

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

Trogarzo 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg of ibalizumab (in 1.33 mL of solution).

Ibalizumab is produced in murine myeloma non-secreting (NS0) 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).

Colourless to slightly yellow, clear to slightly opalescent aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trogarzo, in combination with other antiretroviral(s), is indicated for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

The recommended dose of ibalizumab is a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks.

If the treating physician determines there is no additional clinical benefit for the patient in terms of viral load reduction, discontinuation of ibalizumab treatment should be considered, see section 5.1.

Missed dose

If a maintenance dose (800 mg) of ibalizumab is missed by 3 days or longer beyond the scheduled dosing day, a loading dose (2,000 mg) should be administered as early as possible. Resume maintenance dosing (800 mg) every 2 weeks thereafter.

Elderly

The safety and efficacy of ibalizumab in geriatric patients (≥ 65 years of age) have not been established.

Paediatric population

The safety and efficacy of ibalizumab in children under the age of 18 years have not yet been established. No data are available.

Method of administration

Intravenous use

Diluted ibalizumab solution should be administered by a healthcare professional.

Ibalizumab should be administered as an intravenous infusion. Ibalizumab should not be administered as an intravenous push or bolus.

The duration of the first infusion (loading dose) should be no less than 30 minutes. If no infusion-associated adverse reactions have occurred, the duration of the subsequent infusions (maintenance doses) can be decreased to no less than 15 minutes.

After the infusion is complete, flush with 30 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

All patients must be observed during and for 1 hour after completion of ibalizumab administration for at least the first infusion. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. Prophylactic medication is not warranted prior to each infusion. If the patient does not experience an infusion-associated adverse reaction, the post-infusion observation time can be reduced to 15 minutes thereafter.

For instructions on dilution of the medicinal product before administration, 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.

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Immune reconstitution inflammatory syndrome (IRIS)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of cART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. IRIS was reported in 2 subjects out of 153 treated with ibalizumab in Phase 2b and 3 clinical studies (see section 4.8).

Excipients with known effect

Ibalizumab contains less than 1 mmol sodium (23 mg) in each loading dose of 2,000 mg or maintenance dose of 800 mg and therefore is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the mechanism of action and target-mediated drug disposition of ibalizumab, it is not expected that ibalizumab will have pharmacokinetic drug-drug interactions with other medicinal products.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

It is recommended that women of childbearing potential use an effective method of contraception during treatment.

Pregnancy

There are no data from the use of ibalizumab in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Human immunoglobulin (IgG) is known to cross the placental barrier. Ibalizumab is not recommended during pregnancy.

Breast-feeding

It is unknown whether ibalizumab/metabolites are excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period and ibalizumab should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

There are no data on the effects of ibalizumab on human fertility.

4.7 Effects on ability to drive and use machines

Ibalizumab has a minor influence on the ability to drive and use machines. Dizziness, nausea, fatigue and headache have been reported during treatment with ibalizumab (see section 4.8). Patients experiencing these symptoms should be advised to use caution when driving or using machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were rash (9.2%), diarrhoea (3.9%), dizziness (3.9%), headache (3.9%), nausea (3.9%), fatigue (2.0%) and vomiting (2.0%).

Tabulated list of adverse reactions

A tabulated list of adverse reactions is presented in Table 1. Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1. Tabulated summary of adverse reactions associated with ibalizumab

System organ class	Adverse reaction	frequency*
Immune system disorders	hypersensitivity, immune reconstitution inflammatory syndrome (see below and section 4.4)	Uncommon
Nervous system disorders	dizziness, headache, paraesthesia	Common
	tremor	Uncommon
Cardiac disorders	ventricular extrasystoles, electrocardiogram abnormal	Uncommon
Vascular disorders	hypertension, labile hypertension, orthostatic hypotension	Uncommon
Gastrointestinal disorders	diarrhoea, nausea, vomiting	Common
	dry mouth	Uncommon
Skin and subcutaneous tissue disorders	rash**, dermatitis, dry skin	Common
	papule, pruritus, erythema nodosum	Uncommon
General disorders and administration site conditions	fatigue	Common
	feeling hot	Uncommon
Injury, poisoning and procedural complications	contusion	Uncommon

* Frequency was calculated based on 24 weeks of safety data from 153 subjects enrolled in Phase 2b study TMB-202 (n = 113) and Phase 3 study TMB-301 (n=40), as well as on at least 48 weeks of safety data from 27 subjects from TMB-301 that rolled-over into expanded access study TMB-311.

