ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

Excipient(s) with known effect

This medicinal product contains 4.8 mg of polysorbate 80 in each 500 mg dose.
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

Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1).

The use of Xevudy should take into account information on the activity of sotrovimab against viral variants of concern (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Xevudy should be administered under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible and patients can be monitored during and for at least one hour after administration (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).

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 of Xevudy in children under 12 years old or weighing less than 40 kg have not yet been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on posology can be made.

Method of administration

For intravenous use.

This medicinal product must be diluted prior to administration.

Once diluted, it is recommended that the solution is administered over 15 minutes (when using a 50 mL infusion bag) or over 30 minutes (when using a 100 mL infusion bag) with a 0.2-µm in-line filter.

Xevudy must not be administered as an intravenous push or bolus injection.

For instructions on dilution of the medicinal product, see section 6.6.

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

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 including anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of sotrovimab (see section 4.8). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, administration should be discontinued immediately and appropriate medications and/or supportive care should be given.

Infusion-related reactions

Infusion-related reactions (IRRs) have been observed with intravenous administration of monoclonal antibodies (see section 4.8). These reactions may be severe or life threatening. If an IRR occurs, the infusion may be interrupted, slowed or stopped.

Antiviral resistance

Decisions regarding the use of Xevudy should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses including regional or geographical differences and available information on sotrovimab susceptibility patterns (see section 5.1).

When molecular testing or sequencing data are available, they should be considered to rule out SARS-CoV-2 variants that are shown to have reduced susceptibility to sotrovimab.

Polysorbate

This medicinal product contains 4.8 mg of polysorbate 80 in each 500 mg dose. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

Pharmacodynamic interactions

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of sotrovimab in pregnant women. Animal studies have not been evaluated with respect to reproductive toxicity (see section 5.3). In a cross-reactive binding assay using a protein array enriched for human embryofoetal proteins, no off-target binding was detected. 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 should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is not known whether sotrovimab is excreted in human milk or absorbed systemically after ingestion. Administration of sotrovimab while breast-feeding can be considered when clinically indicated.

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 safety of a 500 mg dose of sotrovimab administered intravenously was evaluated in non-hospitalised patients with COVID-19 in a placebo-controlled randomised study (COMET-ICE, 1049 patients treated in a 1:1 ratio of sotrovimab:placebo), and in two non-placebo controlled randomised studies (COMET-PEAK, 193 patients and COMET-TAIL, 393 patients) (see section 5.1). The most common adverse reactions were hypersensitivity reactions (2%) and infusion-related reactions (1%). The most serious adverse reaction was anaphylaxis (0.05%).

Tabulated list of adverse reactions

The adverse reactions in Table 1 are listed by system organ class and frequency. 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	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity reactions [a] Anaphylaxis	Common Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon
Injury, poisoning and procedural complications	Infusion-related reactions	Common

[a]Such as rash and bronchospasm. Pruritus may also be seen as a manifestation of hypersensitivity reactions.

Description of selected adverse reactions

Infusion-related reactions
IRRs may be severe or life threatening (see section 4.4). Signs and symptoms of IRRs may include fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g. atrial fibrillation), tachycardia, bradycardia, chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness, fatigue and diaphoresis.

Paediatric population

Based on limited data (n=7) from adolescents (aged 12 to less than 18 years and weighing at least 40 kg), there were no new adverse reactions identified beyond those observed in the adult population.

Data (n=3) obtained in children (aged 6 to less than 12 years and weighing at least 15 kg), are too limited to establish safety in this group.

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 national reporting system listed in Appendix V.

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.

A single 2000 mg dose of sotrovimab (4 times the recommended dose) administered by intravenous infusion over 60 minutes has been evaluated in a clinical trial (N=81) without evidence of dose-limiting toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD05

Mechanism of action

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

Antiviral activity

Sotrovimab neutralised wild-type SARS-CoV-2 virus *in vitro* with a half maximal effective concentration (EC_{50}) of 100.1 ng/mL.

