Version 10.1, 06/2019

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

Enspryng 120 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (PFS) contains 120 mg of satralizumab in 1 ml.

Satralizumab is a recombinant humanised immunoglobulin G2 (IgG2) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology (including a pH-dependent binding technology).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enspryng is indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adult and adolescent patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD) (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of neuromyelitis optica (NMO) or NMOSD.

In order to prevent medication errors, it is important to check the PFS label to ensure that the drug being administered is Enspryng.

Posology

Enspryng can be used as a monotherapy or in combination with either oral corticosteroids (OCs), azathioprine (AZA) or mycophenolate mofetil (MMF) (see section 5.1). Please also refer to the full prescribing information for these products.

Loading doses
The recommended loading dose is 120 mg subcutaneous (SC) injection every two weeks for the first three administrations (first dose at week 0, second dose at week 2 and third dose at week 4).

Maintenance doses
The recommended maintenance dose is 120 mg SC injection every four weeks.

Duration of treatment
Enspryng is intended for long-term treatment.

Delayed or missed doses
If an injection is missed, it should be administered as soon as possible; do not wait until the next planned dose.

After the delayed or missed dose is administered, the appropriate treatment interval of two weeks (for loading doses) or four weeks (for maintenance doses) should be maintained between all following doses.

Dosage modification advice for Liver Enzyme Abnormalities
If the alanine aminotransferase (ALT) or aspartate transaminase (AST) elevation is >5x Upper Limit of Normal (ULN) and associated with any bilirubin elevation, treatment with Enspryng must be permanently discontinued.

If the ALT or AST elevation is >5x ULN and not associated with any bilirubin elevation, treatment with Enspryng should be discontinued. Enspryng can be restarted at a dose of 120 mg SC injection every four weeks when the ALT and AST levels have returned to the normal range and based on assessment of benefit-risk of treatment in the patient. If the decision is taken to restart treatment, liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin is observed; Enspryng must be permanently discontinued.

Special populations

Paediatric population
The safety and efficacy of Enspryng in children aged < 12 years of age have not been established. No data are available.

The posology in adolescent patients aged ≥ 12 years of age and adult patients is the same (see sections 5.1 and 5.2).

Elderly
No dose adjustment of Enspryng is required in patients ≥ 65 years of age (see section 5.2).

Renal Impairment
The safety and efficacy of Enspryng have not been formally studied in patients with renal impairment. No dose adjustment is recommended for patients with renal impairment (see section 5.2).

Hepatic Impairment
The safety and efficacy of Enspryng have not been studied in patients with hepatic impairment. No data are available.

Method of Administration

Enspryng 120 mg is administered by SC injection using a single-dose PFS. Enspryng must be administered as a SC injection. The total content (1 ml) of the PFS should be administered.

The recommended injection sites are the abdomen and thigh. Injection sites should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Comprehensive instructions for the administration of Enspryng are given in the package leaflet, see section 6.6.

Administration by the patient and/or caregiver
The first injection must be performed under the supervision of a qualified Healthcare Professional (HCP).

An adult patient/caregiver may administer all other doses of Enspryng at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique.

Patients/caregivers should seek immediate medical attention if the patient develops symptoms of serious allergic reactions and should check with their HCP to confirm whether treatment with Enspryng can be continued or not.

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

Infections

Delay Enspryng administration in patients with an active infection until the infection is resolved (see section 4.2).

Vaccinations

Live and live-attenuated vaccines should not be given concurrently with Enspryng as clinical safety has not been established. The interval between live vaccinations and initiation of Enspryng therapy should be in accordance with current vaccination guidelines regarding immunomodulatory or immunosuppressive agents.

No data are available on the effects of vaccination in patients receiving Enspryng. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enspryng therapy.

Liver enzymes

Mild and moderate elevations of liver transaminases have been observed with Enspryng treatment, most elevations were below 5x ULN, not treatment-limiting and resolved while Enspryng was given (see section 4.8).

ALT and AST levels should be monitored every four weeks for the first three months of treatment, followed by every three months for one year, thereafter as clinically indicated.

Treatment with Enspryng should be discontinued in patients with ALT or AST >5x ULN (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Population pharmacokinetic (PK) analyses did not detect any effect of AZA, OCs or MMF on the clearance of Enspryng.

The potential for treatment with Enspryng to reduce exposure to concomitant medications metabolised by CYP450 isozymes via blockade of IL-6 signalling has been explored using physiologically based pharmacokinetic (PBPK) modelling approaches.

This indicates that suppression of IL-6 signalling by treatment with Enspryng from the low baseline levels seen in the phase III studies will have only a minor impact on exposure of a range of probe CYP450 substrates (≤15% increase in AUC for all substrates of CYPs 1A2, 3A4, 2D6, 2C19). This indicates that the risk of drug interaction is low, however caution should be exercised when Enspryng is administered or discontinued in patients also receiving CYP450 substrates with a narrow therapeutic index.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Enspryng in pregnant women. Studies in monkeys do not indicate harmful effects with respect to reproductive toxicity (see section 5.3).

Enspryng is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether Enspryng is excreted in human breast milk or absorbed systemically after ingestion. However, because IgGs are excreted in human milk and there is preclinical evidence of excretion in milk (see section 5.3), a decision should be made whether to discontinue breast-feeding or to discontinue Enspryng therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

No clinical data are available on the effect of Enspryng on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the Safety Profile

The most frequently reported adverse reactions observed in ≥ 10% of patients treated with at least one dose of Enspryng were: headache, arthralgia and injection-related reactions.

Tabulated summary of adverse reactions

Table 1 summarizes the adverse reactions that have been reported in association with the use of Enspryng as a monotherapy or in combination with IST in clinical trials. Patients in the Enspryng groups in both clinical studies had longer treatment period than those in the placebo (or placebo in combination with IST) groups. Adverse reactions were evaluated during 194 patient-years (PY) in the Enspryng groups and 100 PY in the placebo groups.

Adverse reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Adverse reactions are presented using number of adverse events per 100 patient years and by frequency figures. The corresponding frequency category for each adverse drug reaction is based on frequency figures

and the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 1: Summary of adverse reactions occurring in patients treated with Enspryng in clinical trials

System organ class	Enspryng (n=104)		
	Number of events per 100 PY (All grades)	Frequency (All Grades) n (%)	Frequency Category
Blood and lymphatic system disorders			
Hypofibrinogenaemia	1.55	3 (2.9%)	Common
Psychiatric disorders			
Insomnia	3.10	6 (5.8%)	Common
Nervous system disorders			
Headache	18.07	20 (19.2%)	Very common
Migraine	2.06	4 (3.8%)	Common
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis	2.06	4 (3.8%)	Common
Skin and subcutaneous tissue disorders			
Rash	7.23	9 (8.7%)	Common
Pruritus	4.13	6 (5.8%)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	7.23	14 (13.5%)	Very common
Musculoskeletal stiffness	2.58	5 (4.8%)	Common
General disorders and administration site conditions			
Peripheral oedema	2.58	5 (4.8%)	Common
Injury, poisoning and procedural complications			
Injection-related reactions	17.03	13 (12.5%)	Very common

Description of selected adverse reactions

Injection-related Reactions (IRRs)
IRRs reported in patients treated with Enspryng as a monotherapy or in combination with IST were predominantly mild to moderate, and most occurred within 24 hours after injections. The most commonly reported systemic symptoms were diarrhoea and headache. The most commonly reported local injection site reactions were flushing, erythema, pruritus, rash and pain. None of the injection related reactions required dose interruption or discontinuation.

Infections
In the Enspryng monotherapy study, the rate of infections was lower in patients treated with Enspryng (99.8 events/100 PY [95% CI: 82.4, 119.8]) compared with patients receiving placebo (162.6 events/100 PY [95% CI: 125.8, 206.9]). The rate of serious infections was 5.2 events/100 PY (95% CI: 1.9, 11.3) in patients treated with Enspryng compared with 9.9 events/100 PY (95% CI: 2.7, 25.2) in patients receiving placebo.

