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

NYXTHRACIS 100 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 100 mg of obiltoxaximab.
One vial of 6 mL contains 600 mg obiltoxaximab.

Obiltoxaximab is produced in murine GS-NS0 myeloma cells by recombinant DNA technology.

Excipient with known effect

Each mL of concentrate contains 36 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
NYXTHRACIS is a clear to opalescent, colourless to pale yellow to pale brownish-yellow solution that may contain few translucent-to-white proteinaceous particulates (which will be removed by in-line filtration) with a pH of 5.5 and an osmolality of 277 – 308 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NYXTHRACIS is indicated in combination with appropriate antibacterial drugs in all age groups for treatment of inhalational anthrax due to *Bacillus anthracis* (see section 5.1).

NYXTHRACIS is indicated in all age groups for post-exposure prophylaxis of inhalational anthrax when alternative therapies are not appropriate or are not available (see section 5.1).

4.2 Posology and method of administration

NYXTHRACIS should be given as soon as it is clinically indicated.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of NYXTHRACIS.

Posology

The recommended dosage of NYXTHRACIS in adult patients weighing at least 40 kg is a single intravenous infusion of 16 mg/kg body weight (bw). The recommended dosage of NYXTHRACIS in adult patients weighing less than 40 kg is a single intravenous infusion of 24 mg/kg bw.

Premedication with an antihistamine is recommended before administration of NYXTHRACIS (see sections 4.4 and 4.8).

For dose modifications in case of infusion-related reactions (IRR) see table 1.

Table 1: Obiltoxaximab dose modifications for infusion-related reactions

Severity of IRR	Dose modification
Grade 1–3 Infusion-related reaction	Obiltoxaximab infusion should be interrupted and supportive treatment should be given. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, obiltoxaximab should be permanently discontinued. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, obiltoxaximab should be permanently discontinued. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion is described in table 3. Premedication should be administered.
Grade 4 Infusion-related reaction	Obiltoxaximab infusion should be stopped immediately. Supportive treatment should be given. Obiltoxaximab should be permanently discontinued.

Special populations

Elderly

No dosage adjustment is needed for patients ≥ 65 years of age (see section 5.2).

Paediatric population

The recommended dose for paediatric patients is based on weight as shown in table 2 below.

Table 2: Recommended paediatric dose of obiltoxaximab (weight-based dosing)

Body weight [kg]	Dose [mg/kg bw]
> 40	16
> 15 to 40	24
15 or less	32

Method of administration

Obiltoxaximab must be administered via intravenous infusion over 90 minutes.

Precautions to be taken before handling or administering the medicinal product

The vial should not be shaken. Obiltoxaximab must be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration as an intravenous infusion (see section 6.6).

The diluted obiltoxaximab intravenous infusion must be infused over 90 minutes with the infusion rate described in table 3, using an infusion bag or syringe for infusion and a 0.22 micron inline filter.

Patients need to be monitored closely for signs and symptoms of hypersensitivity throughout the infusion and for at least one hour after administration (see section 4.4). Infusion related reactions should be managed as outlined in table 1.

The line is to be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection at the end of the intravenous infusion.

Table 3: Obiltoxaximab dose, total infusion volume and infusion rate by body weight

Body weight [kg] (weight-based dosing)	Total infusion volume [mL] [infusion bag or syringe]*	Infusion rate [mL/h]
> 40 kg or adult (16 mg/kg bw)		
> 40	250	167
> 15 kg to 40 kg (24 mg/kg bw)		
31 to 40	250	167
16 to 30	100	67
15 kg or less (32 mg/kg bw)		
11 to 15	100	67
5 to 10	50	33.3
3.1 to 4.9	25	17
2.1 to 3	20	13.3
1.1 to 2	15	10
1 or less	7	4.7

* For instructions on dilution of the medicinal product and use of infusion bag or syringe 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.

Infusion-related reactions, hypersensitivity and anaphylaxis

Infusion-related/hypersensitivity reactions were commonly observed during clinical trials with obiltoxaximab in healthy subjects. Due to the risk of severe reactions or anaphylaxis, obiltoxaximab should be administered in monitored settings by personnel trained and equipped to manage anaphylaxis. Patients should be monitored closely throughout the infusion period and for at least one hour after administration.

