Pharmacy Manual: Preparation and Administration guidelines for REGN10933 + REGN10987

Version 4.0 04-Nov-2020

EudraCT Number: 2020-001113-21
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Protocol Title: Randomised Evaluation of COVID-19 Therapy

VERSION CONTROL

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4.0	Richard Haynes	04-Nov-2020	05-Nov-2020

Contents

1. Treatment Overview

Randomisation Part A: Eligible patients may be randomly allocated between the following treatment arms (although not all arms may be available at any one time):

- No additional treatment
- Corticosteroids (children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only)
- Azithromycin
- Intravenous immunoglobulin (children >44 weeks gestational age with PIMS-TS only)

Randomisation Part B: Simultaneously, eligible patients will be randomly allocated between the following treatment arms (provided there are no contraindications and the appropriate consent has been given):

- No additional treatment
- Convalescent plasma
- Synthetic neutralising antibodies (REGN10933+REGN10987)

Second randomisation for patients with progressive COVID-19: participants with progressive COVID-19 may undergo an optional second randomisation between the following treatment arms:

- No additional treatment
- Tocilizumab

2. IMPs in RECOVERY Trial

The treatments used within the RECOVERY Trial may change throughout the duration of the study. This pharmacy manual will only cover the IMP management of REGN109833 and REGN10987 (also known as REGN-COV2). The IMP management of all other drugs can be found in the Pharmacy FAQs on the RECOVERY Trial website.

The other IMPs (corticosteroids, azithromycin, immunoglobulin and tocilizumab) have been managed under the reduced risk of a Type A study. However the pharmacy management of REGN109833 and REGN10987 will require compliance with the additional requirements set out in this manual.

3. IMP descriptions

The investigational medicinal products (IMPs) in Randomisation Part B are described in Table 1 below.

Table 1:

Drug Description	Packaging	Storage Conditions
REGN10933 120mg/mL solution for infusion, single dose glass vial, 11.1mL withdrawable volume	1 vial per carton (Carton dimensions: 70 mm x 46 mm x 42 mm)	2-8°C Protect from light

REGN10987 120mg/mL solution for infusion, single dose glass vial, 11.1mL withdrawable volume	1 vial per carton (Carton dimensions: 70 mm x 46 mm x 42 mm)	2-8°C Protect from light

Each vial is identified by a batch number and a unique medication number (reference number). Please note that any kit numbered vial can be used for any patient. Stock is not patient specific. See Appendix 3 for IMP vial and carton labels details.

4. IMP ordering, supply and receipt

The initial supply of REGN10933 & REGN10987 will be sent by Regeneron (via YourWay which is the approved site in the UK) to each site. Initially there will only be a selected number of sites opened to this arm. Sites will be contacted if they are going to participate in this arm. The Principal Investigator will need to have completed training and delivery details for the IMP provided (on a form that the Oxford RECOVERY team will send) before IMP is shipped.

The initial shipment will contain either 15 or 21 vials of each IMP. Shipments are to be acknowledged in the IWRS system. All shipments will come with a temperature monitoring device. Follow the temperature monitoring device instructions included in the shipment (see Appendix 1 for instructions). Discard the temperature monitoring device after the temperature readout report has been downloaded.

IMP inventory of vials is managed by the IWRS system, so resupply shipments are automatically sent to sites when supply levels are low. The IWRS system will need to be updated after every allocation.

The vials must then be receipted into stock and written onto the master accountability log (see Appendix 2 for a template if required) following local SOPs for receipt of clinical trial materials. Routine receipt and handling of the vials should be done wearing nitrile gloves.

The vials are only for use within the context of the RECOVERY trial. The trial name does not appear on the labels: please ensure stock is segregated appropriately or additional labels added as per local practice.

5. IWRS system

The IWRS system used for the management of REGN10933 and REGN10987 is Cenduit (Cenduit User Guide is available on the RECOVERY website).

Sites will be expected to use the IWRS system to perform the following activities:

- Acknowledge shipments on arrival
- Update kit status to ‘allocated’ after allocating kit to patient
- Update kit status to ‘quarantined’ if there has been a temperature excursion at site
- Update kit status to ‘damaged’ if stock has been damaged at site or was received damaged
- Update kit status to ‘lost’ if stock has been lost at site

The Dashboard allows sites to view:

- In transit shipments
- Recent transactions

5.1 Acknowledging shipments

From user dashboard, in transit shipments click on the shipment number. The user is directed to the site shipment confirmation page and should confirm that drop down menu is displaying the correct shipment number. Follow on screen instructions. There is the option for sites to state whether the whole shipment has been damaged or if individual vials have been damaged, as well as if there has been a temperature excursion during transit. Once complete and submitted the site will receive an email confirmation.

If temperature excursion during transit remember to inform local PI/team that stock has been quarantined, so that the PI can indicate that synthetic neutralising antibodies are not available for randomisation.

5.2 Site material update

To update the kit status sites will need to select the site material update link within the Cenduit system. Under site material update, sites can change individual kit statues from available to allocated, damaged, lost or quarantined. Multiple vials can be selected at a time by holding down the 'control' button. Sites should manually update the kit status of each vial in Cenduit prior to dispensing to patient, from available to dispensed (as the IWRS will check the expiry date)[1].

5.3 Re-supply

Sites will be provided with sufficient IMP for 5 participants initially. Once 4 participants' worth has been recorded as no longer available (eg, allocated, lost etc.) in the IWRS a further supply will be sent. If site activity requires a larger supply this can be requested from the RECOVERY team: either 'medium' (7 participant supply, re-supply once 2 no longer available) or 'large' (9 participant supply, re-supply once 3 no longer available).

6. IMP storage and precautions

All REGN10933 and REGN10987 vials must be stored at 2 – 8°C.

Protected from light.[2]
Single use only.
Do not use beyond expiry date. Note: the IMP is not labelled with an expiry date, but the IWRS will be updated with this information. This is why kit status should be updated on IWRS before the IMP is reconstituted (or see footnote 1).

