OUH General Risk Assessment Form

Tocilizumab Preparation Risk Assessment

It is recommended that all Trusts have in place a policy for the handling of mAbs. This should describe the responsibility of the Chief Pharmacist in defining the requirements needed for mAbs prepared outside the pharmacy, the resources available for handling of mAbs within the organisation, the mechanisms in place for the risk assessment of MAB handling and the clinical areas where mAbs may be used. This should be endorsed at Board level within the Trust and include a commitment to provide the resources necessary to allow the safe preparation of mAbs within the Trust in line with the guidance included within this document. It should also address the subject of the cost of provision of the resources required and how these are linked to the costs passed on to commissioners.

Site	JR Oxford University Hosptials NHS Trust	Division	CSS
Directorate	Covid wards/Pharmacy/ICU	Department	Pharmacy
Location Exact	N/A	Date	21/04/2020

Assessors(s)	
1	Clinical Divisional Pharmacist
2	Medicines Safety Pharmacist
3	Preparative Services Pharmacist
4	Senior Pharmacist Manager

The Hazard or perceived risk

Risks:

1. Risks of exposure to tocilizumab for staff handling the product due to the nature of or mode of action of the agent
2. Risks to patient receiving tocilizumab due to the potential for errors or contamination during the preparation of the product

Cause: Need to determine the most appropriate area to prepare tocilizumab based on agreed MAB risk categories
Affect: Staff could develop a reaction or adverse effect from tocilizumab. Patients may receive inaccurate product, with risk of microbiological contamination
Impact: Minimise potential occupational exposure to staff and risk to patients receiving a dose

Description (Identify who will be affected and how; include the context e.g. clinical, health and safety, financial etc)

1. SPS mAb Guidelines 5th edition November 2015:

Factors that should be considered as part of risk review:

1.1 Internal Exposure Risk via – from COSSH safety data sheet

- Dermal absorption – 8.2 Wear gloves to prepare medicine.
- Inhalation absorption – 8.2 No PPE under normal operations. SmPC 2. vial presentation is a liquid.
- Mucosal absorption – No information, 8.2 Wear gloves to prepare medicine. SmPC 2. liquid formulation.
- Oral Absorption – 11. Not bioavailable by oral administration, SmPC – route of administration IV injection. Paper in mice, decrease in IL-6 activity following oral ingestion[7].

In SmPC 6. no special requirements stated during preparation.

1.2 Antigenicity: SmPC 2. Humanised Ig1 monoclonal antibody

1.3 Toxicity from COSSH safety data sheet and SmPC

- Cytotoxicity - No
- Carcinogenicity - IgG1 monoclonal antibodies not deemed to have intrinsic carcinogenic potential.
- Genotoxicity or Mutagenicity – Non-clinical data reveal no special hazard for human based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Non

mutagenic.

- Teratogenicity or other developmental toxicity – SmPC 4.6 Pregnancy: No data about tocilizumab in pregnant women. 4.6 Patients advised to use effective contraception during and up to 3 months after treatment.
  5.3 Animal studies no direct or diirect harmful effect on pregnancy or embryonal-foetal development, at high doses (>100) there was a slight increased risk of abortion/embryo-foetal death in animals.
- Organ toxicity at low doses – 11.1 Nil organ toxicity at doses < 10mg/day. Note that immunosuppressive, and side-effects during treatment are liver damage and infections.
  MHRA alert in relation to serious cases of liver injury resulting in need for transplantation. However in RA patients on other hepatotoxic medicines and for longer durations.
- Immunogenicity – SmPC 4.8 has occurred; within the context of clinical trials 1.6% of patients developed antibodies and 0.2% had medical significant hypersensitivity reactions.

There is no tool for risk stratification.
Conclusion: No information to indicate high risk.

3. **NPSA injectable risk score – see Appendix 2:**

   Score: 4 or 5 = Amber

4. **RMH monoclonal antibody occupational exposure risk assessment – see Appendix 2:**
   Incorporates health and safety risk – low and NPSA risk – amber
   Overall: Nurse can prepare on ward area with PPE

Summary
SPS document provides guidance on aspects to review to assess the risk, but not a tool for risk classification. The RMH risk assessment takes account of staff health and safety risks and patient risks and concludes that it is suitable for preparation in a ward area.
In the Recovery clinical trial protocol, there is a second randomisation for patients who are critically unwell to receive tocilizumab or no treatment and if required a second dose of tociliziumab to be given at the discretion of the treating physican within a window of 12 to 24 hours after the first dose.
In REMAP-CAP clinical trial protocol, tocilizumab is given at 8mg/kg on measured or estimate body weight. This is a single dose infusion, but can be repeated 12 to 24 hours later if there is insufficient clinical improvement.