**Includes pooled terms “rash”, “rash erythematous”, “rash generalized”, “rash macular”, “rash maculopapular”, “rash pruritic” and “rash papular”.

Description of selected adverse reactions

Rash

Rashes were common. In general, rashes had an early onset (i.e. within 1 to 3 weeks of the first dose of ibalizumab), were mild to moderate in intensity, and resolved within 1-3 weeks with continued ibalizumab administration. In case of rash, it is recommended that the patient be monitored and symptomatic therapy be initiated when appropriate (e.g. corticosteroids and/or anti-histamine medicinal products).

Out of the 153 subjects in Phase 2b and 3 clinical studies, one subject experienced a severe rash (non-serious). This subject had 8 adverse reactions of rash, including 1 event of macular rash, 1 event of generalized rash and 6 events of maculo-papular rash at different times during treatment with ibalizumab. No action was taken with ibalizumab in response to these events.

Immune reconstitution inflammatory syndrome (IRIS)

Out of 153 subjects, two subjects developed immune reconstitution inflammatory syndrome (IRIS; see section 4.4) manifested as an exacerbation of progressive multifocal leukoencephalopathy (serious) and of cryptococcal cutaneous infection (serious), respectively. Both subjects were discontinued from ibalizumab treatment.

Hypersensitivity

One subject out of 153 was reported to have hypersensitivity (allergic reaction) on Day 21 (i.e. 7 days after the 2nd infusion of ibalizumab). As a result, ibalizumab was discontinued.

Immunogenicity

All 153 subjects enrolled in Phase 2b and 3 clinical trials were tested for the presence of anti-ibalizumab IgG antibodies throughout their participation. Only one subject was found to have anti-ibalizumab antibodies. The subject had no adverse reactions associated with the positive immunogenicity result. The subject received ibalizumab therapy for an additional 1.5 years before discontinuing voluntarily with an undetectable viral load (<50 copies/mL).

Laboratory abnormalities

Grade 3 creatinine elevations occurred frequently in subjects with underlying renal disease, risk factors for renal disease, and/or in subjects taking concomitant medications known to be nephrotoxic.

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 known antidote to ibalizumab overdose. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and given appropriate symptomatic treatment. Standard supportive measures should be applied as required, including monitoring of vital signs as well as observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals. ATC code: J05AX23

Mechanism of action

Ibalizumab, a humanized monoclonal antibody of immunoglobulin G type 4 (IgG4), is a CD4 domain 2-directed HIV-1 inhibitor. Ibalizumab blocks HIV-1 from infecting CD4⁺ T cells by binding to domain 2 of CD4 and interfering with the post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

Epitope mapping studies indicate that ibalizumab binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and, therefore, does not interfere with CD4-mediated immune functions.

Ibalizumab is active against HIV-1 group M isolates (subtypes A, B, C, D, E, or O). It is also active against HIV-1 resistant to currently approved antiretroviral medicinal products and exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab and any of the approved classes of anti-retroviral medicinal products.

Resistance

Decreased susceptibility to ibalizumab, as defined by a decrease in Maximum Percent Inhibition (MPI), has been observed in most subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that results in the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120. No relevant remaining effect of ibalizumab is expected in cases of resistance development. Decreased susceptibility to ibalizumab was a finding in the majority of patients who experienced virologic failure up to week 24 in the pivotal study.

Decreased susceptibility to ibalizumab does not alter susceptibility to other approved agents and does not result in the selection of CD4-independent viral isolates.

Clinical efficacy and safety

Trial TMB-301

Phase 3 trial TMB-301 was a single arm, multicenter clinical trial conducted in 40 heavily treatment-experienced HIV-infected subjects with multidrug resistant HIV-1. Subjects were required to have a viral load greater than 1,000 copies/mL and documented resistance to at least one antiretroviral medication from three classes of antiretroviral medications as measured by resistance testing. Subjects must have been treated with antiretrovirals for at least 6 months and be failing or had recently failed therapy (i.e., in the last 8 weeks).