Temperature logs must be maintained using calibrated temperature monitoring equipment in order to demonstrate the study drug has been stored at all times under the correct storage conditions. If

[1] If a site cannot update Cenduit prior to reconstituting the IMP, then they may do so later provided that their local procedure includes a step to check the expiry date on the QP documentation sent with each shipment. This local procedure must be written, locally approved and the master kept in the Site Trial file.
[2] During and after reconstitution, it is no longer necessary to protect from light.

your pharmacy has temperature monitoring in place, the records from this system may be used. Copies must be available for regulatory inspection if required.

The label on the REGN100933 and REGN10987 vials will not contain the expiry date. The expiry date can be found on the packing note and on the QP release document. Ensure that the expiry date on the QP release document is annotated and checked on the master accountability log when receipting, or follow local SOPs. The IWRS will provide a second check of this when the status is updated.

Sponsor's permission is not required for the transport of REGN10933 and REGN10987 vials from one site to another, but temperature monitoring is required for such transfers. Temperature monitoring is not required when transporting the final infusion bag from the aseptic unit to the ward (unless the ward is on a separate site in which case temperature monitoring is recommended, except where a validated shipper is used). The transport and temperature monitoring of stock or final prepared product should be carried out as per site's local SOPs.

6.1 Temperature excursions

When the measured or recorded temperature contains decimals, then number should be rounded to the nearest whole number. For example, if the acceptable temperature range for storage is 2 – 8°C, then:

- Round 1.5, 1.6, 1.7, 1.8, and 1.9 up to 2°C
- Round 8.1, 8.2, 8.3 and 8.4 down to 8°C

Therefore by applying the above rounding rules, measured or recorded temperatures between 1.5 °C to 8.4°C will not be required to report temperature excursions to RECOVERY trial team. Any measured or recorded temperatures outside of these ranges will need reporting back to the RECOVERY trial team using the RECOVERY temperature excursion form (see RECOVERY trial website for a copy of this form) and emailed to recoverytrial@ndph.ox.ac.uk

Affected stock must be physically quarantined until further guidance is given. The affected stock will need to be updated within the IWRS system to 'quarantined'. Remember to inform local PI/team that stock has been quarantined, so that they can indicate that synthetic neutralising antibodies are not available for randomisation. If all stock is affected Oxford can indicate this centrally (e-mail to recoverytrial@ndph.ox.ac.uk), but **must** be informed when new stock arrives so this block can be removed.

6.2 Recall of IMP

In the event of a study medication recall, which necessitates the return of REGN10933 and REGN10987 supplies, sites will be given further information on this as required.
Label the stock as 'quarantined' and hold in a quarantine area, ideally at 2 to 8°C, until the information is received.

7. IMP accountability

Full accountability must be maintained for REGN10933 and REGN10987. Sites may use their own master and patient specific accountability logs. A template master accountability log and patient specific accountability log is available (see Appendix 2).

Sites must update the IWRS system before (or shortly after – see Section 5) each patient dispensing to ensure stock management within the IWRS system is up-to-date.

7.1 Destructions and Returns

Used vials and cartons maybe destroyed as per sites local practice; no approval from sponsor required. If a dose is prepared and not suitable for use or not administered, then record on accountability logs and dispose of as per local SOP; no approval from sponsor required.

Expired vials and unused vials at the end of study are to be returned to Regeneron. Sites will be given further information on this when this occurs.

8. REGN10933+REGN10987 infusion prescribing, preparation and administration

The NPSA risk score is 6 (red) and the health and safety risk is moderate (see Oxford University Hospitals NHS Foundation Trust (OUH) local risk assessment (Appendix 4) and REGN safety data sheets (Appendices 5 and 6). Therefore, OUH have assessed that locally the infusion will be prepared within an aseptic unit. The manufacturer's pharmacy manual previously stated to make in a laminar flow cabinet. They have now removed this requirement. Individual site decisions to prepare this infusion in the aseptic unit or on the ward should be based local procedures and on the outcome of a documented risk assessment and retained within the trial file. All REGN10933+REGN10987 infusions must be prepared using aseptic techniques.

A senior pharmaceutical advisor at the MHRA has confirmed that the preparation of REGN-COV2 mAbs in RECOVERY would not be considered manufacturing.

REGN10933 and REGN10987 vials must only be used for participants allocated to synthetic neutralising antibodies treatment in the RECOVERY study. Vials must not be supplied to patients who have not consented to treatment or to patients who are not part of the RECOVERY study.

8.1 IMP prescribing

REGN10933+REGN10987 infusion should be prescribed as per local policy for clinical trials by a clinician authorised to prescribe. There are currently no known drug-drug interactions with REGN10933 and REGN10987; any potential serious interactions should be reported to Central Coordinating Office (see protocol).
Note: Flushes prescribing can be in line with local SOP.

8.2 IMP preparation

Facilities for preparation: Regeneron recommend that REGN10933 & REGN10987 preparation should always use aseptic technique*. The host trust should undertake a SPS risk assessment, as required for any monoclonal antibody (mAb) under the 'Guidance on the Safe Handling of Monoclonal Antibody (mAb) products', to determine whether it should be prepared in a clinical medicine preparation area (ward) or in the pharmacy aseptic unit. The risk assessment should assess and document how the preparation will protect the safety of staff preparing and the product. A sample risk assessment is included in Appendix 4 which concludes REGN10933 & REGN10987 should be prepared in the pharmacy aseptic unit**.

*The previous requirement from the manufacturer to require preparation in a laminar flow hood or isolator has been removed, because the risk of microbial contamination with this vial presentation of IMP is lower than in other US studies, which used multi-dose FEP bags.

**If preparing in an aseptic unit:

The risk assessment will determine the type of isolator or cabinet to be used to prepare the mAB infusion.

If a trust usually procures dispensed doses of mAbs from another NHS trust or commercial aseptic unit, this is permitted providing the SPS guidance 'Supply of Aseptically prepared doses of IMPs across Legal Boundaries'[3] is followed. The dose must be labelled to comply with Annex 13 but the location of the labelling is determined in SPS guidance.

Routine receipt and handling of the vials should be undertaken wearing nitrile or other protective gloves.

Safety: See safety data sheets in appendices, recommended that sites handled any spill as per local procedures for a mAb spill. If sites do not have mAb spill kits, then a cytotoxic spill kit would contain the necessary components to deal with a mAb spill. The manufacturer has confirmed that potential spills in hospital setting do not require the wearing of respiratory masks with HEPA filters.