Since the clinical trials were conducted in healthy volunteers, obiltoxaximab infusions were stopped at the onset of any reaction. Based on experience with other monoclonal antibodies used in the treatment of serious medical conditions, infusions can generally be completed if managed appropriately. Infusion-related reactions should be managed as outlined in table 1.

Premedication with an antihistamine, e.g. diphenhydramine, is recommended prior to administration of obiltoxaximab (see section 4.2). Diphenhydramine was administered 30 minutes prior to treatment with obiltoxaximab in clinical trials conducted with obiltoxaximab. Premedication with an antihistamine does not prevent anaphylaxis and may mask or delay onset of symptoms of hypersensitivity.

Anthrax meningitis

Obiltoxaximab does not cross the blood-brain barrier and does not prevent or treat anthrax meningitis.

Paediatric population

There have been no studies of safety or PK of obiltoxaximab in the paediatric population (see section 5.2).

Laboratory test interactions

Exposure to NYXTHRACIS may interfere with serological tests for anthrax.

Sorbitol

Each mL of NYXTHRACIS contains 36 mg of sorbitol (see sections 2 and 6.1).
Medicinal products containing sorbitol may be fatal if given intravenously to subjects with hereditary fructose intolerance (HFI). Obiltotoxaximab should not be used in subjects with HFI unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms should be taken from each patient prior to being given this medicinal product.

Infants and toddlers (below 2 years of age) are at particular risk since they may not yet be diagnosed with HFI.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per each 6 mL vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ciprofloxacin

In an interaction study, a single dose of obiltoxaximab was given alone or co-administered with ciprofloxacin in 40 subjects. Twenty subjects received obiltoxaximab alone and 20 subjects received obiltoxaximab plus ciprofloxacin for 9 days. The administration of 16 mg/kg obiltoxaximab intravenous infusion prior to ciprofloxacin intravenous infusion or ciprofloxacin twice daily oral tablet ingestion did not alter the pharmacokinetics of obiltoxaximab. Likewise, obiltoxaximab did not alter the pharmacokinetics of ciprofloxacin administered orally or intravenously.

No other interaction studies have been performed. Since obiltoxaximab is a monoclonal antibody, the risk of interaction is low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of obiltoxaximab in pregnant women, however, human IgG is known to cross the placental barrier.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of NYXTHRACIS during pregnancy.

Breast-feeding

It is unknown whether obiltoxaximab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth and is decreasing to low concentrations soon afterwards. Consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of obiltoxaximab could be considered during breast-feeding, only if clinically needed.

Fertility

Fertility studies have not been conducted with obiltoxaximab.

4.7 Effects on ability to drive and use machines

Obiltoxaximab may have a minor influence on the ability to drive and use machines since headache, dizziness, fatigue and vomiting may occur following administration of NYXTHRACIS (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of obiltoxaximab has been studied only in healthy adult subjects.

The safety of obiltoxaximab was evaluated in 320 healthy subjects (aged 18 to 79 years old) treated with one or two 16 mg/kg intravenous doses in three clinical studies.

Overall 250 of the 320 subjects received a single dose of 16 mg/kg obiltoxaximab. Hypersensitivity related adverse reactions (including rash) occurred in 9% (22/250) of these subjects, with one case of anaphylaxis that occurred during the infusion. The infusion was discontinued in 3% (8/250) due to hypersensitivity or anaphylaxis.

The most frequently reported adverse reactions were headache (4%, 9/250), pruritus (4%, 9/250), and urticaria (2%, 6/250).

Most commonly observed adverse reactions within the first three hours after start of infusion were pruritus (n=7; 2.8%), urticaria (n=6; 2.4%), headache (n=4; 1.6%), rash (n=3; 1.2%), cough (n=3; 1.2%), dizziness (n=3; 1.2%) (includes dizziness and dizziness postural).
The following severe adverse reactions occurred within the first three hours following the infusion: urticaria (n=1, 0.4%), pruritus (n=1, 0.4%) and back pain (n=1, 0.4%).
The most commonly observed adverse reaction within 3 to 24 hours after start of infusion was headache (n=3; 1.2%).