Table 2: Sotrovimab neutralisation data for SARS-CoV-2 variants

SARS-CoV-2 Variant		Fold Reduction in Susceptibility [a]	
Lineage	**WHO Nomenclature**	**Pseudotyped Virus**	**Authentic Virus**
B.1.1.7	Alpha	No change	No change
B.1.351	Beta	No change	No change
P.1	Gamma	No change	No change
B.1.617.2	Delta	No change	No change
AY.1 and AY.2	Delta [+K417N]	No change	Not tested
AY.4.2	Delta [+]	No change	Not tested
B.1.427/B.1.429	Epsilon	No change	Not tested
B.1.526	Iota	No change	Not tested
B.1.617.1	Kappa	No change	No change
C.37	Lambda	No change	Not tested
B.1.621	Mu	No change	Not tested
B.1.1.529/BA.1	Omicron	No change	No change
BA.1.1	Omicron	No change	No change
BA.2	Omicron	16	15.7
BA.2.12.1	Omicron	16.6	25.1
BA.2.75	Omicron	8.3	15.6
BA.2.75.2	Omicron	10	Not tested
BA.2.86[c]	Omicron	100	Not determined
BA.3	Omicron	7.3	Not tested
BA.4	Omicron	21.3	48.4
BA.4.6	Omicron	57.9	115
BA.5	Omicron	22.6	21.6
BF.7	Omicron	74.2	Not tested
BN.1[c]	Omicron	778	Not tested
BQ.1	Omicron	28.5	Not tested

BQ.1.1	Omicron	94	31.2
BR.2	Omicron	10.2	Not tested
CH.1.1	Omicron	12.4	57.3
EG.5.1	Omicron	Not tested	9.5
FL.1.5.1	Omicron	7.5	No change
HK.3	Omicron	8.4	Not tested
HV.1	Omicron	6.4	Not tested
JN.1[c]	Omicron	252	Not tested
XBB.1	Omicron	6.5	Not tested
XBB.1.5	Omicron	11.3	33.3
XBB.1.5.10	Omicron	7.6	Not tested
XBB.1.16	Omicron	6.9	10.6
XBB.1.16.1	Omicron	7.3	Not tested
XBB.1.16.6	Omicron	6.2	Not tested
XBB.2.3	Omicron	5.7	No change
XBF	Omicron	9.4	Not tested
XD	None[b]	Not tested	No change

[a] Based on EC_{50} fold change compared to wild-type. No change: ≤5-fold change in EC_{50} compared to wild-type.
[b] Variant has not been named by the WHO.
[c] The BA.2.86, BN.1 and JN.1 variants contain the K356T substitution.

Antiviral resistance

Cell culture studies: No viral breakthrough was observed when virus was passaged for 10 passages (34 days) in the presence of fixed concentration of antibody at the lowest concentration tested (~10x EC_{50}). Forcing the emergence of resistance variants through an increasing concentration selection method identified E340A as a sotrovimab mAb resistance mutant (MARM). An E340A substitution emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay.

Table 3 shows the activity data for sotrovimab against epitope sequence polymorphisms evaluated in pseudotyped VLP assessments in cell culture using the Wuhan-Hu-1 and Omicron BA.1, BA.2 and BA.5 spike proteins.

Table 3 Sotrovimab pseudotyped VLP assessments in cell culture against epitope substitutions

		Fold Reduction in Susceptibility[a]			
Reference position	**Substitution**	**Wuhan-Hu-1**	**Omicron BA.1**	**Omicron BA.2**	**Omicron BA.5**
337	P337A	No change	-	-	>133
	P337H	5.13	>631	>117	>120
	P337K	>304	-	-	-
	P337L	>192	-	-	-
	P337N	5.57	-	>143	>135
	P337Q	24.9	-	-	-
	P337R	>192	-	-	-
	P337S	No change	>609	>117	>152
	P337T	10.62	-	>117	>120
340	E340A	>100	-	-	-
	E340D	No change	>609	>117	>91.4
	E340G	18.21	-	>117	>91.4