Preparation: Each dose of REGN10933 4g & REGN10987 4g is prepared in an intravenous (IV) infusion bag containing 250mL 0.9% sodium chloride. Do not use an infusion bag containing any other diluents. The infusion bag should be made of Polyolefin (PO) (or Polyvinyl chloride (PVC) containing DEHP). The syringes should be made of polypropylene. The needle gauge must be 18G to 21G. Drug and volume checks should be performed in accordance with local practice.

If sites normally use a venting needle during preparation then this is permitted. Dispensing pins are not recommended, as the manufacturer recommends the use of syringes and stainless steel needles only.

Note: Any kit numbered vial can be used for any patient. Stock is not patient specific.

1. Remove vials from refrigerator and allow to warm to room temperature (minimum 15 minutes, maximum up to 24 hours. There is no requirement to record the duration of the warming time).
2. Obtain one 250mL IV bag of 0.9% sodium chloride
3. Use an appropriate combination of new syringes to withdraw 66.6mL of 0.9% sodium chloride from the IV bag and discard.
4. Using new syringes with new needles withdraw a total volume 33.3mL REGN10933 from three REGN10933 vials (11.1ml from each vial)
5. Add the 33.3mL of REGN10933 to the IV bag, check. Invert gently (do NOT shake) the IV bag 10 times to ensure that the REGN10933 and IV solution are well mixed

[3] https://www.sps.nhs.uk/articles/supply-of-aseptically-prepared-doses-of-imps-across-legal-boundaries-version-2-october-2019/

6. Using new syringes with new needles, withdraw a total volume of 33.3mL of REGN10987 from three REGN10987 vials (11.1ml from each vial)
7. Add the 33.3mL of REGN10987 to the IV bag containing REGN10933. Invert gently (do NOT shake) the IV bag 10 times to ensure that the two investigational products and IV solution are well mixed. Add a closure to entry port of the infusion bag as per local practice.
8. Label the infusion bag ensuring compliance with local practice and Annex 13[4] labelling and ensure that the trial name is clearly stated.
9. Used consumables and empty vials should be placed in an appropriate bin, sealed and disposed of as per local procedures for pharmaceutical waste

The study label should include the following information in addition to standard label UK requirements:

- Study title
- EudraCT number
- Sponsor
- Participant Trial Number
- Statement: 'For Clinical Trial Use Only'

RECOVERY Trial
EudraCT: 2020-001113-21
For Clinical Trial Use Only
Participant No: _____
Sponsor: University of Oxford

The above manufacturing steps are recommended by the manufacturer, however the stability concentration range is 1 – 80mg/mL (total mAb); individual mAb is 0.5mg/mL – 40mg/mL and therefore removal of the equivalent drug volume is not mandated. Sites must ensure that the brand of IV bag being used can hold this additional volume safely and that there is no additional risk of spillage/inadvertent loss when the ward nurse spikes the bag.

Sites may choose to add both mAbs into the IV bag without prior mixing in between. However, sites must ensure proper mixing after both mAb additions.

Expiry of prepared dose: The prepared and labelled infusion bag should be used immediately (within 4 hours). If not used immediately, the prepared IV bag may be kept between 2°C and 8°C for no longer than 36 hours (this includes 4 hours at room temperature including time for warming and administration). If it has been refrigerated, the IV bags must be warmed up to room temperature (at least 30 minutes) prior to administration (stability information provided by manufacturer).

8.3 IMP administration

REGN10933 & REGN10987 will be administered as an IV infusion over 60 minutes ± 15 minutes (including flush). No pre-medication is recommended prior to infusion. A sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter is required for dosing. The filter membrane must be made of polyethersulfone (PES) membrane. The in-line filter and the IV infusion pump must be able to deliver as little as 0.2mL/minute or 12mL/hour accurately. Flush the line with 25-50mL of 0.9% sodium chloride at the end of the infusion.

[4] Annex 13 EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

The patient will be monitored as per local practice post infusion for a biological infusion. All reactions must be reported to the Central Coordinating Office as detailed in the protocol.

It is recommended that nurses who are pregnant or breast feeding do not administer, given IgG do cross the placenta and into breast milk.

9. Contact Details

Contact the Sponsor which is University of Oxford via the generic RECOVERY Trial contact information below for any queries:

Email: recoverytrial@ndph.ox.ac.uk
Tel: 0800 1385451

Appendix 1 - Temperature monitoring device instructions

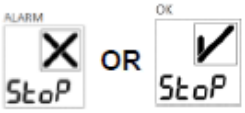
Libero C – Instructions for use

INSTRUCTIONS TO STOP THE LIBERO:

1) Upon receipt, immediately place the medication kits into the storage area, retrieve the temperature monitor and press the "Start/Stop" key for 3 seconds in order to stop the device.

NOTE: alternatively plug the LIBERO directly into a USB port to stop the device

2) When the monitor stops, the display on screen looks as follows:

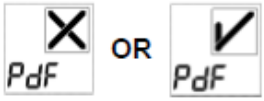


a) If the ✓ icon is displayed: the temperature during transport stayed in the defined range.

b) If the ✗ icon is displayed: a temperature excursion has occurred during the transport.

INSTRUCTIONS FOR DOWNLOADING THE DATA:

1) Plug the LIBERO into the USB port of any PC. The display shows „PdF":



2) Within a few seconds, a PDF evaluation report will automatically be generated and presented in the explorer. In case the auto start functionality is not activated on your PC, go to "desktop" and search for a drive named LIBERO.

3) Copy or "drag & drop" the file from the LIBERO drive to your local drive or network folder.