Tabulated list of adverse reactions

Table 4 presents adverse reactions observed with obiltoxaximab in the 250 healthy human subjects that received a single intravenous dose of 16 mg/kg obiltoxaximab, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions reported in healthy adult subjects

MedDRA System Organ Class	Common	Uncommon
Immune system disorders		Anaphylactic reaction Hypersensitivity
Nervous system disorders	Headache	Dizziness Dizziness postural Hypoaesthesia
Eye disorders		Photophobia
Ear and labyrinth disorders		Ear discomfort
Vascular disorders		Phlebitis

MedDRA System Organ Class	Common	Uncommon
Respiratory, thoracic, and mediastinal disorders	Cough	Throat irritation Dysphonia Sinus congestion Dyspnoea
Gastrointestinal disorders		Lip pain
Skin and subcutaneous tissue disorders	Pruritus, urticaria, rash	Dermatitis allergic Rash generalised Skin exfoliation
Musculoskeletal and connective tissue disorders		Pain in extremity Muscle spasm Muscle twitching Pain in jaw
General disorders and administration site conditions	Infusion site pain	Pain Chest discomfort Chills Fatigue Infusion site swelling Non-cardiac chest pain Tenderness Vessel puncture site pain

Description of selected adverse reactions

Hypersensitivity and anaphylaxis
The adverse reactions reported in the 8 subjects in whom the obiltoxaximab infusion was discontinued for possible hypersensitivity included urticaria, rash, cough, pruritus, dizziness, throat irritation, dysphonia, dyspnoea and chest discomfort. The remaining subjects with hypersensitivity had predominantly skin-related symptoms such as pruritus and rash, and 6 subjects reported cough. The anaphylaxis event was characterised by a diffuse pruritic urticarial rash over most of the body, including neck, chest, back, abdomen, arms, and legs, shortness of breath, and coughing.

There was no evidence that the hypersensitivity reactions and rashes have been triggered by cytokine release; no clinically significant changes in cytokines have been observed.

Immunogenicity
The development of anti-obiltoxaximab antibodies was evaluated in all subjects receiving single and double doses of obiltoxaximab in three clinical studies. Eight subjects (2.5% (8/320)) who received at least one intravenous dose of obiltoxaximab were positive for a treatment-emergent anti-therapeutic antibody (ATA) response. Quantitative titres were low ranging from 1:20 to 1:320. There was no evidence of altered pharmacokinetics or toxicity profile in subjects with an ATA response.

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

In case of overdose, patients should be monitored for any signs or symptoms of adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, specific immunoglobulins, ATC code: J06BB22

Mechanism of action

Obiltoxaximab is a monoclonal antibody that binds the protective antigen (PA) of *B. anthracis*. Obiltoxaximab inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax lethal factor and oedema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

Pharmacodynamic effects

Obiltoxaximab binds free PA with an affinity equilibrium dissociation constant (Kd) of 0.33 nM. *In vitro*, obiltoxaximab binds to PA from the Ames, Vollum, and Sterne strains of *B. anthracis*. The epitope on PA to which obiltoxaximab binds is conserved across reported strains of *B. anthracis*.

In vitro studies in a cell-based assay, using murine macrophages, suggest that obiltoxaximab neutralises the toxic effects of lethal toxin, a combination of PA + lethal factor.

In vivo efficacy studies in New Zealand White (NZW) rabbits and cynomolgus macaques challenged with the spores of the Ames strain of *B. anthracis* by the inhalational route, showed a dose-dependent increase in survival following treatment with obiltoxaximab. Exposure to *B. anthracis* spores resulted in increasing concentrations of PA in the serum of NZW rabbits and cynomolgus macaques. After treatment with obiltoxaximab there was a decrease in PA concentrations in a majority of surviving animals. PA concentrations in placebo animals increased until they died.

Efficacy

Because it is not feasible or ethical to conduct controlled clinical trials in humans with inhalational anthrax, the efficacy of obiltoxaximab administered as monotherapy compared with placebo for the treatment of inhalational anthrax is based on efficacy studies in NZW rabbits and cynomolgus macaques.