	E340I	>190	-	-	-
	E340K	>297	-	-	-
	E340L	>1696	-	-	-
	E340N	>1696	-	-	-
	E340Q	>50	-	-	-
	E340R	>1696	-	-	-
	E340S	68	-	-	-
	E340V	>200	-	-	-
341	V341F	No change	5.89	-	5.83
345	T345P	225	-	-	-
356	K356A	No change	-	>129	>60.3
	K356E	No change	-	-	>51.8
	K356M	No change	-	>132	>86.1
	K356N	No change	-	>101	>86.1
	K356Q	No change	-	70.2	>86.1
	K356R	No change	-	22	>69
	K356S	No change	-	>143	>86.1
	K356T	5.90	>631	>117	>91.4
440	N[b]/K[c]440D	No change	-	5.13	No change
441	L441N	72	-	-	-
	L441R	No change	-	No change	5.88

[a] Based on EC_{50} fold change relative to each spike viral variant. No change: ≤5-fold change; –: depicts not tested.

[b] Wuhan-Hu-1 strain

[c] Omicron lineages

Clinical studies: SARS-CoV-2 viruses with baseline and treatment-emergent substitutions at amino acid positions associated with reduced susceptibility to sotrovimab *in vitro* were observed in patients enrolled in clinical studies who received a 500 mg intravenous infusion of sotrovimab (Table 4). In the COMET-ICE and COMET-TAIL studies, among patients who were treated with a 500 mg intravenous infusion of sotrovimab and had a substitution detected at amino acid positions 337 and/or 340 at any visit baseline or post-baseline, 1 of 32 and none of 33 patients, respectively, met the primary endpoint for progression to hospitalisation for >24 hours for acute management of any illness or death from any cause through Day 29. This single patient had E340K detected post-baseline and was infected with the Epsilon variant of SARS-CoV-2.

Table 4. **Baseline and treatment-emergent substitutions detected in sotrovimab-treated patients at amino acid positions associated with reduced susceptibility to sotrovimab**

Clinical Study	Baseline[a]		Treatment-Emergent[b]	
	Substitutions	Frequency, % (n/N)	Substitutions	Frequency, % (n/N)
COMET-ICE	P337H, E340A	1.3 (4/307)	P337L/R, E340A/K/V	14.1 (24/170)
COMET-TAIL	P337S, E340STOP	0.6 (2/310)	P337L, E340A/K/V	19.5 (31/159)
COMET-PEAK	P337H	0.8 (1/130)	P337L, E340A/K/V	13.5 (15/111)
LUNAR[c]	E340D/Q, K356T	4.6 (9/195)	P337A/H/L/R/S, E340A/D/G/K/Q/V, K356M/R/T	29.5 (46/156)

[a] n = number of sotrovimab-treated patients with a baseline substitution detected at spike amino acid positions 337 or 340. Spike position 356 was also included for the LUNAR study which enrolled patients with Omicron BA.2, BA.4 or BA.5 lineage SARS-CoV-2 variants; N = total number of sotrovimab-treated patients with baseline sequence results.
[b] n = number of sotrovimab-treated patients with treatment-emergent substitutions detected at spike amino acid positions 337 or 340. Spike position 356 was also included for the LUNAR study which enrolled patients with Omicron BA.2, BA.4 or BA.5 lineage variants; N = total number of sotrovimab-treated patients with paired baseline and post-baseline sequence results.
[c] A multicentre, single arm, prospective, genomic surveillance study that followed non-hospitalised immunocompromised patients who received 500 mg intravenous infusion of sotrovimab.

Immunogenicity

Treatment-emergent anti-drug antibodies (ADAs) to a single 500 mg intravenous infusion of sotrovimab were detected in 9% (101/1101) of participants, in controlled clinical studies with follow up durations of 18-36 weeks. No participants with confirmed treatment-emergent ADAs had neutralising antibodies against sotrovimab, and there was no evidence of an association of ADA with any impact on the safety, efficacy, or pharmacokinetics after a single intravenous infusion.

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, non-vaccinated 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 and was conducted when the wild-type Wuhan-Hu-1 virus was predominant, with the highest frequency of variants being Alpha and Epsilon. 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.

