TOCILIZUMAB for Cytokine Release Syndrome (CRS)

Background

Tocilizumab for management of Cytokine Release Syndrome (CRS) induced by Chimeric Antigen Receptor (CAR) products or bispecific antibody of fusion protein treatments can be used within Oxford University Hospitals (OUH) NHS Foundation Trust for adult patients for the following indications:

- **Standard of care:**
  - Licensed indications[1]: CAR T-cell therapy induced CRS in patients with B-cell lymphoma or B-cell leukaemia [NHSE funded; Blueteq required]
  - Unlicensed indications[2]: Bispecific antibody treatment induced CRS in patients with diffuse large B-cell lymphoma (DLBCL) or multiple myeloma (MM) [NHSE funded; Blueteq required]
- **Clinical trials:**
  - Unlicensed indications[2]: CAR product or bispecific antibody/fusion protein treatment induced CRS in patients with haematological malignancies or solid tumours [Sponsor funded]

[1] For other licensed indications, refer to the tocilizumab Summary of Product Characteristics (SmPC)
[2] For off-label use of medications, refer to relevant protocols and OUH policies.

Supply arrangements – max. 4 doses/Patient can be supplied for standard of care indications

Indication	Pharmacy supply [9am-5pm]	Out of hours [OOH] supply
CAR-T cell therapy **– both standard of care[1] and clinical trials**	• Advance dispensing: all 4 doses dispensed from Churchill Cancer Satellite Pharmacy for **Named Patients only** and stored in the Clinical Haematology Ward [CHW] fridge from Day 0 to be readily available when required	• **"Standard PPDU stock"** fridge in the Emergency Drug Cupboard (EDC)
Bispecific antibody (BsAb) treatments **– standard of care** (e.g., glofitamab, epcoritamab, elranatamab, talquetamab)	• Advance dispensing: 1 dose dispensed from Churchill Cancer Satellite Pharmacy for **Named Patients only** and stored in the Clinical Haematology Ward [CHW] fridge from Cycle 1 first BsAb dose until at least second full dose is tolerated without CRS – refer to the individual BsAb protocol for more details. • Additional 3 tocilizumab doses can be dispensed in the event of CRS when required from Churchill Cancer Satellite Pharmacy for **Named Patients only.**	• **"Standard PPDU stock"** fridge in the Emergency Drug Cupboard (EDC)
Bispecific antibody/fusion protein treatments **– clinical trials**	• Dispensing in the event of CRS only (no advance dispensing) for **Named Patients only** requested using **"Time Critical Medicine Request Form"** from Churchill Cancer Satellite Pharmacy [non-IMP] OR using **''Urgent CT Prescription''** from the Churchill Hospital Main Pharmacy [IMP] up to maximum number of doses specified in relevant clinical trial protocol – therefore, not usually stored in the Clinical Haematology Ward [CHW] fridge as each dose should be used immediately after receiving the dose for CRS treatment	• **"Standard PPDU stock"** fridge in the Emergency Drug Cupboard (EDC): **non-IMP** tocilizumab (majority of the clinical trials, except those listed on the EDC fridge door[2]) • **"Clinical Trials IMP stock"** fridge in the Emergency Drug Cupboard (EDC): **IMP** tocilizumab[3]

[1] Currently licensed and commissioned products in the UK (depending on indication): Axicabtagene ciloleucel, Brexucabtagene autoleucel, Tisagenlecleucel; [2] Clinical trials currently using IMP tocilizumab stock - always refer to the latest list attached to the EDC "Clinical Trials (IMP) stock" fridge. [IMP = Investigational Medicinal Product].

Pharmaceutical form and storage requirements

Tocilizumab 20mg/ml Concentrate for Solution for Infusion is the only formulation that can be used for management of CRS **(RoActemra®or Tyenne®** – confirm brand with Pharmacist before prescribing**).**

- Available as: 400mg/20mL, 200mg/10mL and 80mg/4mL vials
- The solution should be clear to opalescent, colourless to pale yellow and free of visible particles.
- **Can be used for INTRAVENOUS administration ONLY.**
- Store unopened vials in a refrigerator at 2-8ºC. Do not freeze. Keep the vial(s) in the outer carton in order to protect from light.

Dosage

Patients weighing ≥ 30kg	8 mg/kg
Patients weighing < 30kg	12 mg/kg

- Tocilizumab can be given alone or in combination with corticosteroids.
- If no clinical improvement in the signs and symptoms of CRS, then **up to a maximum of 4 doses in total** may be administered for licensed and NHSE commissioned CAR and BsAb products [refer to the relevant clinical trial protocols for CAR/BsAb/Fusion protein IMPs].
- The interval between consecutive doses should be **at least 8 hours.**
- **Maximum dose: 800mg per infusion**
- Dose modifications are not usually recommended – always discuss with Consultant. Note that patients with CRS frequently have cytopenias or elevated ALT/AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS.
- **See also relevant CAR-T, bispecific antibody or clinical trial protocol for CRS treatment.**

For administration details – always refer to the latest Medusa monograph [Link] and product SmPC [Link] for most up to date guidance which may supersede the information below.