In these studies, the animals were challenged with aerosolised *B. anthracis* spores (Ames strain) at approximately 200xLD_{50} and thereafter treated with obiltoxaximab at different time points. In treatment studies of inhalational anthrax, animals were administered treatment after exhibiting clinical signs or symptoms of systemic anthrax. In post-exposure prophylaxis studies, animals were treated following exposure to *B. anthracis* but prior to the development of symptoms. Cynomolgus macaques were treated at the time of a positive serum electrochemiluminescence (ECL) assay for *B. anthracis* PA at a mean time of approximately 40 hours post-challenge with *B. anthracis*. In NZW rabbit treatment studies, animals were treated after a positive ECL assay for PA or sustained elevation of body temperature above baseline, at a mean time of approximately 30 hours post-challenge. Survival was assessed at 28 days post-challenge with *B. anthracis* in studies described below.

The efficacy of a single intravenous dose of obiltoxaximab as monotherapy for the treatment of inhalational anthrax was evaluated in one study in NZW rabbit studies and three studies in cynomolgus macaques (AP202, AP204 and AP301); all studies were placebo-controlled, randomized, and GLP-compliant. Studies AR033, AP202 and AP301 were blinded; study AP204 was blinded to group.

Table 5: Survival rates in monotherapy efficacy studies with obiltoxaximab (16 mg/kg)

		Proportion of survival at end of study (% [survived/n])		p-value[2]	95% CI[3]
		Placebo	Obiltoxaximab 16 mg/kg		
Treatment - NZW rabbits					
Study AR033[1]		0 (0/13)	61.5% (8/13)	0.0013*	(0.290, 0.861)
Treatment - Cynomolgus macaques					
Study AP204[1]		6% (1/16)	46.7% (7/15)	0.0068*	(0.089, 0.681)
Study AP202[1]		0 (0/17)	31.3% (5/16)	0.0085*	(0.079, 0.587)
Post-exposure prophylaxis – Cynomolgus macaques					
Study AP301[4]	18 h after exposure	0 (0/6)	100% (6/6)	0.0012*	(0.471, 1.000)
	24 h after exposure	--	83% (5/6)	0.0042*	(0.230, 0.996)
	36 h after exposure	--	50% (3/6)	0.0345	(-0.037, 0.882)

CI: Confidence Interval
[1]Survival assessed 28 days after spore challenge, all randomised animals positive for bacteraemia prior to treatment, treatment triggered by a significant increase in body temperature (study AR033) or by a positive result in the protective antigen-electrochemiluminescence assay (studies AP204 and AP202).
[2]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001) compared to placebo
[3]Exact 95% confidence interval of difference in survival rates
[4]Survival assessed 28 days after spore challenge
*Denotes statistical significance at the 0.025 level

Paediatric population

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

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of obiltoxaximab are linear over the dose range of 4 mg/kg (0.25 times the lowest recommended dose) to 16 mg/kg following single intravenous administration in healthy subjects. Following single intravenous administration of obiltoxaximab 16 mg/kg in healthy, male and female human subjects, the mean C_{max} and AUC_{inf} were 400 ± 91.2 mcg/mL and 5170 ± 1360 mcg·day/mL, respectively. The half-life of obiltoxaximab was approximately 20 days (mean).

Distribution

Mean obiltoxaximab steady-state volume of distribution was 79.7 ± 19.2 mL/kg and greater than plasma volume, suggesting some tissue distribution.

Biotransformation

No formal metabolism studies have been conducted with obiltoxaximab.
However, the disposition of monoclonal antibodies generally involves distribution beyond the vascular space with potential uptake into tissues, and catabolism by proteases to small peptides and amino acids which are subsequently incorporated into the endogenous pool or excreted.

Elimination

Mean obiltoxaximab clearance values were 3.35 ± 0.932 mL/d/kg and much smaller than the glomerular filtration rate, indicating that there is virtually no renal clearance of obiltoxaximab.

Special populations

Effects of gender, age and race
Obiltoxaximab PK were evaluated via a population PK analysis using serum samples from 370 healthy subjects who received a single intravenous dose across 4 clinical trials. Based on this analysis, gender (female versus male), race (non-Caucasian versus Caucasian), or age (elderly versus young) had no meaningful effects on the PK parameters for obiltoxaximab. However, clinical studies of obiltoxaximab did not include sufficient numbers of subjects aged 65 years and over to determine whether their PK differs from younger subjects. Of the 320 subjects in clinical studies of obiltoxaximab, 9.4% (30/320) were 65 years and over, while 2% (6/320) were 75 years and over.