In patients treated with Enspryng in combination with IST, the rate of infections was 132.5 events/100 PY (95% CI: 108.2, 160.5) compared with 149.6 events/100 PY (95% CI: 120.1, 184.1) in patients

receiving placebo in combination with IST; the rate of serious infections was 2.6 events/100 PY (95% CI: 0.3, 9.2) compared with 5.0 events/100 PY (95% CI: 1.0, 14.7) in patients receiving placebo in combination with IST.

Laboratory Abnormalities

Neutrophils
In the double-blinded treatment period, decreased neutrophils were observed in 31.7% of patients treated with Enspryng (monotherapy or in combination with IST) as compared with 21.6% of patients receiving placebo (or placebo plus IST). The majority of neutrophil decreases were transient or intermittent.

9.6% of patients receiving Enspryng had neutrophils below 1 x 10^9/l, compared with 5.4% receiving placebo (or placebo plus IST). These neutrophil levels were not temporally associated with any serious infections.

Platelets
In the double-blinded treatment period, decreases in platelet counts occurred in 24.0% of patients on Enspryng (monotherapy or in combination with IST) as compared with 9.5% of patients receiving placebo or placebo plus IST. The decreased platelet counts were not associated with bleeding events.

The majority of the decreased platelets were transient and not below 75 × 10^9/l. None of the patients had a decrease in platelet count to ≤50 × 10^9/l.

Liver enzymes
In the double-blinded treatment period, elevations in ALT or AST occurred in 27.9 % and 18.3% of patients treated with Enspryng (monotherapy or in combination with IST) respectively, compared with 12.2% and 13.5% of patients receiving placebo or placebo plus IST. The majority of the elevations were below 3x ULN, were transient and resolved without interruption of Enspryng

Elevations in ALT or AST >3x ULN occurred in 2.9% and 1.9% of patients treated with Enspryng (monotherapy or in combination with IST) respectively. These elevations were not associated with increases in total bilirubin.

Elevations of ALT above 5x ULN were observed 4 weeks after initiation of therapy in one patient receiving Enspryng in combination with IST; normalising after discontinuation of Enspryng (see sections 4.2 and 4.4).

Lipid parameters
In the double-blinded treatment period, 10.6% of patients receiving Enspryng (monotherapy or in combination with IST) experienced elevations in total cholesterol above 7.75 mmol/l as compared with 1.4% of patients receiving placebo (or placebo plus IST); 18.3% of patients receiving Enspryng experienced elevations in triglycerides above 3.42 mmol/l as compared with 6.8% of patients receiving placebo. The elevations in lipid parameters did not require dose interruption.

Paediatric population

Frequency, type and severity of adverse reactions in children from 12 years of age are expected to be the same as in adults.

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 experience with overdosage in human clinical trials. A single dose of up to 240mg Enspryng was administered subcutaneously to healthy adult volunteers in a Phase I study and no serious or severe adverse events were observed in the study.
In the event of an overdose, the patient should be closely supervised, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors
ATC code: not yet assigned

Mechanism of action

Satralizumab is a humanised IgG2 monoclonal antibody (mAb) that binds to soluble and membrane-bound human IL-6 receptor (IL-6R) and thereby prevents IL-6 downstream signalling through these receptors.

IL-6 is a pleiotropic cytokine produced by a variety of cell types and is involved in diverse processes such as B-cell activation, differentiation of B-cells to plasmablasts and production of autoantibodies, Th17-cell activation and differentiation, T-regulatory cell inhibition, and changes in blood-brain-barrier permeability. IL-6 levels are increased in cerebrospinal fluid and serum of patients with NMO and NMOSD during periods of disease activity. Some IL-6 functions have been implicated in the pathogenesis of NMO and NMOSD, including production of pathological autoantibodies against Aquaporin-4 (AQP4), a water channel protein mainly expressed by astrocytes in the CNS.

Pharmacodynamic effects

In clinical studies with satralizumab in NMO and NMOSD, decreases in C-reactive protein (CRP), fibrinogen and complement (C3, C4 and CH50) were observed.

Clinical efficacy and safety

The efficacy and safety of Enspryng was evaluated in two pivotal phase III clinical trials (BN40898 and BN40900) in patients with a diagnosis of AQP4-IgG seropositive or seronegative NMO (Wingerchuck 2006 criteria), or with a diagnosis of AQP4-IgG seropositive NMOSD (Wingerchuk 2007 criteria). In retrospect, these patients also met the latest criteria proposed by the international panel for NMO diagnosis. The effect of Enspryng was studied in adult (studies BN40898 and BN40900) and adolescent (aged ≥ 12 to < 18 years) patients (study BN40898). The inclusion of AQP4-IgG seronegative adult NMO patients was limited to approximately 30% in both studies in order for the study population to reflect the real-world NMO patient population.

The primary efficacy measure in both studies was protocol-defined relapses (PDR), based on a pre-specified worsening in the Expanded Disability Status Scale (EDSS) and Functional System Score (FSS) and confirmed by an independent Clinical Endpoint Committee (CEC). The primary endpoint analysis was time to first CEC-confirmed PDR with EDSS/FSS assessment performed within 7 days after symptoms were reported by the patient (adjudicated relapse).

Study BN40898 (also known as SA-307JG or SAkuraSky)

Study BN40898 was a randomised, multicentre, double-blind, placebo-controlled clinical trial to evaluate the effect of Enspryng in combination with stable IST (OCs up to 15 mg/day [prednisolone equivalent], AZA up to 3 mg/kg/day or MMF up to 3000 mg/day; adolescents received a combination

of AZA and OCs or MMF and OCs). The study included 83 AQP4-IgG seropositive and seronegative patients (including 7 adolescents). Patients received the first 3 single doses of Enspryng 120 mg or matching placebo by SC injection in the abdominal or femoral region every 2 weeks for the first 4 weeks and once every 4 weeks thereafter.

Study design and baseline characteristics of the study population are presented in Table 2. The study was event-driven and the double-blind study period for efficacy evaluation ended when a total of 26 adjudicated relapses were observed.

Table 2: Study Design and Baseline Characteristics for Study BN40898

Study Name	**Study BN40898 (N=83)**	
Study design		
Study population	Adolescent and adult patients with NMO or NMOSD, treated with stable IST Age 12-74 years, ⩾ 2 relapses in last 2 years prior screening (with at least one relapse in the 12 months prior to screening), EDSS of 0 to 6.5	
Study duration for efficacy evaluation	Event-driven (26 CEC confirmed protocol-defined relapses) Median follow-up time: Enspryng 100 weeks, placebo 74 weeks	
Treatment groups, in 1:1 randomisation	Group A: Enspryng 120 mg SC Group B: placebo	
Baseline characteristics	Enspryng + IST (n=41)	Placebo + IST (n=42)
Diagnosis, n (%): NMO NMOSD	 33 (80.5) 8 (19.5)	 28 (66.7) 14 (33.3)
AQP4-IgG seropositive status, n (%)	27 (65.9)	28 (66.7)
Mean Age in years (SD) (Min-Max)	40.8 (16.1) (13 – 73)	43.4 (12.0) (14 – 65)
Adolescents (≥12 to <18 years), n (%)	4 (9.8)	3 (7.1)
Gender distribution, n (%) male/ n (%) female	 4 (9.8) / 37 (90.2)	 2 (4.8) / 40 (95.2)
Immunosuppressive therapy (IST), n (%): Oral corticosteroids (OCs) Azathioprine (AZA) Mycophenolate mofetil (MMF) AZA + OCs* MMF + OCs*	 17 (41.5) 16 (39.0) 4 (9.8) 3 (7.3) 1 (2.4)	 20 (47.6) 13 (31.0) 8 (19.0) 0 1 (2.4)

* Combination allowed for adolescent patients

Study BN40900 (also known as SA-309JG or SAkuraStar)

Study BN40900 was a randomised, multicentre, double-blind, placebo-controlled clinical trial to evaluate the effect of Enspryng monotherapy compared to placebo. The study included 95 AQP4-IgG seropositive and seronegative adult patients. Patients received the first 3 single doses of Enspryng

120 mg or matching placebo by SC injection in the abdominal or femoral region every 2 weeks for the first 4 weeks and once every 4 weeks thereafter.

