Pharmacy Institutional Readiness for Exagamglogene autotemcel (Casgevy®): Checklists for Pharmacy Services

Guidance for Chief Pharmacists

Pan UK Pharmacy Working Group for ATMPs

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Pharmacy Institutional Readiness for exagamglogene autotemcel (Casgevy®) – an ex-vivo non-GMO Gene Therapy Medicinal Product

Guidance for Chief Pharmacists

1. Background

Casgevy® is classed as an Advanced Therapy Medicinal Product (ATMP). It is subclassified as a non-genetically modified organism (non-GMO) Gene Therapy medicinal product. Therefore, Chief Pharmacists are required to ensure that governance arrangements in line with the safe and secure handling of medicines are in place to manage this medication within their organisations, as recommended by the SPS document titled "The Role of Pharmacy in the Successful Delivery of Advanced Therapy Medicinal Products Information for Chief Pharmacists". Similar to any other autologous product (i.e. medicine which is manufactured using patient's own cells), it is paramount that chain of custody is maintained to ensure that the correct patient receives the intended product.

Casgevy® is the world's first CRISPR–Cas9 gene editing therapy, which aims to cure sickle cell disease and transfusion-dependent β-thalassemia. This cellular therapy consists of autologous CD34+ human haematopoietic stem and progenitor cells edited by CRISPR/Cas9-technology. The guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break at the critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the BCL11A gene. As a result of the editing, GATA1 binding is irreversibly disrupted and BCL11A expression reduced (see Figure 1). Reduced BCL11A expression results in an increase in γ-globin expression and foetal haemoglobin protein production in erythroid cells, addressing the absent globin in transfusion-dependent β-thalassemia and the aberrant globin in sickle cell disease, which are the underlying causes of disease.

