PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**ENSPRYNG®**

satralizumab injection

Solution, 120 mg/mL, Subcutaneous

Professed Standard

Immunosuppressant
Interleukin receptor inhibitor
(L04AC19)

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RECENT MAJOR LABEL CHANGES

3 Dosage and Administration, 3.2 Recommended Dose and Dosage Adjustment	xx/2021
3 Dosage and Administration, 3.5 Missed Dose	xx/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ENSPRYNG (satralizumab) is indicated:

- As monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients who are anti-aquaporin 4 (AQP4) seropositive.

ENSPRYNG is not intended for acute treatment of an NMOSD relapse.

1.1 Pediatrics

Pediatrics (≥ 12 years of age):

The safety and efficacy of ENSPRYNG in children younger than 12 years of age have not been established. ENSPRYNG was authorised for use in adolescent patients aged 12 or older based on clinical pharmacology data and extrapolation of efficacy and safety from adult NMOSD patients (see CLINICAL TRIALS; and 9.3 Pharmacokinetics, Special Populations and Conditions).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of ENSPRYNG have been studied in a limited number of geriatric patients up to 74 years of age (n=4 aged 65-73; see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment; and 9.3 Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

ENSPRYNG is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- ENSPRYNG should be prescribed by physicians experienced in the management of patients with NMOSD.
- ENSPRYNG is not intended for the acute treatment of an NMOSD relapse.
- In order to prevent medication errors, it is important to check the pre-filled syringe label to ensure that the drug being administered is ENSPRYNG.

3.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

ENSPRYNG must be administered as a subcutaneous (SC) injection.

ENSPRYNG can be used as a monotherapy or in combination with immunosuppressant therapy (IST). In a clinical trial, ENSPRYNG was administered with oral corticosteroids (OCs), azathioprine (AZA), mycophenolate mofetil (MMF), or a combination of these (see CLINICAL TRIALS). Please also refer to the Product Monographs for these products. Withdrawal of ISTs during treatment with ENSPRYNG was not assessed in clinical trials. If background IST is decreased or discontinued, patients should be monitored for signs and symptoms of NMOSD relapse.

The recommended loading dose is 120 mg by SC injection at Weeks 0, 2, and 4 for the first three administrations, followed by a maintenance dose of 120 mg every 4 weeks.

Duration of Treatment

ENSPRYNG is intended for long-term treatment. Use of ENSPRYNG has been studied only in the setting of chronic administration and the effect of discontinuation has not been characterized. Patients who discontinue ENSPRYNG should be closely monitored for signs and symptoms of NMOSD relapse.

Dose Modifications

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 discontinued, and reinitiation is not recommended.

If the ALT or AST elevation is >5x ULN and not associated with any bilirubin elevation, treatment with ENSPRYNG should be discontinued; it can be restarted (120 mg SC injection every 4 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, the liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin is observed the drug must be discontinued, and reinitiation is not recommended. (see WARNINGS AND PRECAUTIONS).

Table 1 – Recommended Dosage for Restart of Treatment After Liver Transaminase Elevation

Last Dose Administered	Recommended Dosage for Restart of Treatment
Less than 12 weeks	Restart at a dosage of 120 mg by subcutaneous injection every 4 weeks.
12 weeks or longer	Restart at a dose of 120 mg by subcutaneous injection at Weeks 0*, 2, and 4, followed by a dosage of 120 mg every 4 weeks.

*"0 weeks" refers to time of the first administration after the missed dose.

Neutropenia

If the neutrophil count is below 1.0 $x10^9$/L and confirmed by repeat testing, ENSPRYNG should be interrupted until the neutrophil count is > 1.0 $x10^9$/L.

Active Infections

Treatment with ENSPRYNG should not be initiated in patients with active infections. In patients

that develop an active infection while taking ENSPRYNG, dosing should be interrupted until the infection is controlled.

Special Dosage Instructions

Pediatric use
There are limited clinical data in patients aged 12 years and older who have a body weight of 40 kg or more. The dosage for this age group does not require adjustments and the patients can safely be treated with the same dosage regimen as the adults (see WARNINGS AND PRECAUTIONS, 6.1 Special Populations).

The safety and efficacy of ENSPRYNG in patients younger than 12 years of age or with a body weight less than 40 kg have not been studied (see WARNINGS AND PRECAUTIONS, 6.1 Special Populations).

Geriatric use
No dose adjustment is required in patients ≥65 years of age (see WARNINGS AND PRECAUTIONS, 6.1 Special Populations; and 9.3 Pharmacokinetics, Special Populations and Conditions).

Renal Impairment
The safety and efficacy of ENSPRYNG have not been studied in patients with moderate to severe renal impairment. Patients with mild renal impairment were included in clinical trials (see WARNINGS AND PRECAUTIONS, 6.1 Special Populations; and 9.3 Pharmacokinetics, Special Populations and Conditions).

Hepatic Impairment
The safety and efficacy of ENSPRYNG have not been studied in patients with hepatic impairment (see WARNINGS AND PRECAUTIONS, 6.1 Special Populations; and 9.3 Pharmacokinetics, Special Populations and Conditions).