Study design and baseline characteristics of the study population are presented in Table 3. The double-blind study period for efficacy evaluation ended 1.5 years after the date of randomisation of the last enrolled patient.

Table 3: Study Design and Baseline Characteristics for Study BN40900

Study Name	**Study BN40900 (N=95)**	
Study design		
Study population	Adult patients with NMO or NMOSD Age 18-74 years, ≥ 1 relapse or first attack in last 12 months prior to screening, EDSS of 0 to 6.5. Patients either received prior relapse prevention treatment for NMOSD or were treatment naïve.	
Study duration for efficacy evaluation	Event-driven (44 CEC confirmed protocol-defined relapses, or 1.5 years after the date of randomisation of the last patient enrolled, whichever comes first) Median follow-up time: Enspryng 95.4 weeks, placebo 60.5 weeks	
Treatment groups, in 2:1 randomisation	Monotherapy: Group A: Enspryng 120 mg SC Group B: placebo	
Baseline characteristics	Enspryng (n=63)	Placebo (n=32)
Diagnosis, n (%): NMO NMOSD	 47 (74.6) 16 (25.4)	 24 (75.0) 8 (25.0)
AQP4-IgG seropositive status, n (%)	41 (65.1)	23 (71.9)
Mean Age in years (SD) (Min-Max)	45.3 (12.0) (21 – 70)	40.5 (10.5) (20 – 56)
Gender distribution, n (%) male/ n (%) female	 17 (27.0) / 46 (73.0)	 1 (3.1) / 31 (96.9)

Primary efficacy

Treatment with Enspryng resulted in a statistically significant 62% reduction in the risk of experiencing an adjudicated relapse (Hazard ratio [HR] [95% CI]: 0.38 [0.16, 0.88]; p [log rank] = 0.0184) when administered in combination with stable IST (study BN40898) and 55% reduction in the risk of adjudicated relapse (HR [95% CI]: 0.45 [0.23, 0.89]; p [log rank] = 0.0184) when used as monotherapy (study BN40900), when compared to placebo.

At 48 weeks, 88.9% and 76.1% of Enspryng-treated patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. At 96 weeks 77.6% and 72.1% of Enspryng-treated patients remained adjudicated relapse -free when used in combination with IST or as monotherapy, respectively. When data from the two studies were pooled, Enspryng treatment resulted in a 58% reduction in risk of adjudicated relapse compared to placebo (HR [95% CI]: 0.42 [0.25-0.71]; p [log rank] = 0.0008) (see Table 4, Figure 1, Figure 2).

The strongest subgroup effect was observed in AQP4-IgG seropositive patients. In AQP4-IgG seropositive patients the relative risk of experiencing an adjudicated relapse in Study BN40898 was reduced by 79% (HR [95% CI]: 0.21 [0.06-0.75]), in Study BN40900 by 74% (HR [95% CI]: 0.26 [0.11-0.63]). At 48 weeks, 91.5% and 82.9% of Enspryng-treated AQP4-IgG seropositive patients

remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. At 96 weeks 91.5% and 76.5% of Enspryng-treated AQP4-IgG seropositive patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. When data across studies BN40898 and BN40900 were pooled, treatment with Enspryng with or without IST led to an overall risk reduction of 75% (HR [95% CI]; 0.25 (0.12-0.50]) in AQP4-IgG seropositive patients (see Table 4, Figure 3, Figure 4). Differences in the time to first adjudicated relapse in AQP4-IgG seronegative patients between those patients receiving Enspryng with or without IST and those receiving placebo with or without IST were not significant (BN40898 and BN40900 pooled: HR [95% CI]: 0.97 [0.41-2.33],).

Table 4: Key Efficacy Endpoints from Study BN40898 and BN40900

	BN40898		BN40900	
	Enspryng + IST (n=41)	Placebo + IST (n=42)	Enspryng (n=63)	Placebo (n=32)
Primary Endpoint				
Risk Reduction (Individual Studies)	62% (HR: 0.38; 95% CI: 0.16, 0.88; p=0.0184)		55% (HR:0.45; 95% CI: 0.23, 0.89; p=0.0184)	
Risk Reduction (Pooled Analysis)	58% (HR: 0.42; 95% CI: 0.25, 0.71; p=0.0008)			
Proportion of adjudicated relapse -free patients at 48 weeks	88.9% (95% CI: 72.81, 95.70)	66.0% (95% CI: 47.65, 79.25)	76.1% (95% CI: 63.55, 84.86)	61.9% (95% CI: 42.66, 76.26)
Proportion of adjudicated relapse -free patients at 96 weeks	77.6% (95% CI: 58.08, 88.82)	58.7% (95% CI: 39.85, 73.43)	72.1% (95% CI: 58.91, 81.75)	51.2% (95% CI: 32.36, 67.23)
Subgroup Analysis of Primary Endpoint (AQP4-IgG seropositive patients)				
Number of AQP4-IgG seropositive patients (n)	27	28	41	23
Risk Reduction (Individual Studies)	79% (HR: 0.21; 95% CI: 0.06, 0.75; p= 0.0086)		74% (HR: 0.26; 95% CI: 0.11, 0.63; p= 0.0014)	
Risk Reduction (Pooled Analysis)	75% (HR: 0.25; 95% CI: 0.12, 0.50; p <0.0001)			
Proportion of adjudicated relapse -free patients at 48 weeks	91.5% (95% CI: 69.64, 97.83)	59.9% (95% CI: 36.25, 77.25)	82.9% (95% CI: 67.49, 91.47)	55.4% (95% CI: 32.96, 73.08)
Proportion of adjudicated relapse -free patients at 96 weeks	91.5% (95% CI: 69.64, 97.83)	53.3% (95% CI: 29.34, 72.38)	76.5% (95% CI: 59.22, 87.21)	41.1% (95% CI: 20.76, 60.41)

Figure 1: Study BN40898 - Time to First Adjudicated Relapse during the Double-blind Period (ITT Population)