Body size- related effects
Clearance at a high body weight (109 kg) was approximately 38% higher than in a reference population. Following weight-based dosing (16 mg/kg) this results in an increase in AUC_{inf} of 12%, which is not clinically meaningful.

Paediatric population
Obiltoxaximab pharmacokinetics have not been evaluated in children. The dosing recommendations in Table 2 (section 4.2) are derived from simulations using a population PK approach designed to match the observed adult exposure to obiltoxaximab at a 16 mg/kg dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction and development.

Central nervous system (CNS) lesions (bacteria, inflammation, haemorrhage and occasionally necrosis) were seen in anthrax-infected non-surviving NZW rabbits and cynomolgus macaques administered intravenously obiltoxaximab (≥4 mg/kg) or control at the time of disease confirmation. Microscopic changes in the non-surviving animals that received obiltoxaximab were due to the presence of extravascular bacteria and not the effect of obiltoxaximab. No dose response relationship for brain histopathology was identified. No treatment-related brain lesions were shown in anthrax-infected surviving NZW rabbits (at day 28) or cynomolgus macaques (up to day 56) after a single administration of obiltoxaximab at doses up to 16 mg/kg and up to 32 mg/kg/dose, respectively. No obiltoxaximab-related neurobehavioural effects were observed in surviving anthrax-infected cynomolgus macaques following treatment with obiltoxaximab.

A single embryonic-fetal development study was conducted in pregnant, healthy NZW rabbits administered 4 intravenous doses of obiltoxaximab up to 32 mg/kg (2 times the human dose on a mg/kg basis) on gestation days 6, 10, 13, and 17. No evidence of harm to the pregnant dam or the

foetuses due to obiltoxaximab was observed. Cumulative exposures in NZW rabbits (10,000 mcg•day/mL) at the NOAEL of 32 mg/kg/dose (n=4 doses) based on $AUC_{0\text{-}15\ days}$ were approximately two-fold the human male and female combined mean AUC at the clinical intravenous dose of 16 mg/kg. C_{max} values following a 32 mg/kg/dose were 1180 mcg•day/mL.

Carcinogenicity, genotoxicity, and fertility studies have not been conducted with obiltoxaximab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Sorbitol (E420)
Polysorbate 80 (E433)
Hydrochloric acid (E507, for pH-adjustment)
Sodium hydroxide (E524, for pH-adjustment)
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

7 years

Diluted solution in infusion bag

After dilution in infusion bag, chemical, physical and microbial in-use stability has been demonstrated for 8 hours at room temperature (20°C – 25°C) or in the refrigerator (2°C – 8°C).

From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Diluted solution in syringe for infusion

Once a diluted solution of NYXTHRACIS has been prepared, it should be administered immediately and not stored. Any unused product should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original packaging 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

600 mg/6 mL of concentrate in vial (type I glass) with rubber stopper and a polypropylene cap with aluminium seal.

Pack contains 1 vial.

6.6 Special precautions for disposal and other handling

Important preparation instructions

- The concentrate for solution for injection should be inspected visually for particles and discoloration prior to administration. NYXTHRACIS is a a clear to opalescent, colourless to pale yellow to pale brownish-yellow solution that may contain few translucent-to-white proteinaceous particulates (which will be removed by in-line filtration).
- Discard the vial if the solution is discoloured or contains foreign particles (see section 3).
- Do not shake the vial.

Preparation and dilution in infusion bag

1. Calculate the milligrams of obiltoxaximab needed by multiplying the recommended mg/kg dose in table 2 (see section 4.2) by the individual patient's body weight in kilograms.
2. Calculate the required volume in millilitres of obiltoxaximab concentrate for solution for infusion and number of vials needed for the dose by dividing the calculated dose in milligrams (step 1) by the concentration, 100 mg/mL. Each single vial allows delivery of 6 mL of obiltoxaximab concentrate for solution for infusion.
3. Select an appropriate size infusion bag of sodium chloride 9 mg/mL (0.9%) solution for injection. Withdraw a volume of solution from the infusion bag equal to the calculated volume in millilitres of obiltoxaximab in step 2 above. Discard the solution that was withdrawn from the infusion bag.
4. Withdraw the required volume of obiltoxaximab concentrate for solution for infusion (calculated from step 2) from the NYXTHRACIS vial(s). Discard any unused portion remaining in the NYXTHRACIS vial(s).
5. Transfer the required volume of obiltoxaximab concentrate for solution for infusion to the selected infusion bag.
6. Gently invert the infusion bag to mix the solution. Do not shake.
7. The infusion must be administered over 90 minutes with the infusion rate described in table 3 (see section 4.2), using a 0.22 micron inline filter.
8. The prepared solution is stable for 8 hours stored at room temperature 20°C to 25°C or 8 hours stored in the refrigerator at 2°C to 8°C.

