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Version 03/03/22

Scottish paediatric and adolescent infection and immunology network pathway for nMABs for non-hospitalised adolescents with COVID-19

Neutralising monoclonal antibodies (nMABs) are recommended as a treatment option through routine commissioning for non-hospitalised 'at risk' adults and children (aged 12 years and above) with COVID-19.

Coronavirus » Interim clinical commissioning policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19 (england.nhs.uk)

The first nMAB available for non-hospitalised patients is Sotrovimab (Xevudy) which both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2. It became available in limited quantities from Dec 2021 for those considered to have the highest risk of progression to severe disease

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Pre-hospitalised patients are eligible to be considered if:

• SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) or lateral flow testing within the last 7 days

AND

• Symptomatic with COVID-19 & showing no signs of clinical recovery

AND

• A member of a 'highest' risk group (as defined in Appendix 1 & Appendix 2).

Treatment with Sotrovimab can be given up to 7 days after symptom onset but preferably given as early as possible

Exclusion criteria

Patients are not eligible for nMAB treatment in the community if they meet any of the following:
- Require hospitalisation for COVID-19
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Children weighing less than 40kg
- Children aged under 12 years

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Serology testing

Where possible, all patients should have samples taken for serology testing against SARS CoV-2 prior to treatment with an nMAB. However, serology results are not a requirement for treatment with nMABs under the criteria specified

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for sotrovimab for special warnings and precautions for use. Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated. If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered

There are no data for the use of sotrovimab in pregnancy. Since sotrovimab is a human immunoglobulin G it has potential for placental transfer from mother to developing foetus. The potential risk or benefit to the developing foetus is unknown. Sotrovimab can be used in pregnancy where the expected benefit to the mother justifies the risk to the foetus.

Highest risk group in paediatrics

In children and young people (aged < 18yr), risks of hospitalisation or death from COVID are very low. Current evidence suggests those in the listed risk groups in the national policy (see table in appendix A of national policy) do not have equivalent risk to older adults with the same conditions.

Studies of pre-hospital nMAbs and/or anti-virals have largely been in adults and there are minimal data to assess benefit of nMAbs to those <18yr, even in symptomatic inpatients. Due to low numbers of severely unwell children and young people, it is challenging to estimate the risks vs benefit, or number needed to treat to prevent hospitalisation, and severe disease. Administration of an intravenous or sub-cutaneous drug to children and young people in hospital brings its own burden, and requires specialised paediatric teams. Nevertheless, equity of care for those deemed to be at risk is vital.

All children and young people who potentially are eligible through the national policy should therefore be discussed with regional paediatric infectious diseases service to confirm eligibility and to consider the risk / benefit and whether to proceed with offer of treatment.

The following should also be taken into account when considering pre-hospital treatment:

- It is generally accepted that comorbidities are additive in terms of risk of hospitalisation or severe disease
- Additional comorbidities that, according to current evidence, should be taken into account in decision making include:

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- Complex neurodisability
- High BMI
- Severe pre-existing respiratory disease
- Complex genetic or metabolic conditions
- Multiple congenital abnormalities

Appendix 2 provides guidance from the RCPCH on the clinical risk factors that should be considered when recommending treatment to non-hospitalised symptomatic, SARS-CoV-2 PCR positive <18yrs.

Pathway to access

On 22nd December 2021 NHS Inform was updated with advice that patients over 12ys of age who fall into the 'at highest risk for COVID-19 group' **may** be eligible for an intravenous infusion of a nMAB if within 7 days of onset of symptoms of COVD-19.

The SG has notified all patients by letter who are over 12ys of age and fall within the 'at highest risk of COVID-19 group'.

All patients were provided with a number to ring in their board of residence.

Individual boards will also be proactively cross referencing lists of new COVID-19 positive PCR results against a local list of the 'at highest risk of COVID-19' to generate daily lists of patients who would potentially be eligible for early treatment.

Age

Adolescents between 12-17ys will be assessed for nMAB use by paediatric services.
If the care of an adolescent aged between 16-18ys lies within adult services then adult services can seek advice from the paediatric MDT if required

Paediatric leads within boards are requested

- To identify their individual board processes of:
  1) receiving and processing a call from an adolescent or family of an adolescent with recently diagnosed COVID-19 and how the call is vetted to check eligibility and exclusion criteria
  2) identifying recently diagnosed high risk adolescent patients from testing data
- Identify a local resource to deliver nMABs i.e. location and nursing/medical supervision
- Design a local process to interact with the national paediatric MDT which will advise on potential benefit of nMAB infusion for 'at risk' adolescents with COVID-19

