SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Xevudy 500 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of sotrovimab in 8 mL (62.5 mg/mL).

Sotrovimab is a monoclonal antibody (IgG1, kappa) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

A clear, colourless or yellow to brown solution, free from visible particles, with a pH of approximately 6 and an osmolality of approximately 290 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute covid-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe covid infection (see section 5.1).

4.2 Posology and method of administration

Xevudy should only be administered by a qualified healthcare provider. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored during and post intravenous infusion in accordance with local guidelines (see Section 4.4).

It is recommended that Xevudy is administered within 5 days of onset of symptoms of COVID-19 (see section 5.1).

Consideration should be given to official guidance on the appropriate use of Xevudy.

Posology

Adults and adolescents (from 12 years and 40 kg body weight)
The recommended dose is a single 500 mg intravenous infusion administered following dilution (see sections 4.4 and 6.6).

Special populations

Elderly
No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy in children under 12 years old or weighing less than 40 kg have not yet been established (see section 5.2). No data are available.
No dosage adjustment is recommended in paediatric individuals ≥ 12 years of age and weighing ≥ 40 kg (see section 5.2).

Method of administration

For intravenous use.

This medicinal product must be diluted prior to administration. For instructions on dilution of the medicinal product, see section 6.6.

Once diluted, attach an infusion set to the infusion bag using standard bore tubing. The intravenous dosing solution is recommended to be administered with a 0.2-µm in-line filter. Prime the infusion set and administer as a single IV infusion for 30 minutes at room temperature.

Treatment must not be administered as an intravenous push or bolus.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Recipients of Xevudy are advised to self-isolate for a period of time from onset of symptoms in accordance with national covid-19 guidelines and in order to minimise transmission of coronavirus.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of Xevudy. 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.

Antiviral resistance

The clinical relevance of the observed decrease in in vitro neutralisation against Omicron BA.2 is not known (see section 5.1 and 5.3).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Sotrovimab is not renally excreted or metabolised by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant therapies that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Concomitant administration of sotrovimab with COVID-19 vaccines has not been studied. Refer to local/national guidelines for vaccine administration and guidance on the risks associated with administration of a SARS-CoV-2 vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of sotrovimab in pregnant women. Since sotrovimab is a human immunoglobulin G (IgG) animal studies have not been evaluated with respect to reproductive toxicity (see section 5.3). No off-target binding was detected in a cross-reactive binding assay using a protein array enriched for human embryofetal proteins. Since sotrovimab is a human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing foetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing foetus is not known.

Sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

Breast-feeding

There are no data on the excretion of sotrovimab in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known.

Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman**.**

Fertility

There are no data on the effects of sotrovimab on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Xevudy has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were hypersensitivity reactions. The most serious adverse reaction was anaphylaxis.

Tabulated list of adverse reactions

The analysis set for intravenous administration provides COMET-ICE data from 523 sotrovimab treated patients with 137 patient-years of exposure; 56% (n = 295) were female and 44% (n = 228) were male; most (54% [n = 281]) were 18 to < 55 years of age, (26% [n = 138]) were 55 to < 65 years of age, (15% [n = 76]) were 65 to < 75 years of age and 5% [n = 28] were >=75yrs. No exposure data for subjects <18 years are available.

The table below presents the adverse reactions from a placebo-controlled randomised study in patients with COVID-19 (COMET-ICE) (see section 5.1) and from spontaneous reporting. Frequencies are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 1: Tabulated list of adverse reactions

System organ class	**Frequency**	**Adverse reaction**

Immune system disorders	Common Rare	Hypersensitivity reactions [a] Anaphylaxis

[a] Includes rash, dermatitis contact, skin reaction, hypersensitivity, multiple allergies, infusion-related reaction and bronchospasm.

Description of selected adverse reactions

Hypersensitivity reactions
In COMET-ICE, hypersensitivity reactions, of grade 1 (mild) or grade 2 (moderate), were reported (9 patients in the Xevudy arm; 5 patients in the placebo arm). None of the reactions in either study arm led to pausing or discontinuation of the infusions.

Paediatric Population
No data are available for paediatric patients <18 years old.