Preparation and dilution in syringe for infusion

1. Calculate the milligrams of obiltoxaximab needed by multiplying the recommended mg/kg dose in table 2 (see section 4.2) by the individual patient's body weight in kilograms.
2. Calculate the required volume in millilitres of obiltoxaximab concentrate for solution for infusion and number of vials needed for the dose by dividing the calculated dose in milligrams (step 1) by the concentration, 100 mg/mL. Each single vial allows delivery of 6 mL of NYXTHRACIS concentrate for solution for infusion.
3. Select an appropriate size syringe for the total volume of infusion to be administered.
4. Using the selected syringe and a 0.22 micron inline filter, withdraw the required volume of obiltoxaximab concentrate for solution for infusion (calculated from step 2). Discard any unused portion remaining in the NYXTHRACIS vial(s).
5. Withdraw an appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to prepare the total infusion volume specified in table 2.
6. Gently mix the solution. Do not shake.
7. Once a diluted solution of obiltoxaximab has been prepared, administer immediately. Do not store solution in syringe. Discard unused product.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

SFL Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1485/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2020

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. MANUFACTURER 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Lonza Biologics, Inc.
101 International Drive
Portsmouth, NH 03801
USA

Name and address of the manufacturer(s) responsible for batch release

AcertiPharma B.V.
Boschstraat 51
4811 GC, Breda
The Netherlands

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.

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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to validate the obiltoxaximab PK method (GCL-160) in human serum, the MAH should submit the results from the assay validation for the following aspects prior to use of the assay for sample analysis for clinical study AH501: interference by PA (63 and 83), EF, LF and ADAs, and assay performance in haemolytic and lipemic serum. Parallelism should be performed with incurred samples from the planned open-label field study AH501.	To be submitted together with the final clinical report of study AH501
In order to evaluate the clinical response, safety and tolerability, including the course of illness and survival in subjects with suspected, probable, or confirmed cases of inhalational anthrax treated with obiltoxaximab, the MAH should conduct, according to an agreed protocol, and submit the results of the final report for the phase 4, open-label field study AH501 upon the occurrence of an anthrax outbreak in the countries where obiltoxaximab is authorised and available.	Annual reports to be submitted Final report will be provided no later than 12 months after the last administration of obiltoxaximab or last data collection in case of retrospective data collection

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

NYXTHRACIS 100 mg/mL sterile concentrate
obiltoxaximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL: 100 mg of obiltoxaximab.

3. LIST OF EXCIPIENTS

Excipients: histidine, sorbitol, E433, hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
600 mg/6 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV after dilution.
For single use only.
Do not shake.

QR code to be included + www.obiltoxaximab-sfl.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED 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 packaging 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

SFL Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1485/001

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(S) OF ADMINISTRATION

NYXTHRACIS 100 mg/mL sterile concentrate
obiltoxaximab
IV after dilution.

2. METHOD OF ADMINISTRATION

For single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 mg/6 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

NYXTHRACIS 100 mg/mL concentrate for solution for infusion
obiltoxaximab

▼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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NYXTHRACIS is and what it is used for

NYXTHRACIS contains the active substance obiltoxaximab. Obiltoxaximab is a monoclonal antibody, a type of protein that attaches to and inactivates the toxins produced by the bacteria that causes anthrax.

NYXTHRACIS is used with antibiotic medicines to treat adults and children with anthrax caused by breathing in the bacteria (inhalational anthrax).

NYXTHRACIS may also be used if you could have come into contact with anthrax bacteria or spores but do not have any symptoms of the disease, and if there is no other treatment available and appropriate.