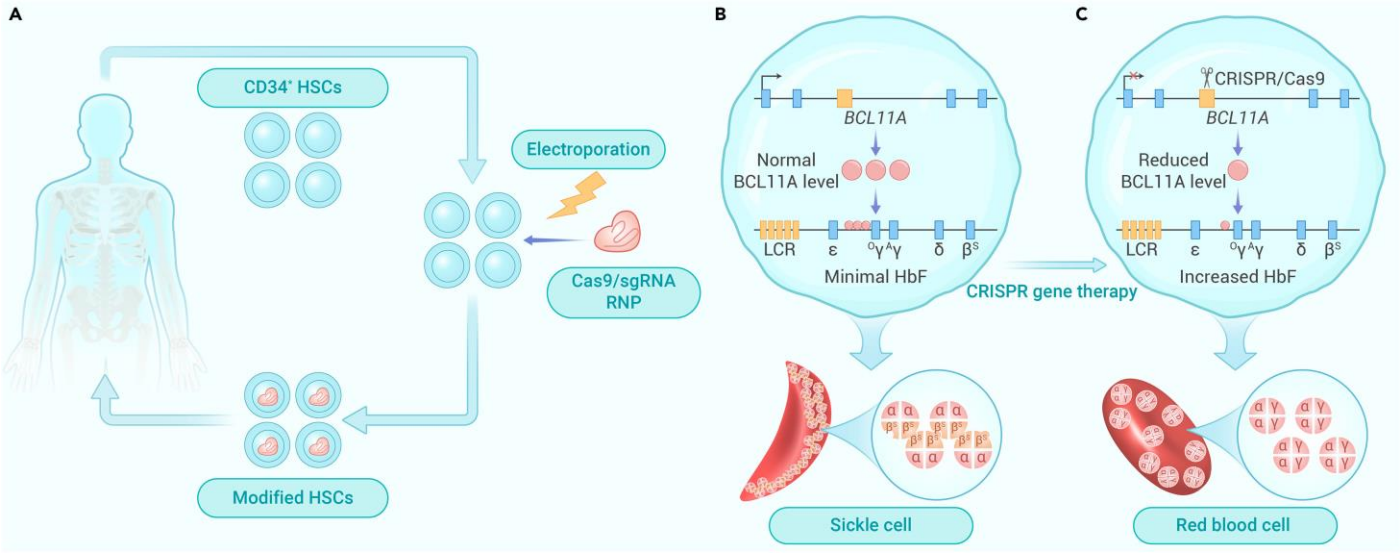

Figure 1. (A). Hematopoietic stem and progenitor cells (HSPCs) taken from the patient are modified ex vivo. Subsequently the modified cellular product is infused back to the patient after conditioning regimen. (B) and (C) CRISPR/Cas 9 precisely targets the erythroid-specific enhancer region of the BCL11A gene resulting in reduce expression of BCL11A in erythroid lineage cells. Reduced BCL11A expression lead so an increase in HbF levels in erythroid cells in vivo, thus restoring functional tetrameric haemoglobin complexes with α-globin in individuals with SCD. Figure taken from (Rao et al., 2024).

2. Purpose

The purpose of this document is to outline the key areas where chief pharmacists should focus pharmaceutical expertise prior to and during the onboarding of Casgevy®.

This document presents a flow diagram outlining a stepwise approach to implementing Casgevy®. It is followed by sample checklists which relate to the various steps presented in the diagram. These are presented as appendices.

It is recognised that Pharmacy Services do not currently have the expertise to handle cellular products and that, routinely, Pharmacy Services may not come directly into contact with the product. However, it is important that where Pharmacy Services are not directly performing some of the outlined steps that the roles and responsibilities of those undertaking these steps are clearly documented in an overarching technical agreement[1] with reference made to organisational pharmacy approved SOPs. The checklists may be used as appendices to local procedures as a way of documenting key steps or as an aid against which to check that local procedures are comprehensive.

[1] **The template for a technical agreement for marketed CAR-T will be a useful guide but will require tailoring for non GMO GTMP Casgevy®** Outsourcing the Receipt, Storage, Preparation and Onward Supply of Marketed Cryopreserved ATMPs – A Template Technical Agreement – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

Process Flow Encompassing Points for Consideration by Chief Pharmacists

Governance

Chief pharmacists should ensure that governance for GTMPs is documented as follows:

1. Centres will need to be able to meet the commissioning requirements set out by NHSE/SMC in order to become a commissioned provider.

2. National clinical approval re patient selection:

   - An approved centre will need to understand the national processes for patient selection if applicable.

3. Local Governance:

   - As referenced in Requirements for Governance and Preparation of Gene Therapy: Pan UK Pharmacy Working Group for ATMPs document organisational governance prior to providing any ATMP is advised. This may involve an ATMP Committee and/or Medicines Management Committee. Even though there is no statutory requirement for a GTMP holding a marketing authorisation to be approved by a Genetic Modification Safety Committee (GMSC), the Pan UK Pharmacy Working Group recommends the use of a risk assessment process as part of a licensed medicine governance process. Local requirements for non-GMO GTMP should be defined prior to implementation of the product in an organisational policy.
   - Implementation sites will be asked to complete Commercial Agreements which can include supply and technical quality agreements with the relevant pharmaceutical company. These will require review by Pharmacy. The commercial agreement will often be signed by the chief pharmacist.
   - Due to the cost of the GTMP, local financial governance requirements may need to be documented in an SOP as there may be a variation to routine standard financial instructions. Financial approval processes should be defined as part of organisational governance.
   - A centre wishing to provide Casgevy® will define additional local governance requirements e.g. for private patients.
   - Pharmacy specific process documents outlining the process for ordering, receipt and product cancellation should be drafted.

An example of a Pharmacy Governance Checklist and Clinical Pharmacist Checklist and has been provided in Appendix 1 and 2.

Risk Assessment

A risk assessment is recommended for all GTMPs regardless of GMO or license status. Therefore, a risk assessment should be completed for this non-GMO GTMP by the requesting clinician in collaboration with other healthcare professionals involved in the handling and management of the product.