When a child/adolescent is deemed potentially eligible locally then a local **responsible paediatric consultant (speciality or general)** should be identified to:

a) Assess the patient over the phone

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b) Information gather to help assess the patient's risk of severe COVID-19 (complete proforma - see appendix 2) This should include a process to confirm availability of the nMab.

c) Present the patient to a national MDT to discuss eligibility

d) Document process of MDT and advice offered

e) Take and document verbal consent

f) Check serology in those who are identified as requiring a nMAB infusion

g) Supervise infusion of nMAB if patient is identified as requiring

h) Follow-up patient at 48hrs if treated or not

i) Write to GP and record in local clinical record if nMAB administered

j) Notify relevant bodies of outcome

National MDT

Guideline and patient assessment proforma - appendix 3, also housed within the Microsoft Teams Group "Paed nMAB MDT"
https://teams.microsoft.com/l/team/19%3aSA1r81EeSg8moebqrylS9qaKjJN0Nmtdkqj35R-PkTY1%40thread.tacv2/conversations?groupId=ae78e109-2243-44dd-b614-3d8b34d46657&tenantId=10efe0bd-a030-4bca-809c-b5e6745e499a

The National MDT will be staffed by Paediatric Infectious Diseases Consultants and/or Paediatricians with an interest in Paediatric Infectious Diseases, and the local responsible **consultant** will present the patient through Microsoft Teams, link as above.

The National MDT will occur at 12:30 every weekday.

The national MDT is an advisory facility.

A copy of the proforma should be **emailed to ALL** the following emails: ggc.paedcovidmdt@ggc.scot.nhs.uk, conor.doherty@ggc.scot.nhs.uk, rosie.hague@ggc.scot.nhs.uk, Katherine.longbottom@ggc.scot.nhs.uk, louisa.pollock@ggc.scot.nhs.uk: laura.jones@nhslothian.scot.nhs.uk, Jill.king@nhs.scot at least 1 hour before time of commencement of MDT. Currently there is no resource to answer telephone queries from clinicians, to schedule meetings at the weekend or to interact directly with families however weekend arrangements can be discussed with oncall paed ID services on an ad hoc basis.

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Pharmacy (see appendix 4 for Sotrovimab patient information leaflet)

Sotrovimab (Xevudy)	
Preparations available	Xevudy (sotrovimab) 500mg/8ml concentrate for solution for infusion
Dose	All patients >12kg and >40kg A single dose of 500mg, given by IV infusion
Methods of administration	Intravenous (IV) infusion **over 30 minutes** The final preparation for infusion must be administered via a 0.2 micron low protein binding in-line filter. Do NOT administer as an IV push/bolus or via any other route.
Compatibility and stability	**Fluids** 0.9% sodium chloride OR 5% glucose **Drugs (Y-site compatibility)** Sotrovimab should be given through a dedicated line and should not be mixed/administered with other medicinal products. **Stability** The diluted solution is intended to be used immediately. If immediate administration is not possible the diluted solution may be stored: • At room temperature (up to 25ºC) for up to 6 hours OR • Refrigerated (2ºC-8ºC) for up to 24 hours from the time of dilution to the *end of administration* Protect from light. **pH & Osmolarity**

	pH 6 (undiluted) 290mOsm/kg (undiluted)

Preparation and administration	***Dilution and administration instructions*** • Using ANTT withdraw 8ml from the vial of sotrovimab and add directly to a 100ml infusion bag of either sodium chloride 0.9% OR glucose 5% • Discard any unused portion left in the vial. Vials are designed for single use only. • Prior to infusion gently rock the infusion bag back and forth 3-5 times. Avoid forming air bubbles. • **DO NOT INVERT OR SHAKE THE BAG.** • Administration is via an IV infusion set with standard bore tubing. Prime the infusion set and administer as a single IV infusion over 30minutes. A 0.2micron low-protein binding in-line filter is required for administration.
Points to note	▪ Administer ONLY in an area where full resuscitation facilities are available ▪ Do not use if visible damage to vial or if particulate matter.
Adverse reaction and suggested monitoring	▪ Hypersensitivity reactions including anaphylaxis can occur. These typically occur within the first 24hrs following administration. (See cautions above). ▪ Monitor temperature, pulse, BP and respiration rate every 15 minutes throughout infusion and <u>for 60 minutes post infusion</u> ▪ For severe hypersensitivity reactions: discontinue infusion immediately For mild/moderate reactions: Slow infusion to over 60mins or stop the infusion and allow reaction to resolve. DO NOT disconnect. After medical review the infusion may be restarted at a slower rate (suggest over 60mins). ▪ Ensure hydrocortisone, chlorphenamine and paracetamol prescribed PRN in case of reaction. **<u>Sotrovimab is a black triangle drug.</u>** All suspected adverse reaction must be reported via the COVID-19 Yellow Card reporting site or Yellow Card App.