Elderly
In study COMET-ICE, 104 (20%) patients received treatment with Xevudy were ≥ 65 years old. The safety profile of these patients was similar to that in adult patients < 65 years old.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific treatment for an overdose of sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral monoclonal antibodies
ATC code: J06BD05.

Mechanism of action

Sotrovimab is a dual action, engineered human IgG1 mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2.

In the COMET-ICE clinical trial post-baseline variants were detected in (i) the sotrovimab epitope of the spike protein and (ii) the receptor-binding motif of the spike protein. Post-baseline epitope substitutions detected in more than 2 participants in the sotrovimab arm at a frequency of >15% included P337L/R and E340A/K/V. Substitutions E340A/V/K and P337L/R confer reduced susceptibility to sotrovimab (>100-fold change in EC_{50} value) in an in vitro pseudotyped VLP system. The clinical impact of these substitutions is not yet known. In the receptor-binding motif of the spike protein, the substitutions K417T, S477N, E484K, and N501Y were detected post-baseline in more than 2 participants in the sotrovimab arm at a frequency of >15%. Sotrovimab retains activity against K417T, S477N, E484K, and N501Y in an in vitro pseudotyped VLP system.

Clinical efficacy

Study 214367 (COMET-ICE) was a Phase II/III randomised, double-blind, placebo-controlled study which evaluated sotrovimab as treatment for COVID-19 in non-hospitalised adult patients who did not require any form of oxygen supplementation at study entry. The study included patients with symptoms for ≤ 5 days and laboratory confirmed SARS-CoV-2 infection. Eligible patients had at least 1 of the following: diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were aged 55 years and older.

The COMET-ICE study was conducted when the dominant form of the coronavirus was the original Wuhan strain.

Patients were randomised to a single 500 mg infusion of sotrovimab (N=528) or placebo (N=529) over 1 hour (Intent to Treat [ITT] population at Day 29). In the ITT population, 46% were male and the median age was 53 years (range: 17-96), with 20% aged 65 years or older and 11% over 70 years. Treatment was given within 3 days of COVID-19 symptom onset in 59% and 41% were treated within 4-5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medicine (22%) and moderate to severe asthma (17%).

The adjusted relative risk reduction in hospitalisation or death by Day 29 in the ITT population was 79% (95% CI: 50%, 91%). The difference was driven by rates of hospitalisation, with no deaths in the sotrovimab arm and two deaths in the placebo arm up to Day 29. No patients in the sotrovimab arm, versus 14 in the placebo arm, required high flow oxygen or mechanical ventilation up to Day 29.

Table 2: Results of primary and secondary endpoints in the ITT population (COMET-ICE)

	Sotrovimab (500 mg IV infusion) N=528	Placebo N=529
Primary endpoint		
Progression of COVID-19 as defined by hospitalisation for >24 hours for acute management of any illness or death from any cause (Day 29)		
Proportion (n, %) [a]	6 (1%)	30 (6%)
Adjusted relative risk reduction (95% CI)	79% (50%, 91%)	
p-value	<0.001	
[a] No participants required intensive care unit (ICU) stay in the sotrovimab arm versus 9 participants in the placebo arm.		

An available case analysis of viral load in response to sotrovimab versus placebo is shown in table 3:

Table 3: Summary of nasal SARS-CoV-2 viral load in log 10 copies/mL at baseline and on Day 8 in the Virology population

	Sotrovimab (500 mg IV infusion)	Placebo
Baseline (log 10 copies/mL)		
n[a]	369	385
Mean (standard deviation)	6.535 (1.6331)	6.645 (1.6632)
Day 8 (log 10 copies/mL)		
n[b]	316	323
Least Squares Mean (standard error)	3.968 (0.0593)	4.219 (0.0589)
Day 8 change from baseline (log 10 copies/mL)		
Least Squares Mean (standard error)	-2.610 (0.0593)	-2.358 (0.0589)
95% CI	-2.726, -2.493	-2.474, -2.243
Least Squares Mean Difference (standard error)	-0.251 (0.0835)	
95% CI	-0.415, -0.087	
p-value	0.003	

[a]Number of participants with available data, above the limit of quantification at baseline
[b] Number of participants with available data at Day 8.