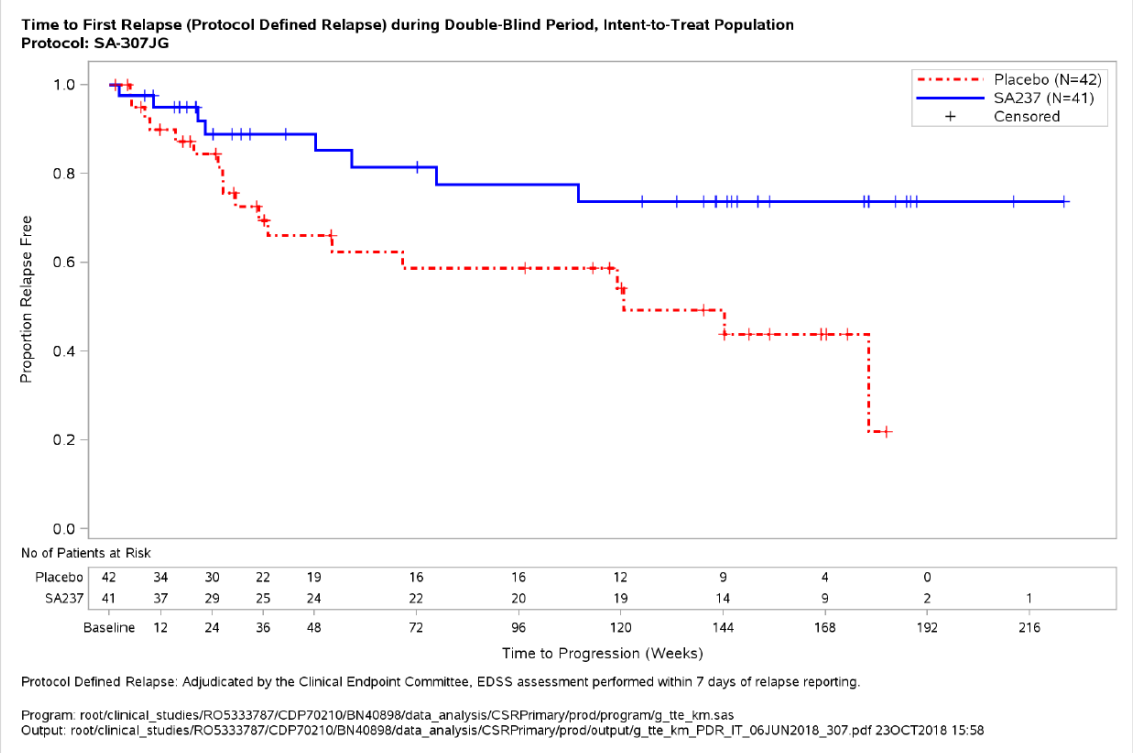


Figure 2: Study BN40900 - Time to First Adjudicated Relapse during the Double-blind Period (ITT Population)

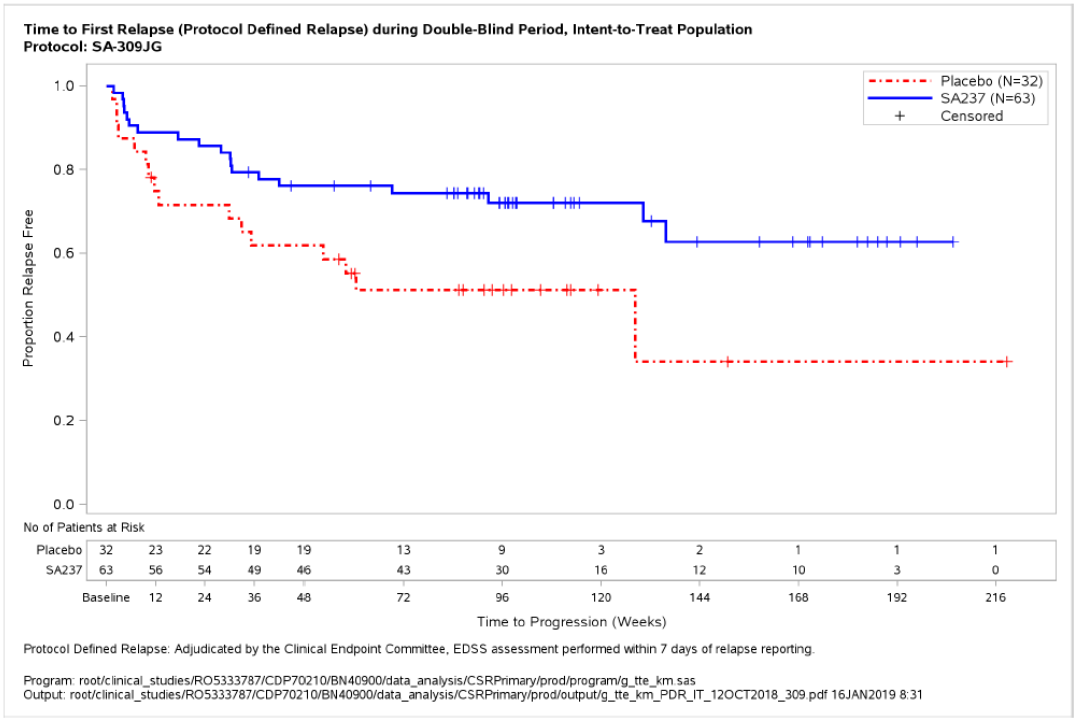


Figure 3: Study BN40898 - Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients

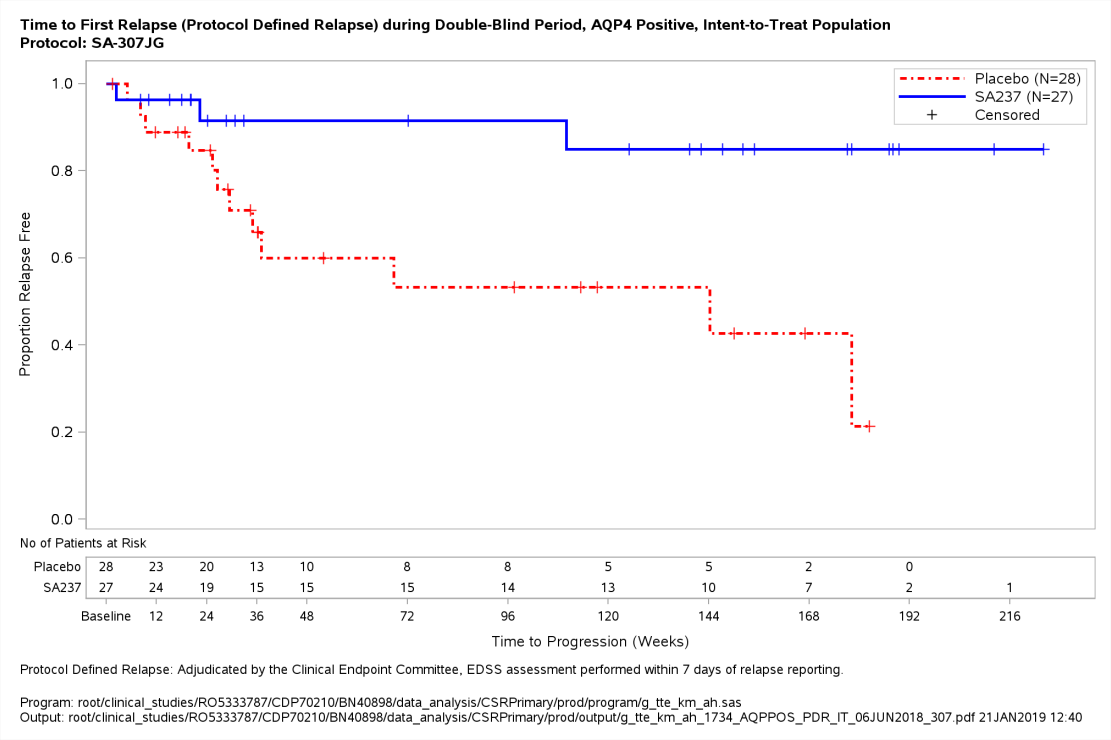
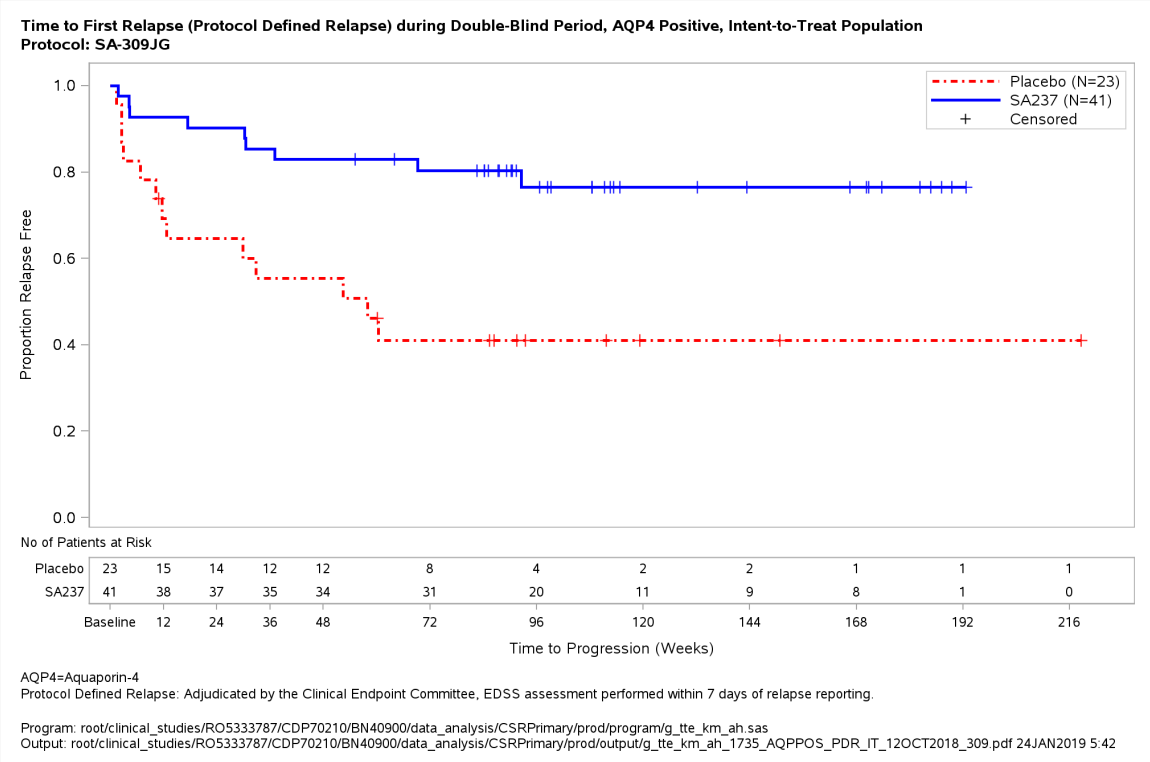


