Ballarat Health Services

DRUG GUIDELINE

Ocrelizumab Intravenous Infusion

SCOPE (Area): **FOR USE IN:** Medical Day Unit.
EXCLUSIONS: Paediatrics (seek Paediatrician advice) and other areas
SCOPE (Staff): Medical, Nursing and Pharmacy

DEFINITIONS

Ab = Antibody
Ag = Antigen
HBcAb = Hepatitis B core antibody
HBsAg = Hepatitis B surface antigen
HBV = Hepatitis B virus
hCG = Human chorionic gonadotropin
HIV = Human immunodeficiency virus
HPV = Human Papilloma Virus
MET = Medical emergency team
MS = Multiple sclerosis
PML = Progressive multifocal leukoencephalopathy
PPE = Personal protective equipment
TB = Tuberculosis

BRAND NAMES

Ocrevus®

PHARMACOLOGY AND PHARMACOKINETICS

Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells. The precise mechanism by which ocrelizumab exerts its therapeutic effects in Multiple Sclerosis (MS) is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis. In clinical trials it has been shown to reduce relapse rate and disability progression events in relapsing remitting and primary progressive MS.

INDICATIONS

- Relapsing Remitting Multiple Sclerosis

CONTRAINDICATIONS

- Known hypersensitivity to ocrelizumab.
- Known hypersensitivity to murine derived proteins.
- Have or have had progressive multifocal leukoencephalopathy (PML).

- Known immunosuppression (due to medical condition or immunosuppressive therapies). Use of ocrelizumab concomitantly with immunosuppressive medications increase risk of serious infections, including opportunistic infection.
- Ocrelizumab is contraindicated in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests.

PRECAUTIONS

- **Hepatitis B -** for patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult Gastroenterologist before starting and during treatment.
- **Vaccinations -** vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion. Administer all necessary immunisations according to immunisation guidelines at least 6 weeks prior to initiation of ocrelizumab.
- **Infusion reactions -** see Adverse Effects below

PREGNANCY AND BREASTFEEDING

Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

- Avoid concomitant administration of ocrelizumab with BCG, belimumab, natalizumab, pimecrolimus, tacrolimus and other immunosuppressants.
- Consider therapy modification if intending to administer ocrelizumab concomitantly with echinacea, fingolimod, leflunomide, nivolumab, roflumilast and tofacitinib.
- Monitor therapy if using ocrelizumab concomitantly with coccidiodides immitis skin test, denosumab, pidotimod, tertomotide and tratuzumab.
- Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion.
- Antihypertensive medications – consider withholding antihypertensive medications 12 hours prior to (and during) ocrelizumab infusion as hypotension may occur as a symptom of infusion-related reaction, during ocrelizumab infusion.

DOSAGE AND ADMINISTRATION

Emergency treatment for anaphylaxis (adrenaline, antihistamine, corticosteroid and resuscitative equipment) must be readily available, as well as oxygen and bronchodilators for other possible infusion reactions. See below for more information.

Check Contraindications and Precautions (above) and Monitoring (below) before prescribing, especially regarding pretreatment screening. Any vaccinations required should be given at least 6 weeks before ocrelizumab commences. For patients on antihypertensive medications, prior to admission Medical staff must decide if they are to be withheld 12 hours prior to (and during) the infusion – see Drug Interactions.

Ensure contraception for women (where appropriate) commences before treatment and for 6 months after each infusion.

Administer via CVC or peripheral line. Compatible with sodium chloride 0.9% only. Prescribe on the BHS IV orders chart (MR/645.0).

Caution: When handling ocrelizumab wear protective clothing including a mask/respirator, safety glasses/face shield, gown and gloves. Ocrelizumab is a non-cytotoxic monoclonal antibody, and the occupational hazard of handling is not known.

1.) Before INITIAL dose:

Ensure PRETREATMENT SCREENING as outlined under 'Monitoring' has occurred and been reviewed

2.) Before ANY infusion (and before preparing the infusion):

Undertake a pregnancy test (if applicable) to exclude pregnancy in women of child-bearing age.