Paediatric population

The Medicines Health products Regulatory Agency has deferred the obligation to submit the results of studies with Xevudy in one or more subsets of the paediatric population in COVID-19 with acute covid disease (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The Medicines Health products Regulatory Agency will review new information on this medicinal product at least every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

The geometric mean C_{max} following a 1 hour IV infusion was 117.6 µg/mL (N = 290, CV% 46.5), and the geometric mean Day 29 concentration was 24.5 µg/mL (N = 372, CV% 42.4).

Distribution

Based on non-compartmental analysis, the mean steady-state volume of distribution was 8.1 L.

Biotransformation

Sotrovimab is degraded by proteolytic enzymes which are widely distributed in the body.

Drug interactions

In vitro pharmacodynamic studies showed no antagonism between sotrovimab and remdesivir or bamlanivimab.

Elimination

The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extends antibody elimination half-life, but does not impact wild-type Fc-mediated effector functions in cell culture. Based on non-compartmental analysis, the mean systemic clearance (CL) was 125 mL/day, with a median terminal half-life of approximately 49 days.

Special populations

Based on population pharmacokinetic analyses, the pharmacokinetics of sotrovimab was not affected by age or gender. Body weight and BMI were significant covariates.

Elderly patients (≥65 years old)

Based on population pharmacokinetic analyses, there was no difference in sotrovimab pharmacokinetics in elderly patients.

Renal impairment
Sotrovimab, is too large to be excreted renally, thus renal impairment is not expected to have any effect on elimination. Furthermore, based on population pharmacokinetic analyses there was no difference in sotrovimab pharmacokinetics in patients with mild or moderate renal impairment. There is limited data in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2).

Hepatic impairment
Sotrovimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, therefore changes in hepatic function are not expected to have any effect on elimination. Furthermore, based on population pharmacokinetic analyses there was no difference in sotrovimab pharmacokinetics in patients with mild to moderate elevations in alanine aminotransferase (1.25 to < 5 x ULN). There is no data in patients with severe elevations in alanine amino transferase (5 to < 10 x ULN).

Paediatric population
The pharmacokinetics of sotrovimab in children and adolescents have not been evaluated.
The recommended dose for adolescents aged from 12 years and from 40 kg body weight is predicted to result in serum concentrations of sotrovimab similar to those in adults based on an allometric scaling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution.

5.3 Preclinical safety data

Anti-viral activity
Sotrovimab neutralised SARS-CoV-2 virus *in vitro* (EC_{50} 100.1 ng/mL). Pseudotyped virus-like particle (VLP) *in vitro* assessments indicate that sotrovimab retains activity against the Alpha, Beta, Gamma, Epsilon, Iota, Kappa, Delta, Lambda, Delta Plus and Mu variant spike proteins with fold changes in EC_{50} value ranging from 0.35-2.3.

A pseudotyped VLP assessment in cell culture showed that the epitope sequence polymorphisms K356T, P337H/K/L/R/T, E340A/K/G/I/Q/V, T345P, and L441N, conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: P337K (>304), E340K (>297), T345P (225), E340V (>200), P337R (>192), P337L (>192), E340I (>190), E340A (>100), L441N (72), E340Q (>50), E340G (18.21), P337T (10.62), K356T (5.90), and P337H (5.13). The presence of the highly prevalent D614G substitution, either alone or in combination, did not alter neutralisation of sotrovimab. Pseudotyped VLP *in vitro* assessments indicate that sotrovimab retains activity against the Alpha (B.1.1.7; UK origin, 2.30-fold change in EC_{50} value); Beta (B.1.351; South Africa origin, 0.60-fold change in EC_{50} value); Gamma (P.1; Brazil origin, 0.35-fold change in EC_{50} value); Epsilon (B.1.427/B.1.429; California origin, 0.70-fold change in EC_{50} value); Iota (B.1.526; New York origin, 0.6-fold change in EC_{50} value); Kappa (B.1.617.1; India origin, 0.7-fold change in EC_{50} value); Delta (B.1.617.2; India origin, 1-fold