GMSC approval of the risk assessment is mandated for GMO IMP and ULM. Where organisations choose not to use their GMSC for marketed and non-GMO GTMP, the risk assessment should be considered as part of the governance process to establish optimal operational implementation of the non-GMO GTMP ***as per Gene Therapy and Preparation which involves assessment of the product, the patient and the waste.***

Approval of the Order

- The commercial operating systems (e.g. Vertex Connects Portal) requires a pharmacist's approval and/or the provision of a pharmacy purchase order. Access to the portal needs to be arranged for trained pharmacy staff to review the order and enter a PO on the portal. This will require an SOP to be defined, recognising that time pressures will exist, the pharmacy SOP should ensure that the process covers all governance aspects detailed above, and any appropriate clinical verification.
- Pharmacy procurement setup should be completed for this product.
- Provisions for prescribing of the drug should be in place (i.e. design of prescription form, build on electronic prescribing system).
- Additionally, links with pharmacy purchasing systems, and prescribing systems will require definition and may form part of this SOP or be documented separately.

An example Clinical Pharmacist Checklist covering product ordering is available in Appendix 2

Mobilisation, Apheresis and Manufacture

- Check for relevant medication restrictions (medicines that must be omitted for a defined time period) when planning the apheresis schedule.
- Stem cell mobilisation with G-CSF + Plerixafor (for Thalassaemia patients) or Plerixafor only (for Sickle Cell patients) will be required prior to apheresis.
- Off-label use of plerixafor should be according to the Trust unlicensed medicine policy.
- Criteria for commissioning of plerixafor is covered by a separate NHS England policy.
- The Apheresis centre will procure the starting material for the autologous GTMP manufacture under their local Human Tissue Authority licence (human application).
- Manufacture of Casgevy® occurs in the UK, therefore an HTA export Licence is not required.
- Local site documentation should be clear that during manufacture, GMP compliance is required and that the Qualified Person employed by the manufacturer has overall responsibility for certification of the product.

Product Receipt

- Pharmacy is responsible for overseeing and approving all procedures relating to the handling and storage of GTMPs. Ex-vivo (cell based) GTMPs are not routinely handled in pharmacy (usually in stem cell laboratories) but receipt, storage, preparation, and issue are pharmacy responsibilities and should be co-ordinated under pharmacy oversight.
- An SOP for receipt of the licensed GTMP is required to include integrity of the product, labelling and temperature compliance during transit. QP certificates/release documents detailing the dose in the vials should be reviewed by an appropriately trained clinical pharmacist as part of product release process.

An example product receipt checklist is available in Appendix 3

Storage

- Casgevy® must be stored in the vapour phase of liquid nitrogen at ≤ -135 °C and must remain frozen until the patient is ready for thaw and administration.
- Vials must be kept in original cartons for storage to maintain Chain of Identity until the vials are prepared for infusion.
- Continuous temperature monitoring and alarms are required. Actions in the event of an alarm should be specified.
- Deviation processes should be clarified e.g. if short period temperature out-of-specification occurs, the SOP should state actions to be taken. Pharmacy should be made aware of any on-site storage deviations.
- Details of the receipt, storage and handing must be covered in the local product specific SOP.

Conditioning Chemotherapy

- Only when the GTMP has been received onsite can myeloablative conditioning start.
- Check for relevant medication restrictions prior to starting myeloablative conditioning and Casgevy® infusion.
- Single agent Busulfan is used for myeloablative conditioning. The dosing regime varies and is patient specific based on pharmacokinetics (PK) ranging from once-a-day administration to every 6 hours for four consecutive days with dose adjusted based on PK. The dose is calculated based on body weight recorded 3-7 days before first day of busulfan administration. Please refer to the national haemoglobinopathy guide for further information on busulfan dosing, PK monitoring and target AUC.
- PK sampling times will depend on the test method and should be confirmed by the laboratory undertaking the testing.
- Myeloablative conditioning will be prepared in the aseptic unit.
- Clinical pharmacist should check myeloablative conditioning regimen and confirm completion of chemotherapy prior to GTMP administration.
- Supportive care should be prescribed with myeloablative conditioning e.g., anti-seizure agents, VOD prophylaxis, anti-emetics.