The trial was composed of three discrete periods:

- Control period (Day 0 to Day 6): Subjects were either monitored on their current failing therapy or received no therapy if they had failed and discontinued treatment within the 8 weeks preceding screening. This was an observational period to establish baseline HIV viral load.
- Functional monotherapy period (Day 7 to Day 13): All subjects received a 2,000 mg loading dose of ibalizumab on Day 7. Subjects on a failing ART regimen continued to receive their failing regimen in addition to the loading dose of ibalizumab. This period was to establish the virologic activity of ibalizumab.
- Maintenance period (Day 14 to Week 25): On Day 14 of the treatment period, viral load was assessed for the primary endpoint, and thereafter the background regimen was optimized to include at least one drug to which the subject's virus was susceptible. The use of an investigational drug as a component of the optimized background regimen was allowed. Beginning at Day 21, an 800 mg maintenance dose of ibalizumab was administered every two weeks through Week 25. This period was to establish the safety and durability of virologic suppression of ibalizumab when used in combination with an optimized background regimen.

The majority of subjects in Trial TMB-301 were male (85%), white (55%) and between 23 and 65 years of age (mean [SD] age: 50.5 [11.0] years). At Baseline, median [Min - Max] viral load and CD4⁺ T cell counts were 35,350 [304 - 743,000] copies/mL and 73 [0 - 676] cells/mm³, respectively. The subjects were heavily treatment-experienced: 53% of participants had been treated with 10 or more antiretroviral drugs prior to trial enrolment; 98% percent had been treated with NRTIs, 98% with PIs, 80% with NNRTIs, 78% with INSTIs, 30% with gp41 fusion inhibitors, and 20% with CCR5 co-receptor antagonists.

The primary efficacy endpoint was the proportion of subjects achieving a $\geq 0.5 \log_{10}$ decrease in viral load from the beginning to the end of the "Functional monotherapy period" as compared to the proportion of subjects achieving a $\geq 0.5 \log_{10}$ decrease from the beginning to the end of the "Control period", as defined above. The results of the primary endpoint analysis are shown in Table 2 below.

Table 2. Proportion of subjects achieving a $\geq 0.5 \log_{10}$ decrease in viral load at the end of the control and functional monotherapy periods

	Proportion of subjects achieving a $\geq 0.5 \log_{10}$ decrease in viral load N=40	95% CI*
End of control period	1/40 (3%)	0.06%, 13%
End of functional monotherapy period	33/40 (83%)**	67%, 93%

*exact 95% confidence interval

** p < 0.0001 based on McNemar's test comparing the proportion of subjects achieving $\geq 0.5 \log_{10}$ decrease in viral load at the end of the control and functional monotherapy periods.

Fifty-five percent of subjects had a $\geq 1 \log_{10}$ reduction in viral load, and 48% of subjects had a $\geq 2 \log_{10}$ reduction in viral load at Week 25. An increase in the mean number of CD4⁺ T-cells of 62 cells/mm³ was observed from Baseline to Week 25 (Intent-To-Treat (ITT) analysis). Week 25

outcomes are shown in Table 3. Subjects with baseline CD4 counts < 50 cells/mm³ were less likely to achieve a HIV-1 RNA of < 200 copies/mL (or < 50 copies/mL) than subjects with > 50 cells/mm³.

Table 3. Virologic response at week 25 by baseline CD4 cell count, integrase inhibitor resistance and Overall Susceptibility Score (OSS)* for study TMB-301

	No. of subjects achieving <50 HIV-1 RNA copies/mL (n/N)	No. of subjects achieving <200 HIV-1 RNA copies/mL (n/N)
Virologic response	17/40 (43%)	20/40 (50%)
CD4 cell counts (cells/ mm ³)		
< 50	3/17 (18%)	4/17 (24%)
50-200	6/10 (60%)	7/10 (70%)
> 200	8/13 (62%)	9/13 (69%)
HIV-RNA (copies/mL)		
< 100 000	16/33 (48%)	19/33 (58%)
≥ 100 000	1/7 (14%)	1/7 (14%)
Resistance		
With INSTI resistance	11/27 (41%)	12/27 (44%)
Without INSTI resistance	6/13 (46%)	8/13 (62%)
OSS		
0	1/5 (20%)	1/5 (20%)
1	5/12 (42%)	6/12 (50%)
2	9/18 (50%)	11/18 (61%)
3	1/3 (33%)	1/3 (33%)
4	1/2 (50%)	1/2 (50%)

* The OSS indicates the number of fully active drugs in a subject's Optimized Background Regimen (OBR) based on both current and available historical resistance test results. Demonstrating drug susceptibility by both genotypic and phenotypic testing was required, when testing by both methods was technically feasible. As an example, an OSS of 2 would indicate that the HIV-1 isolate tested was fully susceptible to two drugs in the OBR.

