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

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
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 Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

A deferral for 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 has been granted (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 Medicines & Healthcare products Regulatory Agency (MHRA) 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

Important preparation instructions

- The concentrate for solution for injection should be inspected visually for particles and discoloration prior to administration. 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).
- 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)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

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