Therefore tocilizumab doses for these two clinical trials are not planned, may be needed urgently and out of hours.

In terms of timely delivery of patient care and balancing preparation risks to staff, it is suitable for preparation in a ward area, by staff wearing PPE – gloves and a surgical face mask.

Refer to the Risk Matrix overleaf to calculate the risk level (risk score)					
Predicted Frequency (likelihood)	2	Predicted Outcome (consequence)	3	Initial Risk Score	6

Precautions in place at the point when risk was identified (Initial Controls)					
N/A					
Additional precautions implemented by the assessor (Current Controls)					
Prepare in a clinical area in response to prescription request, using tocilizumab worksheet and nurse/pharmacy staff wearing gloves and surgical mask.					
Predicted Frequency	2	Predicted Outcome	2	Current Risk Score	4

Best precautions that can be implemented (Best Controls)				
Prepare a worksheet, circulate to staff in clinical areas and add to FAQs for clinical trial				
Action Plan to Implement Best Controls				
No	Action	Responsibility of (Name and Job Title)	By when	Status (Pending, In progress or Complete)
1	Prepare worksheet	Clinical Trials Pharmacist	24 April 2020	Complete
2	Upload to OUH monograph site	MSO team	24 April 2020	Not going ahead
3	Upload to Recovery trial website	Nuffield Department of Public Health	1 May 2020	Complete

Risk Rating (if any) after Implementation of Best Controls					
Predicted frequency	2	Predicted Outcome	2	Target Risk Score	4

Reassessment of risk is required periodically after completion of action plan if risk(s) have not been resolved; please ensure this is tracked via your risk register. The minimum timescale for review based on the current risk level is outlined below:

If the current risk rating is Extreme (RED); the action plan should be reviewed monthly as a minimum.
If the current risk rating is High (Orange); the action plan must be reviewed every 3 months as a minimum.
If the current risk rating is Moderate (Yellow); the action plan must be reviewed every 6 months as a minimum.
If the current risk is Low (Green); the controls/action plan must be reviewed on an annual basis as a minimum.

References:

1. Guidance on the safe handling of Monoclonal Antibody Products, 5th Edition, published November 2015.
2. OUHNHSFT Guidelines for the preparation and manipulation of monoclonal antibodies and related compounds (fusion proteins) March 2016
3. Summary of product characteristics – RoAcetemra 20mg/ml concentrate for solution for infusion (tocilizumab). Roche. Accessed via https://www.medicines.org.uk/emc/product/6673/smpc on 20/04/2020
4. Safety data sheet – Acetemra (tocilizumab). Roche. Accessed via https://www.roche.com/dam/jcr:03c12d25-e84e-4de2-8d15-c254c1c912b5/en/SAP-10129601.20170109.11326.pdf on 20/04/2020
5. Medicines healthcare regulatory authority. Tocilizumab (RoActemra) : rare risk of serious liver injury including cases requiring transplantation. 17/07/19
6. Medusa. Intravenous – Adult Tocilizumab. Accessed via https://medusa.wales.nhs.uk/IVGuideDisplay.asp on 20/04/20
7. Cytokine. 2014 Aug;68(2):86-93. doi: 10.1016/j.cyto.2014.04.003. Epub 2014 May 4.
8. Randomised evaluation of COVID-19 Therapy (Recovery) protocol version 4.0 dated 14 April 2020
9. Randomised, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) Core protocol version 3 dated 10 July 2019
10. Randomised, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) COVID-19 Immune Modulation Therapy Domain-Specific Appendix version 2.0 dated 07 April 2020

Appendix 1: Clinical Trial Protocol details

1. Dose in Recovery[8] Clinical Trial protocol:

- **Tocilizumab** by intravenous infusion with the dose determined by body weight:

Weight*	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

* for lower weights, dosing should be 8 mg/kg
(Note: body weight may be estimated if it is impractical to weigh the patient)

Tocilizumab should be given as a single intravenous infusion over 60 minutes in 100ml sodium chloride 0.9%. A second dose may be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

2. Dose in REMAP-CAP[9,10] Clinical Trial protocol:

For REMAP-CAP the dose of tocilizumab will be 8mg/kg, max dose of 800mg.
The vials available for this study to make the dose are: 200mg/10mL and 80mg/4mL.

Tocilizumab will be administered at a dose of 8mg/kg based on measured or estimated body weight with total dose not exceeding 800mg. Tocilizumab will be administered as an intravenous infusion via a central or peripheral line over a one-hour period. The appropriate dose of drug will be mixed in a 100 ml bag of 0.9% saline, after removing an equivalent volume of saline, 0.4ml/kg, to match the added drug, so that the total volume is 100 mls. The infusion speed must be 10 mls per hour for 15minutes and then increased to 130 mls per hour for the next 45 minutes. After completion of the infusion of active study drug, at least 20 mls of 0.9% saline should be used to flush the drug through the giving set.