- Never use a PDF Editor application to save the PDF file otherwise the embedded data will be lost and no further analysis will be possible.
- Do not rename the PDF report generated when copying it on your local drive/network folder

Appendix 2 – Accountability logs

Sample Patient Accountability Log

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Patient Specific Accountability Log REGN10933 120mg/mL solution for infusion, 11.1mL vial RECOVERY Trial EudraCT: 2020-001113-21

Subject/Patient Initials: _____ **Subject/Patient Trial ID Number:** _____

Date	Visit Number	Dose	Kit Number (enter each kit on a separate line)	Batch Number	Expiry Date	Disp by (Initial)	Check by (Initial)	Vials disp on IWRS	Used vials destroyed	
								Date Initial	QTY	Date Initial

Comments:

Version 1.1 | Date of issue: 04-Nov-2020 | Reason for issue: update to include vial size | Page___ of ___

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Patient Specific Accountability Log REGN10987 120mg/mL solution for infusion, 11.1mL vial RECOVERY Trial EudraCT: 2020-001113-21

Subject/Patient Initials: _____ **Subject/Patient Trial ID Number:** _____

Date	Visit Number	Dose	Kit Number (enter each kit on a separate line)	Batch Number	Expiry Date	Disp by (Initial)	Check by (Initial)	Vials disp on IWRS	Used vials destroyed	
								Date Initial	QTY	Date Initial

Comments:

Sample Master Accountability log

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Kit Number Master Accountability Log REGN10933 120mg/mL solution for infusion, 11.1mL vial RECOVERY Trial EudraCT: 2020-001113-21

Batch Number: **Expiry Date:**

Minimum Stock Level IWRS controlled **Minimum shelf life:**

Date Receipted	Kit No	Receipted by (initials)	To be completed for dispensed items					Returned to sponsor		Updated on IWRS system (Quarantined)	
			Date Dispensed	Subject/ Patient's Initials	Subject/patient Trial ID Number	Dispensed by (initials)	Checked by (initials)	Date Initial	Check Date & Initial	Date	Initials

Comments:

Stock Check Complete (Initial + Date)

Version 1.0 | Date of issue:18-Sept-2020 | Reason for issue: New Log | Page___ of ___

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Kit Number Master Accountability Log REGN10987 120mg/mL solution for infusion, 11.1mL vial RECOVERY Trial EudraCT: 2020-001113-21

Batch Number: **Expiry Date:**

Minimum Stock Level IWRS controlled

Date Receipted	Kit No	Receipted by (initials)	To be completed for dispensed items					Returned to sponsor		Updated on IWRS system (Quarantined)	
			Date Dispensed	Subject/ Patient's Initials	Subject/patient Trial ID Number	Dispensed by (initials)	Checked by (initials)	Date Initial	Check Date & Initial	Date	Initials

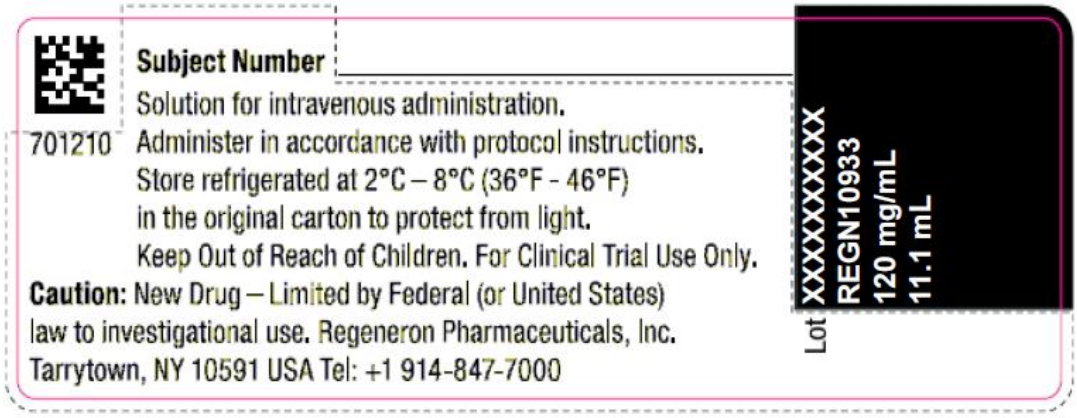
Comments:								
Stock Check Complete (Initial + Date)								

Version 1.0	Date of issue:04-Nov-2020	Reason for issue: new log	Page____ of ____

Appendix 3 – IMP vial and carton labelling

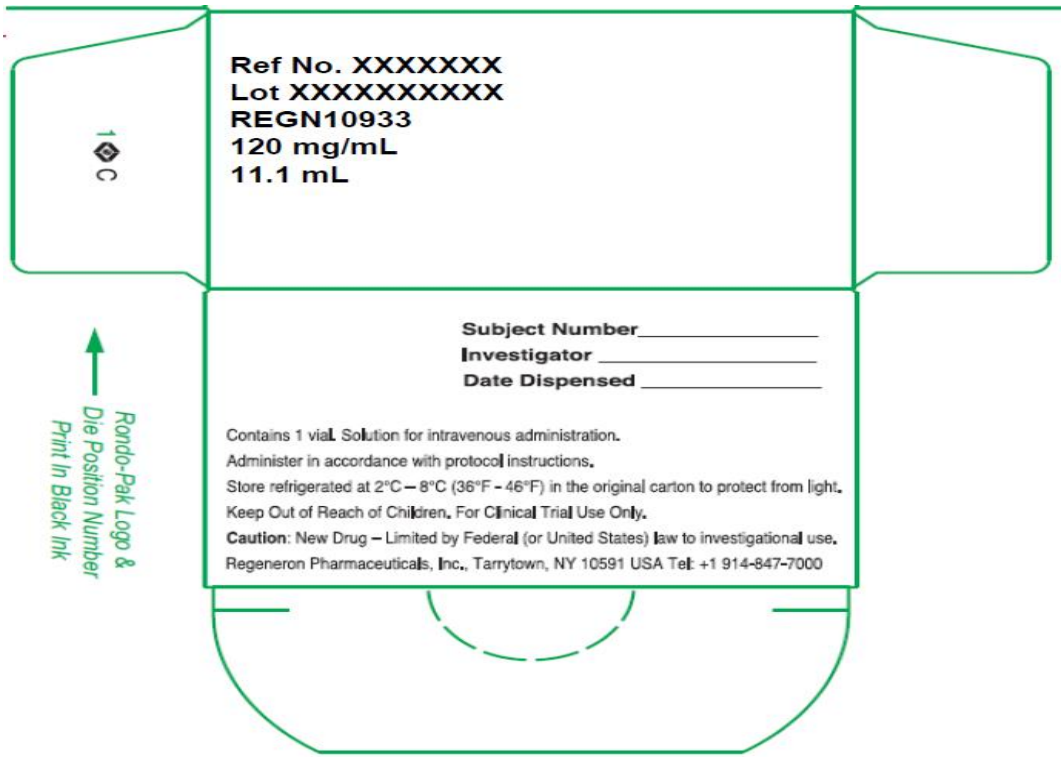
REGN10933 and REGN10987 will be supplied to the studies in 20R sterile glass vial with 11.1 mL withdrawable volume included within a carton. REGN10933 20R Vial Label (Figure 1), REGN10933 20R Vial Carton Label (Figure 2), REGN10987 20R Vial Label (Figure 3), and REGN10987 20R Vial Carton Label (Figure 4) are provided below.