Screen the patient for any signs of active infection which may include urinalysis if risk of urinary tract infection (See Nursing Practice Points for more information).

3.) Before ANY infusion:

Administer premedications to reduce the severity and frequency of infusion reactions:

To be prescribed on the Medication Chart (MR/700.2).

Administer 30 to 60 minutes prior to ocrelizumab administration:

- paracetamol 1000 mg (500mg x TWO) orally AND
- cetirizine 10 mg orally

Administer 30 minutes prior to ocrelizumab administration:

- methylprednisolone 100 mg IV push over 5 minutes

4.) Prior to commencing ocrelizumab, ensure familiarity with possible infusion related reactions and their management:

- Infusion related reactions include pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea and tachycardia. They can occur up to 24 hrs post infusion.
- Hypersensitivity reactions can occur, and severe infusion reactions may be clinically indistinguishable from a Type 1 (IgE-mediated) acute hypersensitivity reaction.
- Generally, the reaction rate is higher with the first infusion than subsequent infusions.
- Most reactions are mild to moderate in severity.

Infusion reaction: If an infusion reaction occurs, **temporarily discontinue the infusion and notify the medical officer.**

- **For mild reactions (chills, shivering, pruritis, urticaria, headache, throat irritation, flushing, mild shortness of breath)** - if an infusion-related reaction occurs stop the infusion immediately and contact HMO for specific advice. Infusion-related reactions are usually reversible with a reduction in rate, or interruption of the infusion, and administration of appropriate symptomatic treatment, if required. In most cases, the infusion can be resumed at a 50% reduction rate (e.g. from 60 mL/hr to 30 mL/hr) when symptoms have completely resolved.
- **For severe reactions including angioedema, hypotension with systolic BP <90 mmHg - stop** infusion and call a MET call.

5. Preparation of infusion- general information (see 6 or 7 below for dose specific information)

Only to be administered in MDU.
Ocrelizumab does not contain any antimicrobial preservative. Prepare using aseptic technique to ensure the sterility of the prepared solution.
Use a dedicated line, and infuse via a low protein binding infusion set with a 0.2 micron filter (such as Smartsite low sorbing infusion set Part number 10010454).
Wear a mask/respirator, safety glasses/face shield, gown and gloves (i.e. appropriate PPE).
Prime the line with sodium chloride 0.9%.
Use a light protective over-bag.
Take observations (blood pressure, heart rate, temperature, respirations, SaO_2 and conscious state) as outlined below.

6.) Initial IV Dose (two identical 300 mg/250 mL infusions, two weeks apart):

Ocrelizumab 300 mg/250 mL infusion preparation:
Use ocrelizumab 300 mg/10 mL vial to prepare infusion.
Withdraw and discard 10 mL of sodium chloride 0.9% from a 250 mL sodium chloride 0.9% IV bag.
Add Ocrelizumab 300 mg (10 mL from ONE vial) to remaining 240 mL sodium chloride 0.9% in the IV bag. Invert the bag to mix gently, do not shake.
Document vial batch number and expiry date on IV chart.

Total Volume: 250 mL.
Final concentration: 1.2 mg/mL.

Starting rate: Take baseline observations and commence at 36 mg/hr (30 mL/hr) for 30 mins. See Initial Dose Infusion table below.

Increase Rate: If no adverse reaction, increase by 36 mg/hr (30 mL/hr) every 30 mins, to a maximum of 216 mg/hr (180 mL/hr). Repeat observations at each rate change or every 30 minutes. Infusion usually takes around 3 hours.

End of infusion: Flush line with sodium chloride 0.9% 100 mL at the same rate the infusion finished at.

Observations are required to continue for at least one hour once the infusion is complete.