A single dose will be administered. If the treating clinician believe there has not been sufficient clinical improvement, repeat administration of the same dose can be administered between 12 and 24 hours after the initial dose.

Appendix 2: Royal Marsden Risk Assessing the risk of handling monoclonal antibodies ('MAB's)
TOCILIZUMAB

Part 1 Health and Safety score (please circle)		
Origin (O)	≥ 75% humanised (suffix – zumab or mumab)	**1**
	Partially humanised (chimeric; suffix –ximab)	**2**
	Completely murine (mouse or hamster protein; suffix –momab)	**3**
Toxicities arising from therapeutic use (T) SPC RoActemra 20mg/ml Concentrate for Solution for Infusion (Roche): Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. This data does not suggest a relevant risk for cancer initiation and progression under tocilizumab treatment. Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential. Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment.	Low risk of harm to the operator	**1**
	Theoretical risk of immunological, cutaneous or haematological adverse effects to the operator with prolonged low-dose exposure	**2**
	Known risk of immunological, cutaneous, haematological or other adverse effects to the operator with prolonged low-dose exposure	**3**
	Known or potential teratogenic or embryotoxic properties	**4**
	Known cytotoxic, radioactive or risk of initiating a cancer	**5**
Health & Safety score (O+T)	**1-3 = low risk, 4-5 = moderate 6+ = high**	**2**

Part 2 NPSA 20 Risk Assessment

NPSA score 4/5 (Amber). Medusa suggests preparation in a pharmacy aseptic unit where possible.
All staff preparing mabs such as tocilizumab should wear PPE – gown, gloves, protective eye wear and masks. (Medium risk)
This is a monoclonal antibody. Reduce direct handling to a minimum and wear appropriate personal protective equipment.
Following a risk assessment, implement risk reduction measures where appropriate which may include preparation in a pharmacy aseptic unit where this is possible.

IV infusion: Risk factors for tocilizumab in sodium chloride 0.9% 100mL bag: Therapeutic risk; Use of concentrate; Complex method; Use of a part vial or more than one vial; Use of pump.

Recovery Score

1	2				6	7	

TOTAL RISK FACTORS: 4 **OVERALL RISK RATING:** Amber

REMAP-CAP Score

1	2		4		6	7	

TOTAL RISK FACTORS: 5 **OVERALL RISK RATING:** Amber

Risk factors	Description	✓
Therapeutic risk	Where there is a significant risk of patient harm if the injectable medicine is not used as intended.	Yes
Use of a concentrate	Where further dilution (after reconstitution) is required before use, i.e. slow iv bolus not appropriate.	Yes
Complex calculation	Any calculation with more than one step required for preparation and/or administration, e.g. microgram/kg/hour, dose unit conversion such as mg to mmol or % to mg.	No
Complex method	More than five non-touch manipulations involved or others including syringe-to-syringe transfer, preparation of a burette, use of a filter.	Recovery No – 3 REMAP-CAP – Yes, possible
Reconstitution of powder in a vial	Where a dry powder has to be reconstituted with a liquid.	No

Use of a part vial or ampoule, or use of more than one vial or ampoule	Examples: 5ml required from a 10ml vial or four x 5ml ampoules required for a single dose.	Yes – more than one
Use of a pump or syringe driver	All pumps and syringe drivers require some element of calculation and therefore have potential for error and should be included in the risk factors. However it is important to note that this potential risk is considered less significant than the risks associated with not using a pump when indicated.	Yes
Use of non-standard giving set/device required	Examples: light protected, low adsorption, in-line filter or air inlet.	No
Total number of product risk factors	**Six or more risk factors = high-risk product (Red).** **Three to five risk factors = moderate-risk product (Amber).** **One or two risk factors = lower-risk product (Green).**	Recovery 4 = AMBER REMAP-CAP 5 = AMBER

Health & Safety Score	NPSA Score	Preparation details
Low	Green	Nurse
Low	Amber	Nurse
Low	Red	Nurse
Moderate	Green	Aseptics/closed system
Moderate	Amber	Aseptics/closed system
Moderate	Red	Aseptics
High	Green	Aseptics
High	Amber	Aseptics
High	**Red**	Aseptics

Where a product has been risk assessed as ‘Aseptics/closed system’, aseptics is preferable but if for any reason this is not possible or practical, the use of a closed-system device is a satisfactory alternative.