Patients were randomised to a single 500 mg infusion of sotrovimab (N=528) or placebo (N=529) over 1 hour. In the Intent to Treat (ITT) population at Day 29, 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 5: 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	
Secondary endpoint		
Progression to develop severe and/or critical respiratory COVID-19 (day 29) [b]		
Proportion (n, %)	7 (1%)	28 (5%)
Adjusted relative risk reduction (95% Cl)	74% (41%, 88%)	
p-value	0.002	

[a] No participants required intensive care unit (ICU) stay in the sotrovimab arm versus 9 participants in the placebo arm.
[b] Progression to develop severe and/or critical respiratory COVID-19 defined as the requirement for supplemental oxygen (low flow nasal cannulae/face mask, high flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Based on population pharmacokinetic analyses, following a 15 minute to 1 hour intravenous infusion of 500 mg, the geometric mean C_{max} was 170 µg/mL (N = 1188, CVb% 53.4), and the geometric mean Day 28 concentration was 39.7 µg/mL (N = 1188, CVb% 37.6).

Distribution

Based on population pharmacokinetic analysis, the geometric mean steady-state volume of distribution was 7.9 L.

Biotransformation

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

Elimination

Based on population pharmacokinetic analysis, the mean systemic clearance (CL) was 95 mL/day, with a median terminal half-life of approximately 61 days.

Special populations

Elderly patients
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.

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).

Paediatric population
Limited data on the pharmacokinetics of sotrovimab in patients aged less than 18 years, has been obtained from the COMET-TAIL study (see section 4.8) and the COMET-PACE study. The COMET-PACE study is an open-label, non-conparator paediatric study, that was terminated prior to completion of recruitment. The recommended dose for adolescents aged from 12 years and from 40 kg body weight was based on an allometric scaling approach, which accounted for effect of body weight changes associated with age on clearance and volume of distribution. This approach is supported by a population pharmacokinetic analysis, which shows comparable serum exposures of sotrovimab in adolescents as those observed in adults. Following intravenous infusion of 500 mg sotrovimab in 7 adolescents, the geometric mean C_{max} was 180 µg/mL (geometric CV% 25.6) and the geometric mean Day 29 concentration was 47.4 µg/mL (geometric CV% 17.0).

Data (n=3) in children (aged 6 to less than 12 years and weighing at least 15 kg), are too limited to establish pharmacokinetics of sotrovimab in this age group.

Other special populations
Based on population pharmacokinetic analyses, the pharmacokinetics of sotrovimab following intravenous infusion were not affected by age, sex or BMI. No dose adjustment is warranted based on these characteristics. Body weight was a significant covariate, but the magnitude of effect does not warrant dose adjustment.

5.3 Preclinical safety data

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.

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 (E 433)
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

4 years.

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 and other handling

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 infusion or 5% glucose for infusion.
2. Withdraw 8 mL from the vial of sotrovimab.
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

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
D24 YK11
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1562/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

WuXi Biologics Co., Ltd.,
108 Meiliang Road,
Mashan, Binhu District,
WuXi, Jiangsu, 214092,
China

Or

Samsung Biologics Co., Ltd.,
300 Songdo bio-daero, Yeonsu-gu
Incheon 21987,
Republic of Korea

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.p.A.
Strada Provinciale Asolana, 90,
43056 San Polo di Torrile, Parma,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xevudy 500 mg concentrate for solution for infusion
sotrovimab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Also contains: histidine, histidine monohydrochloride, sucrose, polysorbate 80 (E 433), methionine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial.

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use.

Press here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
D24 YK11
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1562/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Xevudy 500 mg sterile concentrate
sotrovimab
IV

2. METHOD OF ADMINISTRATION

IV use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xevudy 500 mg concentrate for solution for infusion
sotrovimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects, you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xevudy is and what it is used for

Xevudy contains the active substance sotrovimab. Sotrovimab is a *monoclonal antibody*, a type of protein designed to recognise a specific target on the SARS-CoV-2 virus, the virus that causes COVID-19.

Xevudy is used to treat COVID-19 in adults and adolescents (from 12 years and weighing at least 40 kg). It targets the spike protein that the virus uses to attach to cells, blocking the virus from entering the cell and making new viruses. By preventing the virus from multiplying in the body, Xevudy can help your body overcome the infection and prevent you from getting seriously ill.