Figure 4: Study BN40900 - Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients



Immunogenicity

In Phase III Study BN40898 (in combination with IST) and in Phase III study BN40900 (in monotherapy), anti-drug-antibodies (ADAs) were observed in 41% and 71% of patients receiving Enspryng in the double-blind period, respectively. The ability of ADAs to neutralize Enspryng binding is unknown.

Exposure was lower in ADA positive patients, however there was no impact of ADAs on safety and no clear impact on efficacy nor pharmacodynamic markers indicative of target engagement.

Treatment with satralizumab led to a similar reduction in the risk of experiencing an adjudicated relapse in patients in the phase III studies despite different ADA rates between those studies.

Patients with higher bodyweight and lower exposure were more likely to develop ADAs (irrespective of background treatment with IST), however treatment effect was comparable in all bodyweight groups when used either in combination with IST, or as monotherapy. The recommended dose is appropriate for all patients, and neither dose interruption nor modification is warranted in patients who develop ADAs.

Paediatric population

In study BN40898, there were 7 adolescent patients enrolled. Their mean age was 15.4 years and the median body weight was 79.6 kg. The majority were female (n=6). Four patients were White, 2 were Black/African American, and 1 was Asian. Three (42.9%) adolescent patients were AQP4-IgG seropositive at screening (2 in the placebo group and 1 in the Enspryng group). During the double-blind period, 1 of 3 adolescents in the placebo group and 1 of 4 adolescents in the Enspryng group experienced an adjudicated relapse. Due to the small sample size, the hazard ratio for the primary endpoint of time to first adjudicated relapse in this subgroup was not calculated.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of Enspryng have been characterised both in Japanese and Caucasian healthy volunteers, and in NMO and NMOSD patients. The pharmacokinetics in NMO and NMOSD patients using the recommended dose were characterised using population PK analysis methods based on a database of 104 patients.

The concentration-time course of Enspryng in patients with NMO or NMOSD was accurately described by a two-compartment population PK model with parallel linear and target-mediated (Michaelis-Menten) elimination and first-order SC absorption. Enspryng clearance and volume parameters allometrically scaled by body weight (through power function with the fixed power coefficient of 0.75 and 1 for clearance and volume parameters, respectively). Bodyweight was shown to be a significant covariate, with clearance and Vc for patients weighing 123 kg (97.5th percentile of the weight distribution) increased by 71.3% and 105%, respectively, compared to a 60 kg patient.

Steady state pharmacokinetics were achieved after the loading period (8 weeks) for C_{min}, C_{max} and AUC as follows (mean (±SD): C_{min}: 19.7 (12.2) mcg/ml, C_{max}: 31.5 (14.9) mcg/ml and AUC: 737 (386) mcg.ml/day. Pharmacokinetics were not impacted by background immunotherapy (see section 4.5).

Absorption

The absorption rate constant of Enspryng was 0.251 one/day (95% CI: 0.216 - 0.285) equating to an absorption half-life of around 3 days at the recommended dose (see section 4.2). The bioavailability was high (85.4%; 95% CI: 0.795 - 0.953).

Distribution

Satralizumab undergoes biphasic distribution. The central volume of distribution was 3.46 l (95% CI: 3.21 - 3.97), the peripheral volume of distribution was 2.07 l (95% CI: 1.78 - 2.59). The inter-compartmental clearance was 0.336 l/day (95% CI: 0.261 - 0.443).

Biotransformation

The metabolism of satralizumab has not been directly studied, as monoclonal antibodies are principally cleared by catabolism.

Elimination

The total clearance of satralizumab is concentration-dependent. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMO and NMOSD patients) is estimated to be 0.0601 l/day (95% CI: 0.0524 - 0.0695). The associated terminal $t_{1/2}$ is approximately 30 days (range 22-37 days) based on data pooled from the phase 3 studies.

Special populations

Population pharmacokinetic analyses in adult patients with NMO or NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab. Although body weight influenced the pharmacokinetics of satralizumab, no dose adjustments are recommended for any of these demographics.

Paediatric Population
Data obtained in 8 adolescent patients [13-17 years] who received the adult dosing regimen show that population PK parameters for satralizumab are not significantly different from those in the adult population. Therefore, no dose adjustment is necessary.

Elderly
No dedicated studies have been conducted to investigate the PK of satralizumab in patients ≥ 65 years, however patients with NMO or NMOSD between 65 and 74 years were included in the BN40898 and BN40900 clinical studies.

Population PK analyses based on data from these patients showed that age did not affect the PK of satralizumab.

Renal impairment
No formal study of the effect of renal impairment on the PK of satralizumab has been conducted. However, patients with mild renal impairment (creatinine clearance < 80 ml/min and ≥ 50 ml/min) were included in the BN40898 and BN40900 clinical studies. As anticipated based on the known mechanisms of clearance for satralizumab, the PK in these patients was not impacted and therefore no dose adjustment is required.

Hepatic impairment
No formal study of the effect of hepatic impairment on the PK of satralizumab has been conducted.

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.

Carcinogenicity

No rodent carcinogenicity studies have been performed to establish the carcinogenic potential of satralizumab. Proliferate lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study.

Genotoxicity

No studies have been performed to establish the mutagenic potential of satralizumab. Antibodies are not expected to cause effects on DNA.

Reproductive Toxicity

Pre- and postnatal treatment with up to 50 mg/kg/week satralizumab in pregnant monkeys and their offspring did not elicit any adverse effects on maternal animals, foetal development, pregnancy outcome or infant survival and development including learning ability.

The concentrations of satralizumab in breast milk were very low (<0.9% of the corresponding maternal plasma levels).

Fertility

No effects on male or female reproductive organs were seen with chronic treatment of satralizumab in monkeys.