2. What you need to know before you receive NYXTHRACIS

You should not be given NYXTHRACIS
- if you are allergic to obiltoxaximab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given NYXTHRACIS:

- if you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, or if your child can no longer take sweet foods or drinks because it feels sick, vomits or gets unpleasant effects such as bloating, stomach cramps or diarrhoea.

Allergic reactions that may occur after treatment with NYXTHRACIS can sometimes be severe. You may be given an antihistamine before you are given NYXTHRACIS to reduce the risk of allergic reactions.

Other medicines and NYXTHRACIS
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. You may be given antibiotics (e.g. ciprofloxacin) to help treat inhalational anthrax.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given to you.

It is not known if NYXTHRACIS can harm an unborn baby.

It is not known if NYXTHRACIS passes into breast milk. You and your doctor will decide if you should breast-feed after receiving NYXTHRACIS.

Driving and using machines
NYXTHRACIS may cause side effects such as headache, dizziness, fatigue and vomiting. This may affect your ability to drive or operate machinery.

NYXTHRACIS contains sorbitol (E420)
Sorbitol is a source of fructose (a type of sugar). If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, your doctor may decide that you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.
You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

NYXTHRACIS contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per each 6 mL vial of NYXTHRACIS, that is to say essentially 'sodium-free'.

3. How NYXTHRACIS will be given

NYXTHRACIS will be given to you by a doctor or a nurse. Your doctor or nurse will calculate the dose based on your (or your child's) weight.

Your doctor, nurse or pharmacist will prepare the medicine for infusion.
The NYXTHRACIS solution will be given as an infusion (drip) over 90 minutes into a vein, usually in your arm. You will be monitored while you are given NYXTHRACIS and also for at least one hour after the infusion.
Before you are given NYXTHRACIS, you will usually be given medicines to prevent or reduce allergic reactions.

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

4. Possible side effects

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

Tell your doctor or the person giving you the infusion straight away if you notice any of the following side effects:

Itching, rash, shortness of breath or wheezing – these may be signs of an allergic reaction (hypersensitivity).

Other side effects of NYXTHRACIS include:

Common (may affect up to 1 in 10 people)
- Headache
- Cough
- Infusion site pain
- Itching, skin rash, including an itchy raised rash (hives)

Uncommon (may affect up to 1 in 100 people)
- Allergic reactions
- Dizziness
- Numbness
- Visual sensitivity to light (photophobia)
- Ear discomfort
- Throat irritation
- Hoarse voice
- Sinus congestion
- Shortness of breath
- Lip pain
- Eczema, pealing skin
- Muscle twitching, muscle spasms
- Fatigue
- Chills (feeling of coldness)
- Chest discomfort
- Pain in general, and pain affecting limbs, chest, jaw, muscles, ligaments, tendons, or bones
- Infusion site swelling, pain, or phlebitis (inflamed veins)

Reporting of side effects
If you get any side effects, talk to your doctor,pharmacist 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 NYXTHRACIS

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

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original packaging in order to protect from light.

After dilution in infusion bag, chemical, physical and microbial in-use stability has been demonstrated for 8 hours at room temperature (20°C – 25°C) or in the refrigerator (2°C – 8°C).

After dilution of NYXTHRACIS in a syringe for infusion, it should be administered immediately and not stored. Any unused product should be discarded.

6. Contents of the pack and other information

What NYXTHRACIS contains
- The active substance is obiltoxaximab. Each mL of concentrate contains 100 mg of obiltoxaximab. One vial of 6 mL contains 600 mg of obiltoxaximab.
- The other ingredients are histidine, sorbitol (E420), polysorbate 80 (E433), hydrochloric acid (E507) and sodium hydroxide (E524). See also section 2 “NYXTHRACIS contains sorbitol”.

What NYXTHRACIS looks like and contents of the pack
NYXTHRACIS is a clear to opalescent, colourless to pale yellow to pale brownish-yellow concentrate for solution.
NYXTHRACIS is available in packs containing 1 vial.

Marketing Authorisation Holder
SFL Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

Manufacturer
AcertiPharma B.V.
Boschstraat 51
4811 GC, Breda
The Netherlands

This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease and for ethical reasons it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Further information: www.obiltoxaximab-sfl.eu QR code to be included