Method of administration

INTRAVENOUS infusion over 60 minutes.

Instructions for dilution

Patients weighing ≥ 30kg	Final infusion volume: **100 mL**
Patients weighing < 30kg	Final infusion volume: **50 mL**

- Calculate the volume of tocilizumab concentrate required for the prescribed dose.
- Remove the equivalent volume from the sodium chloride 0.9% infusion bag and discard.
- Withdraw tocilizumab dose from the vial(s) and add to the infusion bag with **sodium chloride 0.9%** using aseptic technique.
- Mix by gently inverting the infusion bag to avoid foaming.
- Any unused product or waste material should be disposed of in accordance with local requirements.

Flushing

Flush the giving set with 50mL sodium chloride 0.9% at the same rate as the infusion was given.

Incompatibilities

This medicinal product must not be mixed with any other medicinal products except for sodium chloride 0.9% solution used for dilution.

Special handling information

This is a monoclonal antibody. Reduce direct handling to a minimum and wear appropriate personal protective equipment.

Adverse effects

- The most commonly reported adverse reactions (occurring in ≥ 5% of patients, including those treated with tocilizumab monotherapy for CRS) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.
- **Hypersensitivity reactions** have been reported, including anaphylaxis, flushing, fever, chills, rash, pruritus, urticaria, headache, hypertension. Note intravenous formulation contains polysorbate 80 (Tween) – please confirm patient is not allergic to this substance before administration.
- Refer to product SmPC for full list of possible side-effects.

Suggested monitoring

- Vital signs (pulse, blood pressure, temperature and respiratory rate) should be checked prior to infusion, after 15 minutes, then every 30 minutes until 1 hour post infusion, and then as required depending on the patient's clinical status.
- Continue patient monitoring for CRS according to relevant therapy protocol.

Other injectable administration

Tocilizumab 162 mg solution for injection in pre-filled pen (any brand) is for subcutaneous use and **MUST NOT** be used for the treatment of CRS.

Tocilizumab stock

Tocilizumab stock can be supplied as:

1) **Commercial stock ("Central Bin Location") supplied from the OUH pharmacy stores [via Pharmacy Purchasing and Distribution Unit (PPDU)].**
   - ✓ Reimbursed by either NHSE (standard of care treatments) or Sponsor (non-IMP stock for clinical trials)
   - ✓ Emergency stock locations – Emergency Drug Cupboard (EDC)
2) **IMP [Investigational Medicinal Product] stock provided by the Sponsor.**
   - ✓ Supplied by the Sponsor (IMP stock for clinical trials) (refer to the specific clinical trial if IWRS controlled)
   - ✓ Emergency stock location – Emergency Drug Cupboard (EDC)

Corresponding documents [available on OUH SharePoint]

H.126.1 Tocilizumab Fridge Poster – Churchill Hospital [Clinical Haematology Ward (CHW) and Emergency Drug Cupboard (EDC)]
H.126.2 Tocilizumab Cancer Pharmacy Guide

References

1. Fresenius Kabi Ltd. Tyenne® 20 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. Last updated 06/11/2023. Available at https://www.medicines.org.uk/emc <Last accessed 14/08/2024]
2. Roche Products Limited. Tocilizumab RoActemra® 20mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated 29/11/2022. Available at https://www.medicines.org.uk/emc <Last accessed 14/08/2024]
3. Medusa NHS Injectable Medicines Guide. Tocilizumab (RoActemra®) 20mg/1mL concentrate for infusion. Intravenous (Adults) Monograph. Version 6 <Last accessed 14/08/2024]
4. National Cancer Drugs Fund list. Available at https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ <Last accessed 14/08/2024]

Document history

Authors/Reviewers	Revision	Approved by	Date	Version	Review date
Nadjoua Maouche, Lead Haematology Pharmacist	New document [CAR.6.4]	Dr Andy Peniket, Haematology Consultant	September 2021	1.0	September 2023
Sandy Hayes, Lead ACT implementation nurse	Format [CAR.6.4]		February 2023	1.1	September 2023
Natalia Czub, Advanced Haematology, ACT Pharmacist, Emma Willcock, Lead Pharmacist Clinical Trials, Emma Christmas, Specialist Chemotherapy Nurse [ACU], Yen Lim, Lead Haematology Pharmacist, Julia Wong, Advanced Pharmacist Cancer Clinical Trials, Karolina Joniak, Clinical Trials Pharmacy Technician Team Manager	CAR.6.4 converted to H.126: indications for use, supply arrangements; dosage, administration updated; General formatting. Corresponding documents added.	Dr Katerina Panopoulou, Consultant Haematologist, CAR-T Lead	August 2024	2.0	August 2026