Initial Doses for ocrelizumab 300 mg/250 mL (1.2 mg/mL) infusion (two identical infusions, two weeks apart)			
Time (min)	**Infusion rate (mL/hr)**	**Volume to be infused (mL)**	**(mg)**
0-30	30	15	18 mg
30-60	60	30	36 mg
60-90	90	45	54 mg
90-120	120	60	72 mg
120-150	150	75	90 mg
150-end	180	25	30 mg

7.) Subsequent IV infusion (600 mg/500 mL infusion, 6 months after initial or most recent dose):

Subsequent doses of ocrelizumab (600 mg/500mL) have 2 different options for administration:

- OPTION 1 – to be used if previous serious infusion related reaction, over 3.5 hours
- OPTION 2 – may be used if NO previous serious infusion related reactions, over 2 hours

The Prescriber must specify when prescribing subsequent ocrelizumab infusions 'OPTION 1' or 'OPTION 2'.

Ocrelizumab 600 mg/500 mL infusion preparation:

Use ocrelizumab 300 mg/10 mL vials to prepare infusion.
Withdraw and discard 20 mL of sodium chloride 0.9% from a 500 mL sodium chloride 0.9% IV bag.
Add Ocrelizumab 600 mg (20 mL from TWO vials) to remaining 480 mL sodium chloride 0.9% in the IV bag. Invert the bag to mix gently, do not shake.
Document vial batch number and expiry date on IV chart.

Total Volume: 500 mL.
Final concentration: 1.2 mg/mL.

OPTION 1 - subsequent ocrelizumab 600 mg/500 mL infusion (6 months after initial or most recent dose) and previous severe infusion related reaction (also see table below):

Starting rate: Take baseline observations and commence at 48 mg/hr (40 mL/hr) for 30 mins.

Increase Rate: If no adverse reaction, increase by 48 mg/hr (40 mL/hr) every 30 mins, to a maximum of 240 mg/hr (200 mL/hr). Repeat observations at each rate change or every 30 minutes. Infusion usually takes around 3.5 hours.

End of infusion: Flush line with sodium chloride 0.9% 100 mL at the same rate the infusion finished at.

Observations are required to continue for at least one hour once the infusion is complete.

OPTION 1 - subsequent ocrelizumab 600 mg/500 mL (1.2 mg/mL) infusion (6 months after initial or most recent dose) and previous severe infusion related reaction

Time (min)	Infusion rate (mL/hr)	Volume to be infused (mL)	(mg)
0-30	40	20	24 mg
30-60	80	40	48 mg
60-90	120	60	72 mg
90-120	160	80	96 mg
120-150	200	100	120 mg
150-180	200	100	120 mg
180-210	200	100	120 mg

OPTION 2 - subsequent ocrelizumab 600 mg/500 mL infusion (6 months after initial or most recent dose) and NO previous severe infusion related reaction (also see table below):

Starting rate: Take baseline observations and commence at 120 mg/hr (100 mL/hr) for 15 mins.

Increase Rate: If no adverse reaction, increase to 240 mg/hr (200 mL/hr) for next 15 min. Repeat observations at each rate change or every 30 minutes. Infusion usually takes around 2 hours.
If no adverse reaction, increase rate to 300 mg/ hr (250 mL/hr) for next 30 minutes.
If no adverse reaction, increase rate to 360 mg/hr (300 mL/hr) for remaining 60 min

End of infusion: Flush line with sodium chloride 0.9% 100 mL at the same rate the infusion finished at.

Observations are required to continue for at least one hour once the infusion is complete.

OPTION 2 - subsequent ocrelizumab 600 mg/500 mL (1.2 mg/mL) infusion (6 months after initial or most recent dose) and NO previous severe infusion related reaction

Time (min)	Infusion rate (mL/hr)	Volume to be infused (mL)	(mg)
0-15	100	25	30 mg
15-30	200	50	60 mg
30-60	250	125	150 mg
60-120	300	300	360 mg

8). Monitor for infusion related reactions:

For more information see 4.) Prior to commencing ocrelizumab, ensure familiarity with possible infusion related reactions and their management.