Figure 1: REGN10933 20R Vial Label



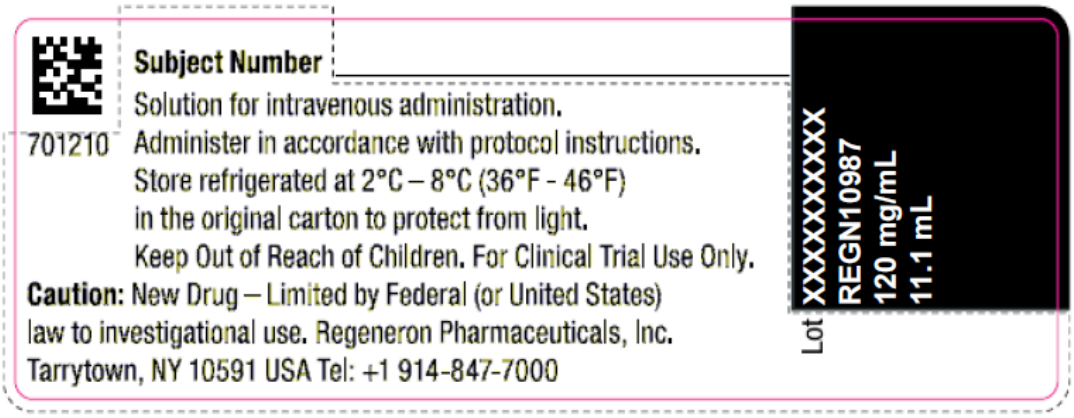
The Lot Number (XXXXXXXXXX) variable information is printed prior to packaging.

Figure 2: REGN10933 20R Vial Carton Label



The Lot Number (XXXXXXXXXX) and the reference number (XXXXXXX) variable information are printed prior to packaging.

Figure 3: REGN10987 20R Vial Label



The Lot Number (XXXXXXXXXX) variable information is printed prior to packaging.

Figure 4: REGN10987 20R Vial Carton Label

The Lot Number (XXXXXXXXXX) and the reference number (XXXXXXX) variable information are printed prior to packaging.

Appendix 4 - OUH local risk assessment

OUH General Risk Assessment Form

REGN10933+REGN10987 Preparation Risk Assessment

The SPS yellow cover document 'Guidance on the safe handling of monoclonal antibody (mAbs) products'[1] recommends 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 Hospitals NHS Trust	**Division**	CSS
Directorate	Covid wards/Pharmacy/ICU	**Department**	Pharmacy
Location Exact	N/A	**Date**	02/10/2020

Assessors(s)	
1	Clinical Trials Pharmacist
2	Preparative Services Pharmacist
3	Senior Pharmacist Manager

The Hazard or perceived risk

Risks:

1. Risks of exposure to REGN10933+REGN10987 (also known as REGN-COV2) for staff handling the product due to the nature of or mode of action of the agent
2. Risks to patient receiving REGN10933+REGN10987 due to the potential for errors or contamination during the preparation of the product

Cause: Novel humanised monoclonal antibodies and not standard practice to combine two mAbs in one infusion. **Affect:** Staff could develop a reaction or adverse effect from REGN10933+REGN10987 from bench preparation. 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 Safety Data Sheet for REGN10933[4] and REGN10987[5]

- Dermal absorption – Section 2: Proteins, in general, can cause skin sensitization. Section 8: wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Wear safety glasses with side shields, chemical splash goggles and full face shield if necessary. Base the choice of skin/eye/face protection on the job activity, potentials for skin contct and solvents and reagents in use.
- Inhalation absorption – Section 2: Although recombinant protein particles are fairly large in size, it is not known if systemic effects can occur following accidental inhalation. Proteins, in general, can cause respiratory sensitization. Section 7: Do not breathe vapour or mist. Section 8: If vials are opened/crushed/broken: choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. The manufacturer have confirmed that wearing of respiratory filter applies to industry and not hospitals.
- Oral absorption – Section 2: the likelihood of systemic effects following accidental ingestion is low,

due to the rapid breakdown of proteins in the digestive tract. IB - Route of administration is IV infusion or SC injection.

- Mucosal Absorption – No information, Section 8. Wear gloves to prepare medicine. Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Wear safety glasses with side shields. Formulation is liquid.
- Exposure/Engineering controls: Section 8: Use local exhaust and/ or enclosure at aerosol/mist-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling.
  Do not cause liquid to become airborne. Manage spills using absorbant material and place in waste container, decontaminate area twice, placing in to waste container and seal.