change in EC_{50} value); Delta Plus (AY.1, India origin, 1.1-fold change in EC_{50} value; AY.2, India origin, 1.3-fold change in EC_{50} value; AY.4.2, India origin, 1.6-fold change in EC_{50} value); Lambda (C.37; Peru origin, 1.5-fold change in EC_{50} value), Mu (B.1.621; Colombia origin,1.3-fold change in EC_{50} value) and Omicron (B.1.1.529/BA.1, South Africa origin, 2.7-fold change in EC_{50} value; BA.1.1, South Africa origin, 3.3-fold change in EC_{50} value) variant spike proteins. Pseudotyped VLP *in vitro* assessments indicate that sotrovimab neutralises the Omicron BA.2 spike variant with a 16-fold reduction in activity (BA.2, South Africa origin, 16-fold change in EC_{50} value), and Omicron BA.3 spike variant with a 7.3-fold reduction in activity (BA.3, South Africa origin, 7.3-fold change in EC_{50} value), relative to wild-type.

Microneutralisation data from authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the Alpha, Beta, Gamma, Kappa, Delta and Omicron BA.1 variants with fold changes in EC_{50} value ranging from 0.4 -4.3

Micro-neutralisation data from authentic SARS-CoV-2 variant viruses indicate the following changes in sotrovimab EC50 and EC90 values relative to wild-type as follows: Alpha, 3-fold change in EC50, 4.1-fold change in EC90; Beta, 1.2-fold change in EC50, 1.3-fold change in EC90; Gamma, 1.6-fold change in EC50. 1.4-fold change in EC90; Kappa, 0.9-fold change in EC50, 1-fold change in EC90; Delta, 0.4-fold change in EC50, 0.6-fold change in EC90; Omicron BA.1, 3.8-fold change in EC50, 4.6-fold change in EC90; Omicron BA.1.1, 4.3-fold change in EC50, 4.2-fold change in EC90.-Sotrovimab neutralises the authentic Omicron BA.2 variant virus with a reduction in activity relative to wild-type as follows: 15.7-fold change in EC50 value, 35.1-fold change in EC90 value.

Carcinogenesis/mutagenesis

Genotoxicity and carcinogenicity studies have not been conducted with sotrovimab.

Reproductive toxicology

Nonclinical reproductive and developmental toxicity studies have not been conducted with sotrovimab in line with international regulatory guidelines for an antibody targeting a virus.

Animal toxicology and pharmacology

No toxicity with sotrovimab was identified in a cynomolgus monkey 2-week repeat-dose IV infusion toxicology study with 105-day recovery period at doses up to 500 mg/kg, the no observed adverse effect level (NOAEL) and highest dose tested. The C_{max} and total exposure AUC [sum of $AUC_{0\text{-}168h}$ after Dose 1 and $AUC_{0\text{-}last}$ after Dose 2 (Day 8)] values at the NOAEL of 500 mg/kg were 13500 µg/mL and 216000 day*µg/mL, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride
Sucrose
Polysorbate 80
Methionine
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

18 months.

Diluted solution for infusion

The diluted solution is intended to be used immediately. If after dilution, immediate administration is not possible, the diluted solution may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2°C to 8°C) for up to 24 hours from the time of dilution until the end of administration.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL Type I borosilicate clear glass single-use vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap.

Pack size: 1 vial.

6.6 Special precautions for disposal

Treatment should be prepared by a qualified healthcare professional using aseptic technique.

Preparation for dilution

1. Remove one vial of sotrovimab from the refrigerator (2°C to 8°C). Allow the vial to equilibrate to ambient room temperature, protected from light, for approximately 15 minutes.
2. Visually inspect the vial to ensure it is free from particulate matter and that there is no visible damage to the vial. If the vial is identified to be unusable, discard and restart the preparation with a new vial.
3. Gently swirl the vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vial.

Dilution instructions

1. Withdraw and discard 8 mL from an infusion bag containing 50 mL or 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose for injection.
2. Withdraw 8 mL of sotrovimab from the vial.
3. Inject the 8 mL of sotrovimab into the infusion bag via the septum.
4. Discard any unused portion left in the vial. The vial is single-use only and should only be used for one patient.
5. Prior to the infusion, gently rock the infusion bag back and forth 3 to 5 times. Do not invert the infusion bag. Avoid forming air bubbles.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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