2. What you need to know before you are given Xevudy

You must not receive Xevudy
- if you are allergic to sotrovimab or any of the other ingredients of this medicine (listed in section 6).
  ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions

Allergic reactions
Xevudy can cause allergic reactions.
➔ See ‘Allergic reactions’ in Section 4.

Infusion-related reactions
Xevudy can cause infusion-related reactions.
➔ See ‘Infusion-related reactions’ in Section 4.

Children and adolescents
Xevudy should not be given to children or adolescents younger than 12 years old or weighing less than 40 kg.

Other medicines and Xevudy
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are **pregnant**, **think you may be pregnant**, or are **planning** to have a baby, **ask your doctor** for advice before receiving Xevudy. Your doctor will advise you whether the benefits of treatment with Xevudy are greater than any likely risks for you and your baby.

It is not known whether the ingredients of Xevudy can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you receive Xevudy.

Driving and using machines

Xevudy is not expected to have any effect on your ability to drive or use machines.

Xevudy contains polysorbate

This medicine contains 4.8 mg of polysorbate 80 in each 500 mg dose. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Xevudy is given

The recommended dose for adults and adolescents (aged 12 years and older and weighing at least 40 kg) is:
- 500 mg (one vial)

The medicine will be made up into a solution and given to you by a drip *(infusion)* into a vein by a doctor or nurse. It takes up to 30 minutes to give you the full dose of medicine. You will be monitored during and for at least 1 hour after your treatment is given.

The 'Instructions for healthcare professionals' below give details for your doctor, pharmacist or nurse on how the Xevudy infusion is made up and given.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

Allergic reactions to Xevudy are **common**, affecting up to 1 in 10 people.
Rarely, these allergic reactions may be severe (*anaphylaxis*), affecting up to 1 in 1,000 people (**rare**).
If you have any of the following symptoms after receiving Xevudy you may be having an allergic reaction and should **get medical help immediately**:
- skin rash, similar to nettle rash (*hives*) or redness
- itching
- swelling, sometimes of the face or mouth (*angioedema*)
- becoming very wheezy, coughing or having difficulty in breathing
- suddenly feeling weak or light-headed (may lead to loss of consciousness or falls).

Infusion-related reactions

Allergic-like reactions when you receive an infusion are **common**, affecting up to 1 in 10 people. These usually develop within minutes or hours but may develop up to 24 hours after treatment or later. Possible symptoms are presented below. If you get any of the following symptoms after receiving Xevudy, you may be having an infusion-related reaction and should **get medical help immediately**:

- flushing
- chills
- fever
- difficulty in breathing
- rapid heartbeat
- drop in blood pressure

Other side effects

Uncommon (may affect up to 1 in 100 people)

- shortness of breath (*dyspnoea*).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xevudy

The healthcare professionals caring for you are responsible for storing this medicine and disposing of any unused product correctly.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not freeze.

Before diluting:

- store in a refrigerator (2°C – 8°C).
- store in the original carton in order to protect from light.

Once diluted, this medicine 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 – 8°C) for up to 24 hours from the time of dilution until the end of administration.

6. Contents of the pack and other information

What Xevudy contains

- The active substance is sotrovimab. Each vial contains 500 mg of sotrovimab in 8 mL concentrate.
- The other ingredients are histidine, histidine monohydrochloride, sucrose, polysorbate 80 (E 433) (see Section 2 “Xevudy contains polysorbate”), methionine and water for injections.

What Xevudy looks like and contents of the pack

Xevudy is a clear, colourless or yellow to brown liquid supplied in a single-use glass vial with a rubber stopper and flip-off aluminium over-seal. Each carton contains one vial.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only.
Please refer to the Summary of Product Characteristics for further information.

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

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.

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 infusion or 5% glucose for infusion.
2. Withdraw 8 mL from the vial of sotrovimab.
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.

The diluted solution of sotrovimab 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) up to 24 hours from the time of dilution until the end of administration.

Administration instructions

1. 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.
2. Prime the infusion set.
3. Administer as an intravenous infusion over 15 minutes (when using a 50 mL infusion bag) or over 30 minutes (when using a 100 mL infusion bag) at room temperature.

Disposal

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