1.2 Antigenicity: IB. Fully Human IgG1 monoclonal antibody

1.3 Toxicity from IB[3] and Safety Data sheet for REGN10933[4] and REGN10987[5]

- Cytotoxicity – SDS Section 11: no data available. Manufacturer states studies will not be carried out to assess cytotoxicity.
- Carcinogenicity – SDS Section 11: no data available. Manufacturer states studies will not be carried out to assess carcinogenicity as the mAbs are targeting an exogenous target they would not expect any findings associated with carcinogenicity
- Genotoxicity or Mutagenicity - SDS Section 11: no data available. Manufacturer states studies will not be carried out to assess genotoxicity or mutagenicity as the mAbs are developed to specifically target the exogenous virus and mAbs are not expected to interact with DNA to cause any concerns with genotoxicity or mutagenicity
- Teratogenicity or other developmental toxicity – IB section 1.6 potential risk of embryo-foetal toxicity(based on observations from non clinical studies, clinical studies, the mechanism of action of REGN10933+REGN10987, as well as risks associated with mAbs in general). IB section 4.3.2 and 6.1.2.3 no reproductive and developmental toxicology studies were performed. SDS section 11: no data available. Manufacturer states studies will not be carried out to specifically addess the teratogenicity or other developmental toxicity as exogenous targeting mAbs are not expected to be associated with reproductive or developmental toxicity.
- Organ toxicity – IB section 4.1.2 and 4.3.1 no observed adverse effect seen in the cynomolgus monkey
- Immunogenicity – IB section 1.6, 6.1.2.1 and 6.1.2.2 potential risk of clinical consequences of Immunogenicity (anti-REGN10933 antibody or anti-REGN10987 antibody formation) and the potential risk of systemic hypersensitivity reactions (including acute infusion reactions and/or injections site reactions) (based on observations from non clinical studies, clinical studies, the mechanism of action of REGN10933+REGN10987, as well as risks associated with mAbs in general). IB section 4.3.3. no drug-related clinical observations at the IV or SC administration sites in the cynomolgus monkey. IB section 5 in the initial 30 subjects no hypersensitivity reactions or infusion related reactions reported when the REGN10933 and REGN10987 were administer together from the same infusion bag.

[There is no tool for risk stratification –> qualitative decision.]

Summary:
Internal exposure risk: Looking at the above data and considering exposure to mABs in general the following should be considered:

- Dermal absorption of mAbs is not considered to be a mechanism of internalisation. However there is a risk of skin sensitisation; wear gloves and water repellant apron to mitigate potential risks.
- Inhalation is considered a viable route of internalisation, there are unknown effects at long term low dose occupational exposure levels. Exposure would be greatest during preparation. Mitigate risk via mask (SPS guidance recommends use of FFP mask) and good aseptic technique.

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- Mucosal absorption is considered a viable route of internalisation with unknown effects at long term low dose occupational exposure levels. Exposure would be greatest during preparation. Mitigate risk via wearing appropriate PPE (mask (SPS guidance recommends use of FFP mask) and eye protection).

Toxicity: Testing requirements for mAbs by the regulators means that the routinely lisited toxicity tests are not mandated. The IB states that there is a potential risk of embryo-foetal toxicity. Due to the limited information available on toxicity from repeated low dose occupational exposure and the potential embryo-foetal toxicity the health and safety risk has been scored as moderate – **also see Appendix 2.** The potential embryo-foetal toxicity to staff could be partly mitigated by not permitting handling, preparation and administration by pregnant and breastfeeding staff.

2. **NPSA injectable risk score – see Appendix 2:**
   Score: 6 – RED

3. **RMH monoclonal antibody occupational exposure risk assessment – see Appendix 2:**
   Incorporates health and safety risk – moderate and NPSA risk – red
   Overall: RMH risk assessment recommends aspectic unit preparation

Conclusion

REGN10933 + REGN10987 are both fully human, non-competing, IgG1 anti-SARS-CoV-2 monoclonal antibodies, which will be given as a combination therapy[3].

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 an aseptic unit is required for preparation.

In the RECOVERY clinical trial protocol, REGN10933 4000mg + REGN10987 4000mg is to be given as a single intravenous infusion as soon as possible after randomisation[5]. Therefore, the dose could be delayed as it needs to be made up within the aseptic unit during their working hours – check with local unit for times.

Staff who are pregnant or breastfeeding should avoid preparing or administrating the IV infusion, due to lack of safety data and potential risk of embryo-foetal toxicity.

Consideration should be given to the experience of staff preparing the product. The NPSA risk assessment highlights greater than 5 manipulation steps (complex method). Ward staff may not be experienced in preparing mAb products and products with this number of manipulations from 6 vials. The increase in the number of preparation steps increases the opportunity for manufacturing error, occupational exposure and/or microbial contamination. To mitigate this particular risk preparation should be undertaken by experienced well trained staff. In some hospitals this may be considered in particular ward environments while others may consider the need of an aseptic unit.

At OUH we recommend that the IMP dose be prepared in pharmacy with clean room facilities in a negative pressure cabinet/isolator with suitable HEPA filtration. Staff must be suitabley trained in aseptic preparation.

Refer to the Risk Matrix overleaf to calculate the risk level (risk score)					
Predicted Frequency (likelihood)	1	Predicted Outcome (consequence)	3	Initial Risk Score	3

Precautions in place at the point when risk was identified (Initial Controls)
N/A

Additional precautions implemented by the assessor (Current Controls)					
Due to insufficient safety data around the long term risks to the operator and the complexity of preparation, the REGN10933+10987 infusion should be prepared within the Trust's Aseptic Unit in response to each patient's prescription request					
Predicted Frequency	1	Predicted Outcome	3	Current Risk Score	3

Best precautions that can be implemented (Best Controls)				
Action Plan to Implement Best Controls				
No	Action	Responsibility of (Name and Job Title)	By when	Status (Pending, In progress or Complete)
1	Request OUH Aseptic Unit trial set up	Clinical Trials Pharmacist		Pending

Risk Rating (if any) after Implementation of Best Controls					
Predicted frequency	1	Predicted Outcome	3	Target Risk Score	3
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. SPS Yellow Cover Document: Guidance on the safe handling of Monoclonal Antibody Products, 5th Edition, published November 2015. Accessed via www.SPS.nhs.uk
2. OUHNHSFT Guidelines for the preparation and manipulation of monoclonal antibodies and related compounds (fusion proteins) March 2016
3. Investigator's Brochure REGN10933+REGN10987 Edition 3 10Jul2020
4. Safety Data Sheet for REGN10933, 14th May 2020
5. Safety Data Sheet for REGN10987, 14th May 2020
6. RECOVERY protocol Version 9.1, 18th Sept 2020
7. Alexander M et al. Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer trament by healthcare personnel. Internal Medicine Journal 2014; 44.