Trial TNX-355.03

Study TNX-355.03 was a multicenter, randomized, double-blinded, placebo-controlled, multi-dose, 3-arm safety and efficacy study in 82 subjects with HIV-1 and who were failing or had failed highly active antiretroviral therapy. Subjects all received OBR plus 1 of the following regimens: alternating intravenous (IV) infusions of 15 mg/kg ibalizumab and placebo, weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 15 mg/kg ibalizumab every 2 weeks (Arm A); 10 mg/kg ibalizumab IV infusions weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 10 mg/kg ibalizumab every 2 weeks (Arm B); or weekly placebo IV infusions for the first 9 doses (through the Week 8 visit), then IV infusions of placebo every 2 weeks (Placebo arm). Patients in all three arms also received an OBR. As of Week 16, patients in Placebo arm who experienced virologic failure had the option of receiving 15 mg/kg open-label ibalizumab every 2 weeks and/or switching to a new OBR. Patients in Arm A and B arm who experienced virologic failure had the option of switching to a new OBR.

At Week 2, the mean viral load decrease was 0.87 log₁₀ copies/mL in Arm A, 1.15 log₁₀ copies/mL in Arm B and 0.38 log₁₀ copies/mL in the Placebo arm (p=0.003 vs Arm A, p<0.001 vs Arm B).

By Week 16, i.e. prior to the possible switching of patients in the Placebo arm to the 15 mg/kg dose of ibalizumab every 2 weeks and/or to change in OBR for all patients, mean viral load decrease was 1.07 log₁₀ copies/mL in Arm A, 1.33 log₁₀ copies/mL in Arm B and 0.26 log₁₀ copies/mL in the Placebo arm (p=0.002 vs Arm A, p<0.001 vs Arm B).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Trogarzo in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following the recommended dose regimen (a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks), ibalizumab concentrations reached steady-state levels after the first 800 mg maintenance dose with mean trough concentrations over 30 µg/mL throughout the dosing interval. The median time to maximum serum concentration (T_{max}) of 2,000 mg and 800 mg is 1 hr and 10 min, respectively. Ibalizumab is administered as an IV infusion. The bioavailability is 100% by definition.

Distribution

The volume of distribution of ibalizumab is approximately 4.8 L, which is comparable with vascular space, based on the performed population pharmacokinetics analysis.

Biotransformation

Specific metabolism studies were not conducted because ibalizumab is a protein. Ibalizumab is expected to degrade to small peptides and individual amino acids.

Elimination

Following single-dose administrations of 10 and 25 mg/kg of ibalizumab, clearance is 0.5 to 0.36 mL/h/kg and elimination half-life is 37.8 and 64.1 hours, respectively. The elimination is nonlinear and concentration-dependent.

Linearity/non-linearity

Ibalizumab administered as a single agent exhibits nonlinear pharmacokinetics at a dose range of 0.3-25 mg/kg. Following administration of ibalizumab, at the clinically relevant dose range of 800-2,000 mg, the maximum serum concentration (C_{max}) increased dose proportionally, whereas the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner. Such non-linear effects in clearance are common for monoclonal antibodies targeting cell surface molecules, such as CD4. This behaviour is characteristic of saturable (capacity-limited) elimination kinetics.

Special populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates (age, body weight, sex, baseline CD4⁺ cell count) on ibalizumab pharmacokinetics. The results suggest that ibalizumab concentration decreases as body weight increases. The body weight range was very narrow in the population PK model, and the impact of body weight may not be precisely estimated. However, the effect is unlikely to impact virologic outcome and does not warrant a dose adjustment.

Renal impairment

No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of ibalizumab. Renal impairment is not anticipated to impact the pharmacokinetics of ibalizumab.

Hepatic impairment

No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of ibalizumab. Hepatic impairment is not anticipated to impact the pharmacokinetics of ibalizumab.

Paediatric population

Ibalizumab pharmacokinetics have not been evaluated in paediatric patients.

Elderly population

Ibalizumab pharmacokinetics in geriatric patients (≥ 65 years of age) is limited ($n = 5$). Results are similar to the adult population (≥ 18 to 65 years of age), however no definite conclusions can be drawn.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of *in vitro* and *in vivo* safety assessments.