Repeat dose toxicity

Nonclinical studies with monkeys, a responder species with cross-reactivity to satralizumab did not reveal special hazards for humans based on safety pharmacology, acute and repeated dose toxicity endpoints. When up to 50 mg/kg satralizumab was administered to cynomolgus monkeys once a week in 4- and 26-week repeated-dose SC toxicity studies, no toxicity changes considered to be caused by drug administration were observed. The only relevant change in these studies was increase in blood IL-6 level, which was considered to be the result of the pharmacological action (IL-6R neutralising action) of satralizumab, and not associated with any adverse findings. Treatment with satralizumab elicited an immune response with anti-drug antibodies in most of the treated animals, which was, however, not affecting the pharmacological response and did not result in any adverse events.

Local Tolerance

The SC injection of the clinical formulation of satralizumab did not elicit any adverse reaction at the administration site in monkeys.

Tissue cross-reactivity

Tissue cross-reactivity detected with satralizumab in monkey and human tissues reflects the sites of IL-6R expression. No relevant tissue cross-reactivity was detected in other tissues.

Cytokine release syndrome

Based on in vitro studies with human blood, the risk of the release of pro-inflammatory cytokines with satralizumab is considered low in terms of incidence and increase in cytokines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Aspartic Acid
L-Arginine
Poloxamer 188
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) until ready to use. Do not freeze. Do not use the syringe if it has been frozen. Always keep the syringe dry.

Keep the PFS in the outer carton in order to protect from light and moisture.

Enspryng, if unopened and kept in the outer carton, can be removed from and returned to the refrigerator, if necessary. If stored at room temperature, the total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30°C.

6.5 Nature and contents of container

1 ml solution in a PFS (polymer) with a staked-in, stainless steel needle, fitted with a chlorinated butyl rubber-polypropylene rigid needle shield and sealed with a chlorinated butyl rubber plunger stopper. The PFS is labelled and assembled with a needle safety device (NSD), plunger rod, and extended finger flanges (EFF).

Pack size of 1 PFS.

6.6 Special precautions for disposal and other handling

Enspryng is supplied in a single-dose PFS assembled with a needle safety device. After removing the carton from the refrigerator, open the sealed carton and carefully lift the PFS out of the carton by holding the barrel. It is important to let the PFS reach room temperature by waiting for 30 minutes before initiating the administration process.

Do not use the medicine if the liquid is cloudy, discoloured, has visible particles in it or if any part of the PFS appears to be damaged.

After removing the cap, the injection must be started within 5 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

Comprehensive instructions for the administration of Enspryng are given in the package leaflet, see section 7.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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 CONDITIONAL MARKETING AUTHORISATION> <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)

Chugai Pharma Manufacturing Co., Ltd.
(CPMC) 5-1, Ukima 5-Chome, Kita-ku,
Tokyo, 115-8543
Japan

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

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Whylen
Germany

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 (PSURs)**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

<An updated RMP shall be submitted by {CHMP agreed deadline}.>

- **<Additional risk minimisation measures>**

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

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

Description	Due date
<Post-authorisation efficacy study (PAES):>	
<Non-interventional post-authorisation safety study (PASS):>	

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

<This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:>

<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
<Non-interventional post-authorisation safety study (PASS):>	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Enspryng 120 mg solution for injection in pre-filled syringe
Satralizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 120 mg satralizumab

3. LIST OF EXCIPIENTS

Excipients: L-Histidine, L-Aspartic Acid, L-Arginine, Poloxamer 188, Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe
120 mg/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

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

Allow the syringe to sit at room temperature outside the box for 30 minutes before use

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze
Keep the pre-filled syringes in the outer carton in order to protect from light and moisture

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

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

enspryng 120 mg

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

PRE-FILLED SYRINGE LABEL

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

Enspryng 120 mg solution for injection
Satralizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg/1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Enspryng 120 mg solution for injection in pre-filled syringe
Satralizumab

▼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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 Enspryng is and what it is used for

What Enspryng is

Enspryng contains the active substance satralizumab.
- This belongs to a group of medicines called "monoclonal antibodies".
- Monoclonal antibodies are a type of protein which recognise and attach to a specific substance in the body.

What Enspryng is used for
- Enspryng is for treatment of 'neuromyelitis optica spectrum disorders' (NMOSD).
- It is used in adults and young people from 12 years of age.

What is NMOSD

NMOSD is an autoimmune disease of the central nervous system that mainly affects the optic nerves and spinal cord.
- The damage to the optic nerves causes swelling - leading to pain and loss of sight.
- The damage to the spinal cord causes weakness or loss of movement in the legs or arms, loss of feeling, and problems with bladder and bowel function.

In a 'relapse', or an 'attack' of NMOSD, there is swelling in the nervous system. The swelling causes people to have new symptoms, or have symptoms that they have had before.

How Enspryng works

Enspryng blocks the action of a protein called 'interleukin-6' (IL-6).
- This protein is involved in swelling in the body.
- Enspryng reduces the risk of a relapse or attack of NMOSD.

2. What you need to know before you use Enspryng

Do not use Enspryng:
- if you are allergic to satralizumab or any of the other ingredients of this medicine (listed in section 6).

If any of the above apply to you or you are not sure, do not use Enspryng and talk to your doctor, pharmacist or nurse before using Enspryng.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Enspryng if any of the below apply to you (or if you are not sure).

Infections

You cannot use Enspryng while you have an infection. **Tell your doctor or nurse straight away if you think you have any signs of infection** before, during or after Enspryng treatment such as:
- fever or chills
- cough that does not go away
- sore throat
- herpes (such as cold sore, shingles or genital sores)
- skin redness, swelling, tenderness or pain
- feeling or being sick, diarrhoea or belly pain.

Your doctor will wait until the infection has gone before giving you Enspryng or allowing you to continue to inject Enspryng.

Vaccinations

You cannot have Enspryng if you are having some vaccines ('live' or 'live attenuated'). **Tell your doctor if you have recently been given any vaccine** or might be given a vaccine in the near future.
- Your doctor will check if you need any vaccines before you start Enspryng.
- Do not have 'live' or 'live attenuated' vaccines (for example BCG for tuberculosis or vaccines against yellow fever) while you are having Enspryng.

However, your doctor may recommend that you are given a seasonal flu vaccine.

Liver enzymes

Enspryng can increase the amount of some liver enzymes in your blood. Your doctor will do blood tests to check these amounts and monitor how well your liver is working. **Tell your doctor or nurse straight away** if you have any of these signs of increased liver enzymes during or after Enspryng treatment:
- yellowing of the skin and the whites of the eyes (jaundice)
- dark coloured urine
- feeling and being sick

Children and young people

Do not give this medicine to children under 12 years of age. This is because it has not yet been studied in this age group.

Other medicines and Enspryng

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, and herbal medicines.

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 or pharmacist for advice before taking this medicine.

Your doctor may advise you to stop breast-feeding if you are to be given Enspryng. It is not known whether Enspryng is passed into breast milk.

Driving and using machines

Enspryng is not likely to affect you being able to drive, cycle or use any tools or machines.

3. How to use Enspryng

Read carefully and follow the enclosed instructions in section 7, "Instructions for use" at end of this leaflet on how to administer Enspryng.

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How to use Enspryng

- Enspryng is given by injection under the skin (sub-cutaneously).
- Each time the entire content of the syringe is injected.

At the start, your doctor or nurse may inject Enspryng. However, your doctor may decide that you (if you are an adult patient) or your adult caregiver can inject Enspryng.

- You or your caregiver will get training on how to inject Enspryng.
- Talk to your doctor or nurse if you or your caregiver have any questions about giving injections.

How much Enspryng to use

Each injection contains 120 mg of satralizumab. The first injection will be given under the supervision of your doctor or nurse.

- The first three injections are given once every two weeks. These are called 'loading doses'.
- After this, the injection is given every four weeks. This is called the 'maintenance dose'. Keep taking Enspryng once every four weeks for as long as your doctor tells you to.

