:

1. European Medicines Agency. Ocrevus 300 mg concentrate for solution for infusion. Accessed November 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	09/01/2020	Not applicable.	Prof Chris McGuigan

Comments and feedback welcome at ahmp@hse.ie .