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Interactions	No interaction studies have been performed. Sotrovimab is not renally excreted nor is it metabolised by cytochrome P450 enzymes, therefore interaction with concomitant therapies that are renally excreted or that are substrates, inducers or inhibitors or CYP enzymes are unlikely.

Appendix 1: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC)[7].

Cohort	Description
Down's syndrome	All patients with Down's syndrome
Sickle cell disease	All patients with a diagnosis of sickle cell disease
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior • Patients receiving radiotherapy within the last 6 months

Patients with a haematologic malignancy	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant
	• Autologous HSCT recipients in the last 12 months
	• Individuals with haematological malignancies who have
	  ○ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or
	  ○ anti-CD20 monoclonal antibody therapy in the last 12 months
	• Individuals with chronic B-cell lymphoproliferative disorders receiving systemic treatment or radiotherapy within the last 3 months
	• Individuals with chronic B-cell lymphoproliferative disorders with hypogammaglobulinaemia or reduced peripheral B cell counts
	• Individuals with acute leukaemias and clinically aggressive lymphomas who are receiving chemotherapy or within 3 months of completion at the time of vaccination

[7] For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment

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	• Individuals with haematological malignancies who have received anti-CD38 monoclonal antibody or B-cell maturation agent (BCMA) targeted therapy in the last 6 months • Individuals with chronic B-cell lymphoproliferative disorders not otherwise described above

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:
	  ○ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin)
	  ○ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals
	  ○ Not been vaccinated prior to transplantation
	• Non-transplant patients who have received a comparable level of immunosuppression
	• Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression

Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Primary immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID)

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	• Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

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Appendix 2: RCPCH guidance

Non-hospitalised patient cohorts in the 12-17 years age range considered at highest risk from COVID-19 and to be prioritised for consideration of treatment with neutralising monoclonal antibodies when symptomatic and SARS-CoV-2 PCR positive.

CYP at significant risk
Neuro-disability • Complex life-limiting neuro-disability with recurrent respiratory infections/ compromise
CYP at significant risk if 2 or more of these risk factors are present
Primary immunodeficiency • Common variable immunodeficiency (CVID) • Primary antibody deficiency on immunoglobulin (or eligible for immunoglobulin replacement) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes /autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) **Secondary Immunodeficiency** • HIV CD4 count <200 cells/mm3 • Solid organ transplant • HSCT within 12 months, or with GVHD • CAR-T therapy in last 24 months

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- Induction chemotherapy for acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, chemotherapy for acute myeloid leukaemia (AML), relapsed and /or refractory leukaemia or lymphoma

Immunosuppressive treatment

- Chemotherapy within the last 3 months
- Cyclophosphamide within the last 3 months
- Corticosteroids >2mg/kg/day for 28 days in last 4 weeks
- B cell depleting treatment in the last 12 months

Other conditions

- High BMI (>95th Centile)
- Severe respiratory disease (e.g. CF or bronchiectasis with FEV1 <60%)
- Tracheostomy or long term ventilation
- Severe asthma (PICU admission in 12 months)
- Neurodisability and/or neurodevelopmental disorders
- Severe cardiac disease
- Severe chronic kidney disease
- Severe liver disease
- Sickle Cell disease or other severe haemoglobinopathy
- Trisomy 21
- Complex genetic or metabolic conditions associated with significant comorbidity
- Multiple congenital anomalies associated with significant comorbidity

COVID-19 - guidance for management of children admitted to hospital and for treatment of non-hospitalised children at risk of severe disease | RCPCH

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Appendix 3: Proforma for national paediatric MDT for assessment of benefit of nMAB for adolescents aged 12-16y with recently diagnosed COVID-19 (symptoms and PCR result < 5 days)

(Available as separate downloadable word document in files section on MS Teams General channel of paed nMAB MDT)

Name	
CHI	
Age	
Date	
Responsible clinician & email address	
Hospital at which infusion can take place	
Discussion with - parent/guardian - patient - carer	
Any reason to think the patient lacks capacity (for those over 16 years old)? - Yes - No	
Date of COVID PCR or lateral flow test (specify)	
Date of onset of symptoms:	
Current symptoms (and whether the adolescent is improving)	
Variant (if known)	
Vaccination status - how many vaccines has the adolescent had? 0 / 1 / 2 / 3	