Appendix 1: Clinical Trial Protocol details

1. **Dose in Recovery[6] Clinical Trial protocol:**

2.4.2 Main randomisation part B [UK only]:

Eligible patients may be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing. **Participants in this randomisation should have a serum sample sent to their transfusion laboratory prior to randomisation in which presence of antibodies against SARS-CoV-2 may be tested.**

- **No additional treatment**
- **Convalescent plasma** Single unit of ABO compatible convalescent plasma (275mls +/- 75 mls) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12 hour interval between 1st and 2nd units). ABO identical plasma is preferred if available. The second transfusion should not be given if patient has a suspected serious adverse reaction during or after the first transfusion.
- **Synthetic neutralising antibodies (adults and children aged ≥12 years[c] only).** A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250ml 0.9% saline infused intravenously over 60 minutes +/- 15 minutes as soon as possible after randomisation

[c] Older children who weigh <40kg will also not be eligible for this treatment.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

For randomisation part B, the randomisation program will allocate patients in a ratio of 1:1:1 between each of the arms. If the active treatment is not available at the hospital, the patient does not consent to receive convalescent plasma, or is believed, by the attending clinician, to be contraindicated for the specific patient, then this fact will be recorded via the web-based form and the patient will be excluded from Randomisation part B.

Appendix 2: Royal Marsden Risk Assessing the risk of handling monoclonal antibodies ('MAB's)
REGN10933

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)	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	5

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Appendix 2: Royal Marsden Risk Assessing the risk of handling monoclonal antibodies ('MAB's)
REGN10987

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)	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	5

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Part 2 NPSA 20 Risk Assessment
NPSA score 6 (Red).
All staff preparing mabs such as REGN10933+REGN10987 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 REGN10933+REGN10987 in 250mL sodium chloride 0.9% bag: Therapeutic risk; Use of concentrate; Complex method; Use of a part vial or more than one vial; Use of pump; Use of non-standard giving set/device required.

1 2 3 4 5 6 7 8 TOTAL RISK FACTORS: 6 OVERALL RISK RATING: RED

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.	Yes
Reconstitution of powder in a vial	Where a dry powder has to be reconstituted with a liquid.	No

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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 – 3 vials of REGN10933 and 3 vials of REGN10987
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 – fluid displacement or linear peristaltic infusion pump required
Use of non-standard giving set/device required	Examples: light protected, low adsorption, in-line filter or air inlet.	Yes – 0.2micron in-line or add-on filter made of polyethersulfone membrane required
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).**	6 = RED

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

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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.

Appendix 5 – REGN10933 Safety Data Sheet

REGENERON **SAFETY DATA SHEET**

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Regeneron Pharmaceuticals, Inc. **777 Old Saw Mill River Road** **Tarrytown, NY 10591** **Main: +1 (914) 847-7000** **Fax: +1 (914) 847-7991** **E-mail:**	**Emergency telephone number:**	1-(914) 847-2222 (U.S. and Canada) 24-hour Availability

SDScoordinator@regeneron.com

Product identifier	**REGN10933, Labeled Drug Product, Lot 9046600001**
Synonyms	**Anti-SARS-CoV-2 REGN10933 LDP**
Trade names	None identified
Chemical family	Monoclonal antibody
Relevant identified uses of the substance or mixture and uses advised against	Active pharmaceutical for research and development purposes only.
Note	The pharmacological, toxicological, and ecological properties of this product/mixture have not been fully characterized. This data sheet will be updated as more data become available.
Issue Date	May 14, 2020

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture	
Regulation (EC) 1272/ 2008 [GHS]	Not classified - substance not yet fully tested.
Directive 67/548/EEC or 1999/45/EC	Not classified - substance not yet fully tested.
Label elements	**pictogram**
CLP/GHS hazard	

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None required

SECTION 2 - HAZARDS IDENTIFICATION ...continued

CLP/GHS signal word	Warning
CLP/GHS hazard statements	None required
CLP/GHS precautionary statements	None required
Risk (R) Phrase(s)	None required
Safety Advice	None required
Other hazards	REGN10933 LDP is a monoclonal antibody. As the product/mixture has not yet been tested in humans, hazards associated with exposure are not known. In a workplace setting, the likelihood of systemic effects following accidental ingestion is low, due to the rapid breakdown of proteins in the digestive tract. Although recombinant protein particles are fairly large in size, it is not known if systemic effects can occur following accidental inhalation. Proteins, in general, can cause skin and/or respiratory sensitization.
US Signal word	Caution
US Hazard overview	Contains a recombinant protein. Substance not yet fully tested.
Note	This substance is not classified as dangerous/hazardous according to Directive 67/548/EEC, Regulation EC No 1272/2008 (EU-CLP), and applicable US regulations. Its pharmacological, toxicological, and ecological properties have not been fully characterized. The CLP/GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
REGN10933 LDP	N/A	N/A	12.0%	Not classified	Not classified

Note The REGN10933, LDP ingredient listed above is the active ingredient. The remaining components are non-hazardous and/or present at amounts below reportable limits. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures **Attention Needed**

Immediate Medical No. If exposed or concerned: Get medical advice/attention.

SECTION 4 - FIRST AID MEASURES …continued

Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit toxic gases of carbon monoxide and carbon dioxide, oxides of nitrogen and other nitrogen-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. As product is an aqueous solution, it is not expected to be flammable or explosive.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency	**procedures**
	Environmental precautions

If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe mist/spray.

No information identified. Monoclonal antibodies are expected to break down rapidly in the environment.

SECTION 6 - ACCIDENTAL RELEASE MEASURES...continued

Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. Do not breathe vapor or mist.
Conditions for safe storage including any incompatibilities	-80°C
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Wash hands, face and other potentially exposed areas immediately in the event of physical contact.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
REGN10933 LDP	--	--	--

Exposure/Engineering controls	Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/ or enclosure at aerosol/mist-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling. High-energy operations such as spraying should be done within an approved emission control or containment system.
Respiratory protection	If handling bulk product or vials are opened/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. In situations with significant potential for aerosolization, the use of a properly fitted air-purifying respirator with appropriate HEPA filters is recommended.
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION…continued

Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, and full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Liquid
Color	Colorless to Light Yellow
Odor	Odorless
Odor threshold	No information identified.
pH	6.0
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	No information identified.

