HSE Prescribing Protocol

Ocrelizumab (Ocrevus®)

for

the Treatment of Relapsing Multiple Sclerosis (RMS) and Primary Progressing Multiple Sclerosis (PPMS)

This document is intended for use by healthcare professionals only.

This guideline should be used in conjunction with the full prescribing and administration details in the Ocrelizumab (Ocrevus®) Sumary of Product Characterisics (SmPC)
https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf[1]

INDICATIONS FOR USE[1]

TREATMENT	INDICATIONS	ICD10	Protocol Code
Ocrelizumab (Ocrevus®)	For the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	G35	MS103a
	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.	G35	MS103b

TREATMENT[1]

	TREATMENT	DOSE	ROUTE	FREQUENCY	Rate
Initial Dose	Ocrelizumab	300mg	Intravenous infusion	Day 1	See SmPC for details
		300mg	Intravenous infusion	Day 15	
Subsequent Doses	Ocrelizumab	600mg	Intravenous infusion	Every 6 months	
	The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose				

Patients should be monitored during each 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.

Treatment with ocrelizumab 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 (IRRs).

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.

ELIGIBILTY CRITERIA:

- Patient has confirmed diagnosis of RMS as per one of the indication(s) above
- Patients is aged 18 years or older
- A *Patient Eligibility* form for ocrelizumab has been completed and added to the patient's clinical records. (A copy of the form is available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/multiple-sclerosis.html)
- Patient must attend for medical appointments and investigations as determined by the clinical team.

EXCLUSION CRITERIA:

Patients who do not meet the eligibility criteria above

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.
- 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:

See SmPC

PREMEDICATIONS[1]

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.

If patients did not experience a serious IRR with any previous ocrelizumab infusion, a shorter infusion time can be considered for subsequent doses (see SmPC for information).

Infusion adjustments in case of infusion related reactions (IRRs) (see SmPC for full information).

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.

Missed doses

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.

BASELINE TESTS AND MONITORING:

- Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.
- Discuss vaccination status with the patient, as appropriate. All vaccinations must be completed at least 6 weeks prior to treatment initiation.
- Ongoing monitoring for malignancy via national screening programs should be carried out– including standard breast cancer screening.

Table 1: Recommended baseline tests and schedule of assessments for patients treatment with Ocrelizumab

Assessment	Baseline	Within 4 Weeks of Each Infusion	Annually
MRI	X[1]		X
Full Blood Count & Film	X	X	
Neutrophil, IgG, IgA and IgM Titres	X	X	
EDSS Score	X	X	
Urea & electrolytes, Serum Creatinine	X		
Liver profile (including AST, GGT and albumin)	X		
HIV Serology	X		
Hepatitis B virus serology: anti-Hepatitis B core Antibody, Hepatitis B Surface Antigen and anti-Hepatits B Surface Antibody	X		
Hepatitis C virus serology	X		
Varicella Zoster Virus (VZV) Serology -	X[2]		
Evaluation for active or latent TB as per local guidelines	X		
Serum Pregnancy Test	X[3]		
JCV PCR	X[4]		

[1] Within 3 months prior to treatment

[2] VZV vaccination of antibody-negative patients should be considered. VZV vaccination should be administered at least 6 weeks in advance of treatment.

[3] If female of childbearing potential

[4] If transitioning from natalizumab (Tysabri®) due to positive John Cunningham Virus (JCV) antibodies, it is recommended to complete a cerebrospinal fluid JCV PCR as well as a review of a recent MRI to assess for evidence of PML prior to commencing to ocrelizumab (Ocrevus®) therapy.

SPECIAL WARNINGS AND PRECAUTION FOR USE

See SmPC for full information on other Special Warnings and Precautions for Use

SUPPORTIVE CARE:

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

ADVERSE EFFECTS

The adverse effects listed are not exhaustive. Please refer to the SmPC 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.

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

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 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf

REVISION HISTORY

Version	Date	Amendment	Approved By