General Administration Information

- **Infusion preparation:** As above
- **Final concentration:** 1.2 mg/mL
- **Infusion pump:** Alaris PC with LVP and Guardrails
- **Routes of administration:**
  - IV injection: No
  - IV intermittent infusion: No
  - IV continuous infusion: Yes
  - IM injection: No
  - Subcut injection: No
- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS)

Consider referral to Infectious Disease Specialty if any infection related abnormal results.
Pathology (ideally within one month prior to commencing therapy):

- Hepatitis B surface antigen, surface antibody and core antibody serology (sAb, sAg, cAb), Hepatitis C serology. **To be performed at least 3 to 6 months prior unless recent exposure risk requiring repeat testing**.
- Varicella IgG serology (consider vaccination if negative or equivocal).
- HIV 1 and 2 serology.

- Treponemal serology.
- Interferon Gamma Assay Tuberculosis screening (Quantiferon Gold®) and for people at high risk of TB Chest X-ray also.
- Human Papilloma Virus (HPV) testing and Pap smear.
- Liver function tests.
- Full Blood Examination.
- Serum urea, electrolytes and creatinine.
- Pregnancy hCG in females of child bearing age
- Malignant skin cancers - caution should be taken in patients who have a history of malignant skin cancers. Skin assessment and dermatology review should be considered in patients at high risk of skin cancers. This includes patients with previous history of immunosuppressive therapy, fair skin, and high previous sun exposure, past history of skin malignancies or suspected skin malignancies.
- MRI Brain and/or Spinal cord (MS protocol) will be required within 6 months prior to commencing therapy

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NURSING PRACTICE POINTS

- **Patients should be asked to report symptoms of allergy (e.g. shortness of breath, chest tightness). Contact the doctor in event of adverse events for immediate review and monitoring.**
- **Ask patients to contact their doctor urgently if they have persistent fever, other signs of infection or bruising, bleeding or pallor.**
- **Patients require close monitoring and regular observations as outlined above.**
- Check if patients have signs of:
    - Fever and/or chills
    - Signs of common cold, bronchitis or influenza infection
    - Urinary tract infection (may require urinalysis)
    - New onset, or worsening of neurological signs or symptoms of MS that can be similar to signs and symptoms of progressive multifocal leukoencephalopathy (PML).

  Ocrelizumab administration must be delayed in patients with an active infection until the infection resolved. Ocrelizumab must be discontinued if PML is confirmed. **Contact the doctor to discuss if patient has these signs and symptoms.**
- **Inform patients that Infusion Related Reactions can occur up to 24 hours after infusion and to seek medical review immediately if experiencing infusion related reactions.**
- All injections, infusions and lines are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.
- Record the batch and expiry date of the ocrelizumab vials used.
- Infusions require an independent double check by 2 Registered Nurses prior to commencement.
- All lines, IV bags and protective equipment (except goggles and respirator) require disposal in a cytotoxic waste container.

ADVERSE EFFECTS

- **Infusion reactions** (34-40%) – see Dosage and Administration
- **Pulmonary symptoms** - patients who experience severe pulmonary symptoms, such as bronchospasm or asthma exacerbation, must have their infusion interrupted immediately and permanently. After administering symptomatic treatment, monitor the patient until the pulmonary symptoms have resolved because initial improvement of clinical symptoms could be followed by deterioration.
- **Malignancies** - including breast cancer, melanoma and lymphoproliferative disorders and lymphoma may occur with use of immunomodulatory medicines.

- **Infections**: upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections, Herpes virus infections including oral herpes, herpes zoster, herpes simplex, and genital herpes, Human Papilloma virus, tuberculosis.
- Refer to full prescribing information for more detailed information.

DRUG PRESENTATIONS AND STORAGE

Ocrelizumab 300 mg/10 mL vial.

Refrigerate between 2-8°C. Protect from light. Do not freeze. Do not shake.