Allergic reaction

Tell your doctor straight away or go to the Emergency department of your nearest hospital, if you experience any signs of allergic reactions during or after the injection such as:

- tight chest or wheezing
- feeling short of breath
- fever or chills

- severe dizziness or light-headedness
- swelling of the lips, tongue, face
- skin itching, hives or rash.

Do not take the next dose until you have informed your doctor and your doctor has told you to take the next dose.

If you use more Enspryng than you should

Because Enspryng is given in one pre-filled syringe, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If you accidentally inject Enspryng more frequently than told to by your doctor, call your doctor. Always take the outer carton with you when you go to see the doctor.

If you forget to use Enspryng

For the treatment to be fully effective, it is very important to keep having the injections.

If your doctor or nurse is giving your injections and you miss an appointment - make another one straight away.

If you are injecting Enspryng yourself and you miss an injection - give it as soon as possible. Do not wait until the next planned dose. After giving the missed dose, your next dose should be given either:
- for loading doses - two weeks later
- for maintenance doses – four weeks later

Check with your doctor, pharmacist or nurse if you are not sure.

If you stop using Enspryng

Do not suddenly stop using Enspryng without asking your doctor first. 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.

Injection-related reactions (Very common: may affect more than 1 in 10 people)
In most cases these are mild reactions, but some can be serious.
Tell your doctor or nurse straight away if you have any of these signs during or after the injection - particularly in the first 24 hours after the injection:
- redness, itching, pain or swelling where the injection is given
- rash, red or itchy skin or hives
- feeling flushed
- headache
- throat irritation, swelling or pain
- feeling short of breath
- low blood pressure
- fever or chills
- feeling tired or dizzy
- feeling or being sick or diarrhoea
- fast heart rate, fluttering or pounding heart (heart palpations).

Tell your doctor or nurse straight away if you have any of the signs above.

Other side effects:
Very common (may affect more than 1 in 10 people):
- headache
- joint pain

Common (may affect up to 1 in 10 people)
- stiffness
- migraine
- being unable to sleep
- swelling in your lower legs, feet or hands
- rash or itching
- allergies or hay fever
- low fibrinogen levels in the blood (a protein involved in blood clotting) shown in tests.

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 Enspryng

- 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 pre-filled syringe label and carton after 'EXP'. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C) until ready to use. Do not freeze. Do not use the syringe if it has been frozen. Always keep the syringe dry. Keep the pre-filled syringes in the outer carton in order to protect from light and moisture.
- If unopened and kept in the outer carton, Enspryng can be taken out of and returned to the refrigerator.
- If stored at room temperature, the total time out of refrigeration should not be longer than 8 days at a temperature that does not exceed 30°C.

Do not use this medicine if you notice that it is cloudy, discoloured or contains visible particles. Enspryng is a colourless to slightly yellow liquid.

Do not use the pre-filled syringe if it is cracked or broken. Check the pre-filled syringe and needle safety device for any damage.

After removing the cap, the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enspryng contains
- The active substance is satralizumab. Each pre-filled syringe contains 120 mg of satralizumab in 1 ml.

- The other ingredients are L-Histidine, L-Aspartic Acid, L-Arginine, Poloxamer 188, Water for injection.

What Enspryng looks like and contents of the pack
- It is a colourless to slightly yellow liquid.
- Enspryng is a solution for injection.
- Each pack of Enspryng contains 1 pre-filled syringe.

Marketing Authorisation Holder and Manufacturer

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in <{MM/YYYY}>.

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

7. Instructions for Use

What do I need to know to use the Enspryng pre-filled syringe safely?

Read this Instructions for Use:

- **Before you start using your pre-filled syringe**
- **Each time you get a prescription refill.**

This is because it may contain new information.

- This information does not take the place of talking to your healthcare provider about your medical condition or treatment.
- Your healthcare provider will decide if you or a caregiver can give you injections of Enspryng at home. They will also show you or a caregiver the correct and safe way to use the syringe before you use it for the first time.
- Talk to your healthcare provider if you have any questions.

Important Information

- Each syringe is pre-filled with a medicine called Enspryng.
- Each carton of Enspryng contains only 1 pre-filled syringe.
- Each pre-filled syringe can be used only once.

Do not:

- Share your syringes with other people - you may give them a serious infection or get a serious infection from them.

Do not:

- Take the needle cap off until you are ready to inject Enspryng.
- Use the syringe if it has been dropped or damaged.
- Try to take the syringe apart at any time.
- Leave the syringe unattended.
- Re-use the same syringe.

How should I store the Enspryng pre-filled syringe?

See section 5. How to store Enspryng

-

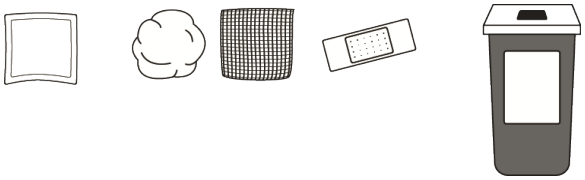
Do not:

- Freeze the syringe.
- Use the syringe if it has been frozen.

Supplies needed to give your injection
Each Enspryng carton contains:

- 1 pre-filled syringe for one-time use only.

Not included in the carton:



- 1 alcohol pad
- 1 sterile cotton ball or gauze
- 1 small bandage
- 1 puncture-resistant sharps container for safe disposal of the needle cap and used syringe. See Step 21 “Disposing of Enspryng” at the end of these Instructions for Use.

Enspryng pre-filled syringe
(See Figure A and Figure B)
Before use:

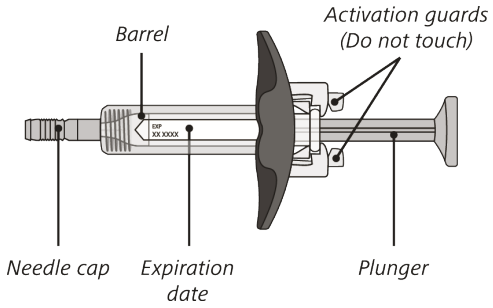


Figure A

After use:

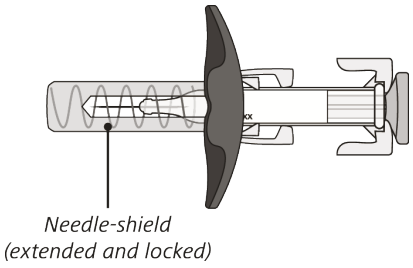


Figure B

The syringe has a needle-shield that automatically covers the needle when the injection is complete.

Prepare to use Enspryng

1. Take the carton containing the syringe out of the refrigerator and place it on a clean, flat work surface (like a table).
2. Check the expiration date on the back of the carton **(See Figure C)**. **Do not** use if the carton has expired.
3. Check that the front of the carton is sealed **(Figure C)**. **Do not** use if the seal has been broken.

If the expiration date has passed or the seal is broken, do not use. Then go to Step 21 "Disposing of Enspryng" and contact your healthcare provider.

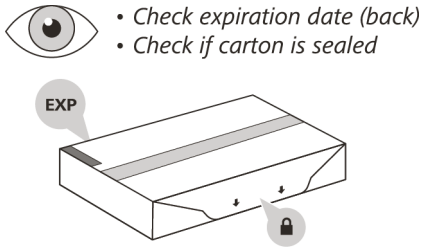


Figure C

4. Open the sealed carton **(See Figure D)**.

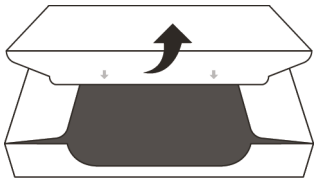


Figure D

5. Carefully lift the syringe out of the carton by holding the barrel **(See Figure E)**.

   Do not:

   - turn the carton upside down to remove the syringe.
   - touch the activation guards - this may damage the syringe.
   - hold the plunger or needle cap.