Toxicity to reproduction and development

A pre- and post-natal developmental study was performed in cynomolgus monkeys. Ibalizumab was administered to pregnant females at a 110mg/kg weekly dose from gestation Day 20-22 until parturition (approximately 22 doses/animal). This dose was administered as it is at least 10-fold the estimated free clinical AUC and C_{max} for the 800 mg Q2W dose. Ibalizumab was generally well tolerated in pregnant monkeys and in their offspring, when evaluated through 180 ± 2 days post-partum. There were no ibalizumab-related adverse effects (maternal, foetal, or infant) at 110 mg/kg (No-Observed-Adverse-Effect Level, NOAEL). However, CD4⁺ cells in infants of treated females were temporarily suppressed from BD14-91 compared to control, but there was no further impact on immunocompetence of the infants. The relevance of this effect for human pregnancy and lactation remains unknown. Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for developmental effects was 110 mg/kg.

Genotoxicity, carcinogenic potential

Genotoxicity and carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium chloride
Polysorbate 80
Histidine
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

5 years

Diluted solution

If not administered immediately, store the diluted ibalizumab solution below 25°C for up to 4 hours, or in a refrigerator (2°C to 8°C) for up to 24 hours. If refrigerated, allow the diluted ibalizumab solution to stand at room temperature (20°C to 25°C) for at least 30 minutes but no more than 4 hours prior to administration.

6.4 Special precautions for storage

Store and transport refrigerated (2°C to 8°C).

Do not freeze.

Keep the vial in the outer 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

2 mL vial (Type I borosilicate glass) sealed with a stopper (butyl rubber) and an aluminum crimp cap.

Pack of 2 vials.

6.6 Special precautions for disposal and other handling

This medicinal product should be inspected visually for particulate matter and discoloration prior to administration. Vials containing non-diluted ibalizumab or infusion bag containing diluted ibalizumab must be discarded if solution is cloudy, if there is pronounced discoloration or if there is foreign particulate matter.

Ibalizumab is administered intravenously (IV), after diluting the appropriate number of vials in 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. See Table 4 below for the appropriate number of vials required to prepare both the loading dose of 2,000 mg and the maintenance doses of 800 mg.

Table 4. Recommended ibalizumab dose and number of vials per administration

Ibalizumab dose	Ibalizumab vials (Total volume to be withdrawn)
Loading dose of 2,000 mg	10 vials (13.3 mL)
Maintenance dose of 800 mg	4 vials (5.32 mL)

Ibalizumab concentrate for solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove the flip-off cap from the vial and wipe with an alcohol swab.

- Insert sterile syringe needle into the vial through the center of the stopper and withdraw 1.33 mL from each vial (NOTE: a small residual amount may remain in the vial, discard unused portion) and transfer into a 250 mL intravenous bag of sodium chloride 9 mg/mL (0.9%) solution for injection. Other intravenous diluents must not be used to prepare the ibalizumab solution for infusion.
- Once diluted, the ibalizumab solution should be administered immediately.
- Discard partially used vials or empty vials of ibalizumab and any unused portion of the diluted ibalizumab solution in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Theratechnologies Europe Limited
4th Floor, 2 Hume Street, Dublin 2, D02 DV24, Ireland
Tel: 00800 08250830
Tel.: +49 (0) 30 3119 6151
medinfo.eu@theratech.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1359/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

WuXi Biologics Co, Ltd
108 Meiliang Road,
MaShan Binhu District,
Wuxi, 214092,
China

Name and address of the manufacturer responsible for batch release

MIAS Pharma Limited
Suite 2 Stafford House, Strand Road,
Portmarnock, Co. Dublin, D13 H525
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.(see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
<p>Post-authorisation efficacy study (PAES):</p> <p>In order to further characterise the efficacy of ibalizumab in combination with other anti-retroviral medicinal products, for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, the MAH should conduct and submit the results of a study based on data from a product registry. This study should be conducted according to an agreed protocol.</p>	<p>Final report submission: 31-Oct-2026</p>

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (Contains 2 vials of 200 mg)

1. NAME OF THE MEDICINAL PRODUCT

Trogarzo 200 mg concentrate for solution for infusion
ibalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg of ibalizumab

3. LIST OF EXCIPIENTS

Sucrose
Sodium chloride
Polysorbate 80
Histidine
Hydrochloric acid
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.
2 vials

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

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 and transport refrigerated.
Do not freeze.
Keep the vial in the outer 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