Issue & Transportation to clinical area

The SmPC mandates that preparation occurs in the clinical area. Chief Pharmacists should ensure that the medicine is handled by trained staff. Where this is delegated e.g. to the stem cell laboratory, the Chief Pharmacist should ensure that the following are included in the approved SOP:

- Confirmation that myeloablative conditioning is completed
- Release of cell by pharmacy or with pharmacy oversight according to local governance agreements
- Procedure for retrieval from liquid nitrogen tank/freezer required or reference to SOP if no different to routine.
- Transportation on dry ice/vapour phase dewar to clinical area to ensure that vials remain at ≤-135°C.
- The product is transported by stem cell lab staff (i.e. trained staff).
- Communication with pharmacy for booking out, and billing purposes, if required.

Pharmacy checks will be documented as part of the clinical pharmacist checklist (see **Appendix 2** for an example checklist)

Clinical Area Preparation

- Information regarding the transfer of product to the ward and administration should be captured on the risk assessment. A clinical area preparation checklist has been included in **Appendix 4**.
- Handling and administration should be undertaken by trained and competent staff according to local organisational policy.
- A national preparation worksheet has been designed, outlining the step-by-step preparation instructions for Casgevy® which may be helpful to incorporate into local systems.
- Casgevy® is thawed and administered at bedside.
- A dose of Casgevy® may be contained in one or more cryopreserved patient specific vial(s). When the dose consists of multiple vials, thaw and administer one vial at a time.
- Each vial should be infused within 20 minutes of thaw.
- Details regarding withdrawal of Casgevy® from the vial have been outlined in the SmPC.

Administration & Monitoring

- The pharmacist with clinical responsibility for the patient needs to be an expert on any required pre-medication, concomitant medication, and post GTMP administration medication. They also need to be aware of toxicity management and contra-indicated medicines.
- Resources available include SmPC and company literature.
- The clinical subgroup of the Pan UK Pharmacy Working Group for ATMPs will endeavour to produce specific clinical guidelines where risk assessment deems it appropriate.

Appendix 1

NEW LICENSED/UNLICENSED ATMP PRODUCT PHARMACY GOVERNANCE CHECKLIST

Product Name	Generic: Brand Name:		
Supplier			
Manufacturer (If different to above)			
Regulatory status	☐ Licensed ☐ Unlicensed		
Type of ATMP (Tick as many as apply)	☐ Gene Therapy Medicinal Products (GTMP)- Specify the type: ☐ In vivo ☐ Ex vivo Containment level (if applicable): _____ ☐ Tissue Engineered Products (TEP) ☐ Somatic Cell Therapy Medicinal Products (sCTMP) ☐ Combined ATMPs		
Governance Arrangements			
Checking step	Status	Checker initial	Date
NHSE commissioned treatment site status (licensed only)	☐ Site Selected as a site ☐ Site Not Selected as a site ☐ Not Applicable		
JACIE accreditations (For admin of immune effector cells, allo and auto transplantation, apheresis, cell processing)	☐ Accredited ☐ Not Accredited		
HTA licensing status	☐ Covered under current HTA licence		
	☐ New licence required- licensed issued		
	☐ New licence required- application in progress		
Technical Agreement	☐ Established ☐ Not Established		
Site qualification status by manufacturer	☐ Qualified (audit and inspection conducted) ☐ Not Accredited		
Local Governance approvals (medicine management/ATMP committee)	☐ Approval issued ☐Approval in progress ☐ Application not submitted ☐ Approval by other committees Specify:		
Trust funding process	☐ Approved ☐ Not Approved		