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Underlying diagnoses (please specify risk groups as per appendix 1 & 2)	
Co-morbidities (e.g. neurodisability, pre-existing respiratory disease, immunosuppression, complex genetic or metabolic conditions, multiple congenital abnormalities)	
Wt(kg) & BMI	
Current medication	
Date, discussion and advice offered at MDT Names of those present	

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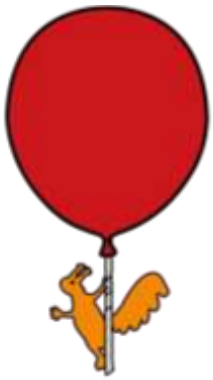
Appendix 4



NHS Greater Glasgow and Clyde

Royal Hospital for Children Glasgow

Information about

Sotrovimab for COVID-19

This leaflet has been written for parents and carers about the use of sotrovimab for the treatment of COVID-19.

Name of drug

Sotrovimab

Brand name: Xevudy

What is sotrovimab?

Sotrovimab, which is also known as Xevudy, is a biological medication known as a 'neutralising' monoclonal antibody (nMab). It is specifically designed to stop the virus that causes COVID-19 from entering healthy cells, effectively 'neutralising' the virus. Sotrovimab also works to clear infected cells from the body. Sotrovimab is not an alternative to vaccination.

Why is it important for my child to receive this medicine?

Sotrovimab may be prescribed to help protect your child from becoming unwell or requiring hospital admission because of symptoms associated with COVID-19. Most children who get COVID-19 have very mild or no symptoms even if they have other medical problems. However, sotrovimab may still help if your child already has an illness, or takes a medicine, that could put them at risk of developing more severe symptoms associated with COVID-19. A study from the US has shown that when patients who are at risk of developing severe COVID-19 disease are given sotrovimab within five days of symptom starting, the likelihood of requiring hospital admission or becoming seriously unwell is reduced.

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Please tell the doctor or nurse if your child:

- Is allergic to sotrovimab itself
- Has a known allergy to any of the following: histidine, histidine monohydrochloride, polysorbate 80
- Has a known allergy to any food or medicines

When should sotrovimab be given?

It is important for sotrovimab to be given in the early stages of a COVID-19 infection to provide the best possible chance of stopping hospitalisation. The NHS have advised that sotrovimab should ideally be given within FIVE days of a positive PCR or LFD and within FIVE days of symptoms starting. In some circumstances, following approval, this may be extended to SEVEN days.

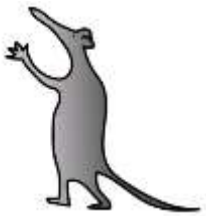
What is the dose of sotrovimab?

Sotrovimab is given **ONCE only**. Your child will receive a single 500mg dose which will be put into either a 50mL syringe or a 100mL bag of sodium chloride 0.9%.

How is sotrovimab given?

Sotrovimab is given by an injection into a vein. The injection takes at least 30 minutes to complete. This means your child will need to come to hospital and stay while they have the treatment and for at least one hour after the injection has finished.

When should sotrovimab start working?



It is important to remember that sotrovimab is a preventative medicine designed to help stop your child from developing severe disease requiring hospitalisation. It is not expected to improve any current symptoms your child may have.

What are the side effects of sotrovimab?

The only reported side effects are allergic reactions and reactions to the injection. Commonly reported side effects include:

- Rash
- Nausea
- Chills
- Dizziness

- Injection site reactions including itchy skin, redness of skin, pain/tenderness and swelling

Rarely some patients may experience a severe allergic reaction, which is why your child will be monitored in hospital for an hour after the injection has finished.

Can other medicines be given at the same time as sotrovimab?

You can give your child's regular medicines as normal before your child receives sotrovimab. Please tell the doctor what medicines your child takes. . **Sotrovimab is not expected to interact with any medicines.**

Will this affect vaccines?

Sotrovimab is not expected to affect vaccines. It is not necessary to delay routine vaccinations after receiving sotrovimab as long as your child is well and no longer needs to isolate.

The COVID-19 vaccine should not be given for at least 28 days after your child tested positive for COVID-19, whether or not they have had sotrovimab. If your child is eligible for the COVID-19 vaccine they should receive the vaccine as soon as possible after that.

Who should I contact for further details?

If you have any questions about your medication whilst you are in hospital, please do not hesitate to ask one of the Pharmacy team.

Who should I contact if concerned about side effects after leaving hospital?

If your child has symptoms that you feel may require medical attention contact NHS24 by dialling 111. If you would usually contact your specialist team for advice, then do so.

This leaflet only gives general information. You should discuss specific questions about your own child with the medical team who looks after them.

Royal Hospital for Children

NHS Greater Glasgow & Clyde

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