Vapor pressure	No information identified.
Vapor density	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Relative density	No information identified.
Water solubility	Soluble.
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	Not applicable (Mixture)
Molecular formula	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	Stable under normal handling and storage conditions.
Chemical stability	No information identified.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

Route of entry	Not expected to be well-absorbed by inhalation, skin contact, or ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
REGN10933 LDP	--	--	--	--

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

Irritation/Corrosion	No data available.
Sensitization	No data available.
STOT-single exposure	No data available. As the product contains material that is derived from protein, there is potential for the mixture to cause an allergic response in humans.
STOT-repeated exposure/Repeat-dose toxicity	No data available.
Reproductive toxicity	No data available.
Developmental toxicity	No data available.
Genotoxicity	No data available.
Carcinogenicity	No data available.
Aspiration hazard	No data available.
Human health data	See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
REGN10933 LDP	--	--	--

Persistence and Degradability	No data available. Monoclonal antibodies are proteins likely to break down rapidly in the environment.
Bioaccumulative potential	No data available.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.
Note	The environmental characteristics of this mixture have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Used product should be disposed of according to local, state, and federal regulations. All wastes containing the material should be properly labeled.

Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this substance is not regulated as a hazardous material/ dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this substance is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Substance not fully tested - avoid exposure.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Caution - substance not yet fully tested.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	Not applicable.

SECTION 16 - OTHER INFORMATION …continued

Full text of H phrases, P phrases and GHS classification	Not applicable.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Revisions	This is the first version of this SDS.
Disclaimer	The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.

Appendix 6 – REGN10987 Safety Data Sheet

REGENERON **SAFETY DATA SHEET**

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591
Main: +1 (914) 847-7000
Fax: +1 (914) 847-7991
E-mail:

SDScoordinator@regeneron.com

Emergency telephone number: 1-(914) 847-2222 (U.S. and Canada)

24-hour Availability

Product identifier	**REGN10987, Labeled Drug Product, Lot 9047100001**
Synonyms	**Anti-SARS-CoV-2 REGN10987 LDP**
Trade names	None identified
Chemical family	Monoclonal antibody
Relevant identified uses of the substance or mixture and uses advised against	Active pharmaceutical for research and development purposes only.
Note	The pharmacological, toxicological, and ecological properties of this product/mixture have not been fully characterized. This data sheet will be updated as more data become available.
Issue Date	May 14, 2020

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Regulation (EC) 1272/ 2008 [GHS]	Not classified - substance not yet fully tested.
Directive 67/548/EEC or 1999/45/EC	Not classified - substance not yet fully tested.

Label elements: **pictogram**

CLP/GHS hazard

None required

SECTION 2 - HAZARDS IDENTIFICATION …continued

CLP/GHS signal word	Warning
CLP/GHS hazard statements	None required
CLP/GHS precautionary statements	None required
Risk (R) Phrase(s)	None required
Safety Advice	None required
Other hazards	REGN10987 LDP is a monoclonal antibody. As the product/mixture has not yet been tested in humans, hazards associated with exposure are not known. In a workplace setting, the likelihood of systemic effects following accidental ingestion is low, due to the rapid breakdown of proteins in the digestive tract. Although recombinant protein particles are fairly large in size, it is not known if systemic effects can occur following accidental inhalation. Proteins, in general, can cause skin and/or respiratory sensitization.
US Signal word	Caution
US Hazard overview	Contains a recombinant protein. Substance not yet fully tested.
Note	This substance is not classified as dangerous/hazardous according to Directive 67/548/EEC, Regulation EC No 1272/2008 (EU-CLP), and applicable US regulations. Its pharmacological, toxicological, and ecological properties have not been fully characterized. The CLP/GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
REGN10987, LDP	N/A	N/A	12.0%	Not classified	Not classified

Note The REGN10987 LDP ingredient listed above is the active ingredient. The remaining components are non-hazardous and/or present at amounts below reportable limits. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures	**Attention Needed**
Immediate Medical	No. If exposed or concerned: Get medical advice/attention.

SECTION 4 - FIRST AID MEASURES …continued

Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit toxic gases of carbon monoxide and carbon dioxide, oxides of nitrogen and other nitrogen-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. As product is an aqueous solution, it is not expected to be flammable or explosive.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency	**procedures**
	Environmental precautions

	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe mist/spray.
	No information identified. Monoclonal antibodies are expected to break down rapidly in the environment.

SECTION 6 - ACCIDENTAL RELEASE MEASURES...continued

Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. Do not breathe vapor or mist.
Conditions for safe storage including any incompatibilities	-80°C
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Wash hands, face and other potentially exposed areas immediately in the event of physical contact.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
REGN10987, LDP	--	--	--

Exposure/Engineering controls	Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/ or enclosure at aerosol/mist-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling. High-energy operations such as spraying should be done within an approved emission control or containment system.
Respiratory protection	If handling bulk product or vials are opened/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. In situations with significant potential for aerosolization, the use of a properly fitted air-purifying respirator with appropriate HEPA filters is recommended.
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION...continued

Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, and full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Liquid
Color	Clear to light yellow
Odor	**Odorless**
Odor threshold	No information identified.
pH	6.0
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	No information identified.

Vapor pressure	No information identified.
Vapor density	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Relative density	No information identified.
Water solubility	Soluble.
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	Not applicable (Mixture)
Molecular formula	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	Stable under normal handling and storage conditions.
Chemical stability	No information identified.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

Route of entry	Not expected to be well-absorbed by inhalation, skin contact, or ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
REGN10987, LDP	--	--	--	--

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

Irritation/Corrosion	No data available.
Sensitization	No data available.
STOT-single exposure	No data available. As the product contains material that is derived from protein, there is potential for the mixture to cause an allergic response in humans.
STOT-repeated exposure/Repeat-dose toxicity	No data available.
Reproductive toxicity	No data available.
Developmental toxicity	No data available.
Genotoxicity	No data available.
Carcinogenicity	No data available.
Aspiration hazard	No data available.
Human health data	See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
REGN10987, LDP	--	--	--

Persistence and Degradability	No data available. Monoclonal antibodies are proteins likely to break down rapidly in the environment.
Bioaccumulative potential	No data available.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.
Note	The environmental characteristics of this mixture have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Used product should be disposed of according to local, state, and federal regulations. All wastes containing the material should be properly labeled.

Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this substance is not regulated as a hazardous material/ dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this substance is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Substance not fully tested - avoid exposure.
Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Caution - substance not yet fully tested.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	Not applicable.

SECTION 16 - OTHER INFORMATION ...continued

Full text of H phrases, P phrases and GHS classification	Not applicable.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Revisions	This is the first version of this SDS.
Disclaimer	The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.