Supply agreement	☐ Signed ☐ In progress		
Pharmacy arrangements			
Checking step	Status	Checker initial	Date
NPSA ATMP risk assessment	☐ Completed and submitted to the committee ☐ Not Completed ☐ Not applicable		
ATMP preparation	☐ No preparation required ☐ Preparation by SCL/nurses- worksheet designed: ☐ Yes ☐ No		
Prescription build status on the electronic system	☐ Product built		
	☐ Request form completed and submitted by the lead clinical pharmacist, awaiting build ☐ Request form not completed		
Product added to Pharmacy Ordering system	☐ Yes ☐ No		
ATMP added to formulary	☐ Yes ☐ No		
Pharmacy specific documents (Covering ATMP ordering, receipt, storage, clinical check etc.)	☐ SOP covering pharmacy process finalised ☐SOP covering pharmacy process drafted		
Financial arrangements			
Blueteq required*	☐ Yes- Blueteq available ☐ Yes- Blueteq not available ☐ No		
Arrangements in place to track the product and seek reimbursement by medicine finance team	☐ Yes ☐ No		
Pharmacist final check sign off: Pharmacist name and signature:		Date:	

*Blueteq will only be enabled once regional contracts have been signed off between regional commissioner and commissioned provider.

Appendix 2

CASGEVY CLINICAL PHARMACIST CHECKLIST

Part 1: Approval/Ordering

Product Name				
Supplier				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**To be Checked/ completed by***
National patient selection approval confirmation (Patient MDT ID code)	☐			PH
BlueTeq Form A (Apheresis) completed ID number:	☐ ----------			CT
Patient consent documented	☐			CT
Purchase order raised PO number:	☐ ----------			PT
Pharmacist check on manufacturer's ordering portal completed	☐			PH
Pharmacist final check all details complete (Print name, sign, date)	Print Name	Signature and Date		PH
Comments (NOTE: Record patient weight)				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT)**

CASGEVY CLINICAL PHARMACIST CHECKLIST

Part 2: Mobilisation
(To be completed with each mobilisation attempt)

Product Name				
Supplier				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**To be Checked/ completed by***
Mobilisation attempt number:	1st / 2nd / 3rd			CT
BlueTeq Form A (Apheresis) completed ID number:	☐ ----------			CT
Medication restrictions checked	☐			CT and PH
Patient weight (kg)				CT
Blood tests checked (e.g. renal function)	☐			CT and PH
Mobilisation prescription prescribed	☐			CT
G-CSF counselling (if self-administering) inc. dose & timing	☐			PH
Mobilisation prescription clinically verified	☐			PH
Plerixafor doses ordered	☐			PH
Total number of plerixafor doses used	----------			PH
Pharmacist final check all details complete (Print name, sign, date)	Print Name	Signature and Date		PH
Comments				

*** Pharmacist (PH), Clinical Team (CT)**

CASGEVY CLINICAL PHARMACIST CHECKLIST

Part 3: Myeloablative chemotherapy

Product Name				
Supplier				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**Teams involved***
Receive Casgevy® on pharmacy dispensing system when receipt confirmed by stem cell lab	☐			SCL, PH and PT
Medication restrictions checked	☐			CT and PH
Patient weight (kg)				CT
Blood tests checked (e.g. full blood count, renal & liver function, virology)	☐			CT and PH
Myeloablative conditioning prescribed & clinically verified	☐			CT and PH
Supportive medicines prescribed	☐			CT and PH
Pharmacist final check all details complete (Print name, sign, date)	Print Name	Signature and Date		PH
Comments				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT), Stem Cell Lab (SCL)**