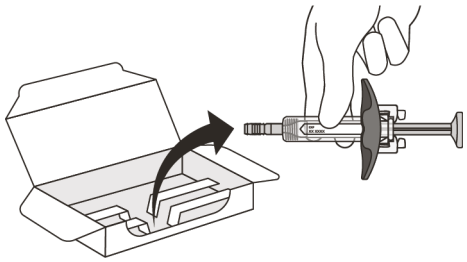


Figure E

Check the syringe

(See Figure F)

6. Check the expiration date on the syringe. **Do not** use the syringe if it has expired.
7. Check the syringe for any damage. **Do not** use if it is cracked or broken.

8. Check that the liquid through the viewing window is clear and colourless to slightly yellow. **Do not** inject the medicine if the liquid is cloudy, discoloured, or has particles in it.

    - There may be some small air bubbles in the syringe. This is normal and you should not try to remove them.

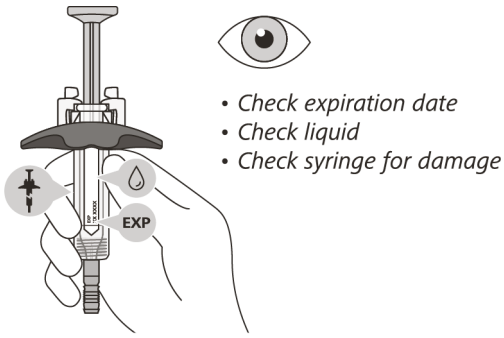


Figure F

If the expiry date has passed, the syringe is damaged or the liquid is cloudy, discoloured or has particles in it, do not use. Then go to Step 21 "Disposing of Enspryng" and contact your healthcare provider.

Let your syringe warm up

9. Once you have checked the syringe, place it on a clean, flat work surface (like a table) for **30 minutes** - this will allow it to reach room temperature. **(See Figure G).**

    It is important to let the syringe gently warm up as injecting cold medicine may feel uncomfortable and make it harder to push.

    Do not:

    - speed up the warming process in any way, such as using a microwave or placing the syringe in warm water.
    - remove the needle cover while the syringe is reaching room temperature.

Figure G

Wash your hands

10. Wash your hands with soap and water. **(See Figure H).**

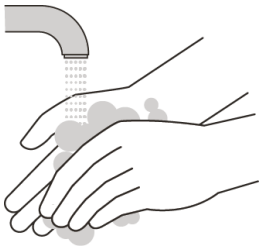


Figure H

Choose the injection site

11. Choose your injection site in either:

- the lower part of your stomach (abdomen) or
- the front and middle of your thighs. **(See Figure I).**

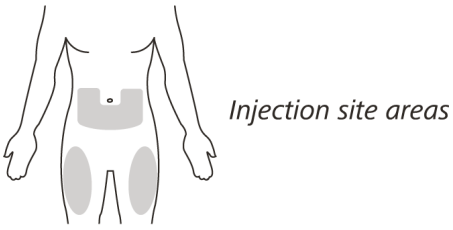


Figure I

Do not

- inject into the 5 cm area around your belly button.
- inject into moles, scars, bruises, or areas where the skin is tender, red, hard or broken.

Choose a different injection site for **each new injection - choose a different place to inject which is at least 2.5 cm away from the place where you last injected.**

Clean the injection site

12. Wipe the injection site with an alcohol pad and let it air dry.

Do not:

- fan or blow on the area which you have cleaned.
- touch the injection site again before you give the injection.

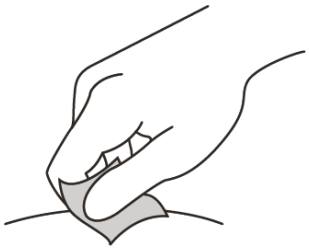


Figure J

Inject Enspryng

13. Hold the barrel of the syringe between your thumb and index finger. With your other hand, pull the needle cap straight off. You may see a drop of liquid at the end of the needle - this is normal and will not affect your dose **(See Figure K)**.

- **Use the syringe within 5 minutes of removing the cap or the needle may clog.**

Do not:

- take the needle cap off until you are ready to inject Enspryng.
- put the needle cap back on once it has been removed as this may damage the needle.
- touch the needle or let it touch any surfaces after removing the needle cap.

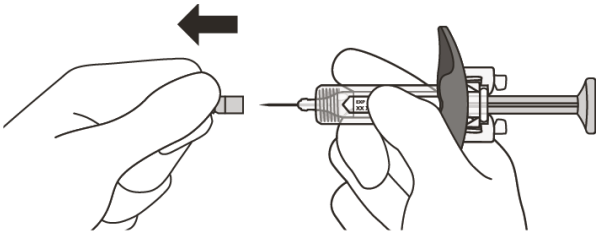


Figure K

14. Throw away the needle cap in a puncture-resistant sharps container immediately. See Step 21 “Disposing of Enspryng”.
15. Hold the barrel of the syringe using your thumb and index finger. With your other hand, pinch the area of skin you have cleaned. **(See Figure L)**
16. Use a quick, dart-like motion to insert the needle at an angle between 45° to 90° **(See Figure L).**

Do not:

- insert the needle through clothing.
- change the angle of the injection.
- insert the needle again.

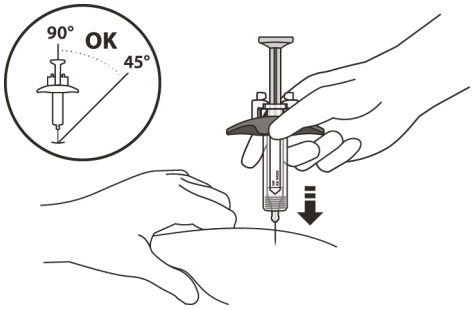


Figure L

17. After the needle is inserted, let go of the pinched skin.
18. Slowly inject all of the medicine by gently pushing the plunger all the way down until it touches the activation guards **(See Figure M).**

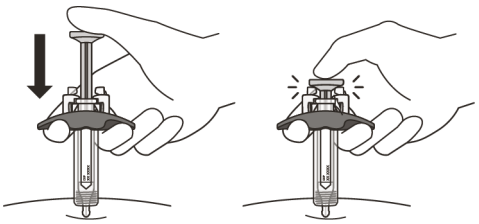


Figure M

19. Gently release the plunger and allow the needle to come out of the skin at the same angle it was inserted **(See Figure N)**.

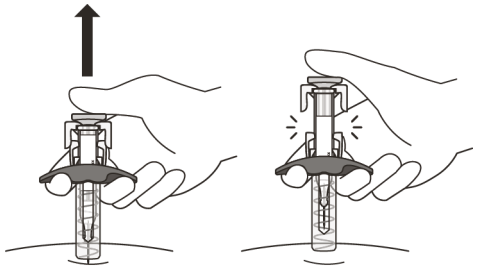


Figure N

- **The needle will now be covered by the needle-shield.** If the needle is not covered, carefully place the syringe into a puncture-resistant sharps container to avoid injury. See Step 21 “Disposing of Enspryng”.

Taking care of the injection site

20. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site but **do not** rub it. If needed, you may also cover the area you injected with a small bandage. If the medicine gets into contact with your skin, wash the area with water.

Disposing of Enspryng

21. Do not try to re-cap your syringe. Put your used syringe in a sharps disposal container immediately after use **(See Figure O)**. **Do not** throw away (dispose of) the syringe in your household waste and do not recycle them.

Figure O

- Ask your healthcare provider or pharmacist for information about where you can get a "sharps" container or what other types of puncture-resistant containers you can use to safely dispose of your used syringes and needle caps, if you do not have one.
- Dispose of the used sharps disposal container as instructed by your healthcare provider or pharmacist
- **Do not** dispose of your used sharps disposal container in your household waste
- **Do not** recycle your used sharps disposal container.