Theratechnologies Europe Limited
4th Floor, 2 Hume Street,
Dublin 2, D02 DV24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1359/001

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
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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trogarzo 200 mg sterile concentrate
ibalizumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Trogarzo 200 mg concentrate for solution for infusion ibalizumab

▼ 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 start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trogarzo is and what it is used for
2. What you need to know before you use Trogarzo
3. How to receive Trogarzo
4. Possible side effects
5. How to store Trogarzo
6. Contents of the pack and other information

1. What Trogarzo is and what it is used for

What Trogarzo is

Trogarzo contains the active substance ibalizumab. This is a type of protein called a ‘monoclonal antibody’ that can attach to a specific target in the body. It belongs to a group of medicines called ‘antiretrovirals’.

What Trogarzo is used for

Trogarzo is used in adults to treat HIV infection that has not responded to a number of HIV treatments in the past.

Your doctor has prescribed Trogarzo to help control your HIV infection.

Trogarzo is used in combination with other medicines.

It will be used together with other HIV medicines called ‘antiretrovirals’.

How Trogarzo works

The HIV virus infects cells in your blood called ‘CD4’ or ‘T-cells’. Trogarzo attaches to the CD4 receptor and blocks HIV from entering and infecting your blood cells. This will reduce the amount of virus in your body, and keeps it at a low level. This helps your body to increase the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body to fight infection.

2. What you need to know before you use Trogarzo

You must not be given Trogarzo:

- if you are allergic to ibalizumab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before being given Trogarzo.

Warnings and precautions

Look out for side effects

Trogarzo can cause serious side effects that you need to tell your doctor or nurse about straight away. These include:

- **signs of a new infection** (called ‘immune reconstitution inflammatory syndrome’)

Tell your doctor or nurse straight away if you get any of the above (for more information see ‘Serious side effects’ in section 4).

Passing HIV to others

This medicine reduces the amount of HIV in your body. When this is stably kept at undetectable levels, the chances that you can still pass on HIV to your sexual partners become negligible. You can still pass on HIV when taking this medicine, if you have detectable levels of HIV in your body. Talk to your doctor or nurse about how to avoid infecting other people.

Children and adolescents

Do not give this medicine to children and adolescents below 18 years of age. This is because Trogarzo has not been studied in this age group.

Other medicines and Trogarzo

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

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you could get pregnant while taking Trogarzo, you need to use a reliable method of barrier contraception (for example, a condom) with other methods of contraception including oral contraceptive (the pill) or other hormonal contraceptives (for example, implants or injections), to prevent pregnancy.

Breast-feeding

Women who are HIV-positive must not breast feed because HIV infection can be passed on to the baby in breast milk. It is unknown if Trogarzo can pass into breast milk.

If you are breast-feeding, or thinking about breast-feeding:

→ **Talk to your doctor immediately.**

Driving and using machines

Do not drive or use machines after you have been given Trogarzo if you do not feel well enough. Headache, feeling dizzy, feeling sick (nausea) or feeling tired are common side effects of Trogarzo and can affect your ability to drive or use machines.

Trogarzo has a low sodium content

Trogarzo contains less than 1 mmol sodium (23 mg) in each dose and therefore is essentially sodium-free.

3. How to receive Trogarzo

You will be given Trogarzo under the supervision of an experienced doctor or nurse.

Trogarzo is used in combination with other medicines called ‘antiretrovirals’.

How much Trogarzo you will be given

The recommended dose of Trogarzo is:

- a single dose of 2,000 mg on the first occasion
- followed by a maintenance dose of 800 mg every 2 weeks.

Trogarzo will be added to a drip (infusion bag) containing a sodium chloride (saline) solution before use.

More than one vial of Trogarzo will be needed to get the required dose.

How you will be given Trogarzo

The drip (infusion) will be given into a vein over 15 to 30 minutes. Your doctor or nurse will monitor you during the Trogarzo infusion and for a period of time after your infusion.

If you miss a dose of Trogarzo

- It is very important that you are given Trogarzo every 2 weeks as instructed by your doctor.
- Do not change the schedule of your Trogarzo infusions or any of your other antiretroviral medicines without talking to your doctor first.
- If you miss an appointment, ask your doctor straight away when to schedule your next dose.