CASGEVY CLINICAL PHARMACIST CHECKLIST

Part 4: Receipt/Release/Issue

Product Name				
Supplier				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**Teams involved***
Receive Casgevy® on pharmacy dispensing system when receipt confirmed by stem cell lab *(if not already done)*	☐			SCL, PH and PT
Myeloablative chemotherapy completed	☐			PH to check
Patient is fit to receive Casgevy® infusion	☐			CT to confirm PH to check confirmation
Clinically check Casgevy® prescription	☐			PH to check
Cells authorised by pharmacy and cell release communicated to the SCL *(By checking certification of analysis, checking the dose and matching patient identification)*	☐			PH and SCL
Issue Casgevy® on Pharmacy Dispensing system	☐			PH and PT
BlueTeq Form B (product administration) completed ID number:	☐ ----------			CT
Pharmacist final check all details complete (Print name, sign, date)	Print Name		Signature and Date	
Once cells are administered to patient, file the following in the product specific folder which is kept in Pharmacy: • Copy of certificate of analysis (if available) • Copy of the completed cell receipt checklist (provided by SCL) • Copy of the completed preparation and administration worksheet • Completed copy of this checklist				
Comments (NOTE: Record patient weight)				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT), Stem Cell Lab (SCL)**

Appendix 3

Ex-vivo GTMP Receipt Checklist

Product Name			
Patient Name			
Patient Date of Birth (dd/mm/yyyy)			
COI Number			
Donor Identification Number			
Relevant patient virology details			
Supplier			
Manufacturer (if different to above)			
Courier Job Number (& other ref no)			
Date & time received			
Received by			
Checking step\data	**Yes / No / NA Data**	**Checker Initials**	**Date & time**
Tamper-evident ties intact? Outer Inner	 Yes / No Yes / No		
Transit data logger temperature checked on receipt as per requirement	Yes / No		
Data logger within specification (no alarms)	Yes / No		
All required documentation received: Shipping log Returns documents Certificate of Analysis / QP release	 Yes / No / NA Yes / No / NA Yes / No / NA		
COI ID number matches	Yes / No		
Patient name matches	Yes / No		
Patient date of birth matches	Yes / No		
Donor Identification Number matches	Yes / No		

Appendix 3 (cont.)

Checking step\data	Yes / No / NA Data	Checker Initials	Date & time
Overwrap			
Dose as prescribed and within range	Yes / No		
Quantity received – no of vials / bags			
Product integrity visual check	Pass / Fail		
Products labelled correctly	Pass / Fail		
Lot/batch number			
Within Expiration Date	Yes / No		
Storage requirements			
Time and Date product placed into storage			
Storage location			
Receipt documented	Yes / No		
1st Check (Print name, sign, date)	***Print Name***	***Signature***	***Date***
2nd Check (Print name, sign, date)	***Print Name***	***Signature***	***Date***
Completed receipt checklist sent to Pharmacy			
Comments			

Appendix 4

Ex-vivo Clinical Area Preparation Checklist

Process Set Up/Governance	Yes / No	Checker Initials	Date & time
Roles and responsibilities documented	Yes / No		
Is the medicine a Class I Gene Therapy or non-GMO GTMP*	Yes / No		
Is the shelf life <4hrs post thaw/reconstitution*	Yes / No		
Does the SmPC or Pharmacy Manual allow preparation in a clinical area	Yes / No		
Is a Pharmacy approved Worksheet and SOP available	Yes / No		
Has the governance process approved clinical area preparation	Yes / No		
Is the clinical area appropriate for preparation e.g., enough space for equipment and staff members	Yes / No		
Are operators trained and competent	Yes / No		
Is a process in place for communicating patient readiness to Pharmacy/SCL (to avoid prolonged GTMP storage in the clinical area)	Yes / No		
Required PPE is available	Yes / No		
Required waste container(s) available	Yes / No		
Approval	***Print Name***	***Signature***	***Date***

*If the answer is no to either of these questions, then check that clinical area preparation is optimal.

The Pan UK Pharmacy Working Group for ATMPs would like to thank the following people for their contribution towards this document:

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