If you stop having Trogarzo

Keep having Trogarzo infusions until your doctor tells you to stop. If you stop and there is a gap in your treatment, the level of HIV virus in your blood may begin to rise. This is less likely if you receive Trogarzo regularly and without gaps in treatment.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Serious side effects

Talk to your doctor or nurse straight away if you get any of the following serious side effects:

- Signs of a new infection, changes in your immune system, can happen when you start using HIV medicines. Your immune system might get stronger and begin to fight infections that have been hidden in your body for a long time (this is called 'immune reconstitution inflammatory syndrome'). Look out for new signs of infection after receiving Trogarzo; these can be different from person to person depending on the type of infection that was hidden and might include fever, headache, difficulty breathing, stomach ache, coughing and swollen glands (lumps and bumps on your body, neck, armpit or groin).
- Allergic reaction (hypersensitivity).

Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

Common (may affect up to 1 in 10 people):

- skin rash
- diarrhoea
- feeling sick (nausea) or being sick (vomiting)
- dizziness
- headache
- feeling tired
- dry skin
- dermatitis – a type of eczema with dry itchy skin
- pain and feeling numb in hands, feet or legs

Uncommon (may affect up to 1 in 100 people):

- tremor
- feeling dizzy, faint or light headed when standing up
- dry mouth
- feeling hot
- spots or swelling
- itchy skin, or skin damage
- bruising
- abnormal heartbeat
- high blood pressure or frequent changes in blood pressure

Seen in tests:

- abnormal results on tests of the heart's electrical activity (electrocardiogram)

Tell your doctor or nurse if you notice any of the side effects listed above.

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 Trogarzo

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 vial label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

6. Contents of the pack and other information

What Trogarzo contains

- The active substance is ibalizumab.
- One vial contains 200 mg of ibalizumab in 1.33 mL of solution.
- The other excipients are sucrose, sodium chloride (see section 2 'Trogarzo has a low sodium content'), polysorbate 80, histidine, hydrochloric acid, water for injections.

What Trogarzo looks like and contents of the pack

Trogarzo is a colourless to slightly yellow, clear to slightly opalescent concentrate for solution for infusion (sterile concentrate), with no visible particles.

The pack size is 2 glass vials per carton.

Marketing Authorisation Holder and manufacturer

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This leaflet was last revised in month YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Method of administration

Intravenous use

Diluted ibalizumab solution should be administered by a healthcare professional.

Ibalizumab should be administered as an intravenous infusion. Ibalizumab should not be administered as an intravenous push or bolus.

The duration of the first infusion (loading dose) should be no less than 30 minutes. If no infusion-associated adverse reactions have occurred, the duration of the subsequent infusions (maintenance doses) can be decreased to no less than 15 minutes.

After the infusion is complete, flush with 30 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

All patients must be observed during and for 1 hour after completion of ibalizumab administration for at least the first infusion. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. Prophylactic medication is not warranted prior to each infusion. If the patient does not experience an infusion-associated adverse reaction, the post-infusion observation time can be reduced to 15 minutes thereafter.

Instructions on dilution of ibalizumab before use

Ibalizumab is administered intravenously (IV), after diluting the appropriate number of vials in 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. See the table below for the appropriate number of vials required to prepare both the loading dose of 2,000 mg and the maintenance doses of 800 mg.

Recommended ibalizumab dose and number of vials per administration

Ibalizumab dose	Ibalizumab vials (total volume to be withdrawn)
Loading dose of 2,000 mg	10 vials (13.3 mL)
Maintenance dose of 800 mg	4 vials (5.32 mL)

Ibalizumab concentrate for solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove the flip-off cap from the vial and wipe with an alcohol swab.

- Insert sterile syringe needle into the vial through the center of the stopper and withdraw 1.33 mL from each vial (NOTE: a small residual amount may remain in the vial, discard unused portion) and transfer into a 250 mL intravenous bag of sodium chloride 9 mg/mL (0.9%) solution for injection. Other intravenous diluents must not be used to prepare the ibalizumab solution for infusion.
- Once diluted, the ibalizumab solution should be administered immediately.
- Discard partially used vials or empty vials of ibalizumab and any unused portion of the diluted ibalizumab solution in accordance with local requirements.

Precautions to be taken before handling or administering the medicinal product

This medicinal product should be inspected visually for particulate matter and discoloration prior to administration. Vials containing non-diluted ibalizumab or infusion bag containing diluted ibalizumab must be discarded if solution is cloudy, if there is pronounced discoloration or if there is foreign particulate matter.