3.3 Reconstitution

Not Applicable.

3.4 Administration

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 Patient Medication Information.

The first injection must be performed under the supervision of a qualified healthcare professional (HCP) and patients should be monitored for symptoms of hypersensitivity after injection. An adult patient may self-inject ENSPRYNG or the patient's caregiver may administer ENSPRYNG at home after receiving instruction on injection technique, 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.

3.5 Missed Dose

If an injection is missed, for any reason other than increases in liver enzymes, it should be administered as described in Table 2.

Table 2 - Recommended Dosage for Delayed or Missed Doses

Last Dose Administered	Recommended Dosage for Delayed or Missed Doses
Less than 8 weeks during the maintenance period or missed a loading dose	Administer 120 mg by subcutaneous injection as soon as possible, and do not wait until the next planned dose. **Maintenance period** After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks. **Loading period** If the second loading dose is delayed or missed, administer as soon as possible and administer the third and final loading dose 2 weeks later. If the third loading dose is delayed or missed, administer as soon as possible and administer the 1st maintenance dose 4 weeks later.
8 weeks to less than 12 weeks	120 mg by subcutaneous injection at 0* and 2 weeks, followed by 120 mg every 4 weeks.
12 weeks or longer	120 mg by subcutaneous injection at 0*, 2, and 4 weeks followed by 120 mg every 4 weeks.

*"0 weeks" refers to time of the first administration after the missed dose.

4 OVERDOSAGE

There is no experience with overdose in patients with NMO or NMOSD. No serious or severe adverse events were observed in healthy adults that received a single dose of 240 mg SC ENSPRYNG.

In the event of an overdose, the patient should be closely supervised, treated symptomatically, and supportive measures instituted as required.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution, in single-use, pre-filled syringe, 120 mg/mL	L-arginine, L-aspartic Acid, L-histidine, poloxamer 188, and water for injection.

ENSPRYNG (satralizumab) injection is available as a sterile, preservative-free, clear, colourless to slightly yellow solution in a single-use pre-filled syringe (PFS) with needle safety device (NSD).

Each ENSPRYNG carton contains one single-use 120 mg pre-filled syringe.

Description

ENSPRYNG is a recombinant humanized immunoglobulin G2 (IgG2) monoclonal antibody against the human interleukin-6 receptor (IL-6R), produced in Chinese hamster ovary cells by recombinant DNA technology.

6 WARNINGS AND PRECAUTIONS

General
In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

Cardiovascular
Elevated blood lipids have been observed in clinical trials with ENSPRYNG. Patients with severe cardiac impairment were excluded from clinical trials with ENSPRYNG.

Dependence/Tolerance
No studies on drug abuse and dependence have been conducted.

Driving and Operating Machinery
No studies on the effects on the ability to drive and use of machines have been performed. In clinical trials, some patients experienced symptoms such as vertigo that may affect ability to drive and use machines. Patients experiencing such symptoms should be advised to avoid operating machinery until symptoms subside.

Carcinogenesis and Mutagenesis
Carcinogenesis and mutagenesis studies have not been performed (see NON-CLINICAL TOXICOLOGY).

Hepatic/Biliary/Pancreatic
Liver Enzymes

Mild and moderate elevations of liver transaminases have been observed with ENSPRYNG treatment. Most elevations were below 5x ULN and not treatment-limiting and resolved while ENSPRYNG was given.

ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for 1 year, thereafter as clinically indicated. For treatment discontinuation recommendations, please refer to Dosage and Administration, Recommended Dose and Dosage Adjustment.

Immune

Infections

Serious, severe, and opportunistic infections may occur in patients taking immunosuppressive agents including ENSPRYNG (see 7.2 Clinical Trial Adverse Reactions). ENSPRYNG administration should be delayed in patients with an active infection until the infection is controlled (see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment).

Vigilance for the timely detection of serious infection is recommended for patients receiving treatment with ENSPRYNG, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. A patient who develops a new infection during treatment with ENSPRYNG should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Patients should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Injection site and hypersensitivity reactions

In clinical trials, mild to moderate local and systemic injection-related reactions were more common in patients taking ENSPRYNG (see 7.2 Clinical Trial Adverse Reactions). Advise patients to seek medical attention if they experience serious or severe allergic reactions to ENSPRYNG. If an anaphylactic or serious hypersensitivity reaction occurs, ENSPRYNG should be discontinued.

Vaccinations

Live or 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/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 immunizations in agreement with current immunization guidelines prior to initiating ENSPRYNG therapy.

Monitoring and Laboratory Tests

Neutrophil Count

Decreases in neutrophil counts have occurred following treatment with ENSPRYNG (see 7.2 Clinical Trial Adverse Reactions). Neutrophil counts should be monitored 4 to 8 weeks after start of therapy and thereafter as clinically indicated. For recommended dose delay, see 3.2 Recommended Dose and Dosage Adjustment.

Peri-Operative Considerations

There is no experience with bleeding events in patients taking ENSPRYNG that developed

abnormal clotting factors; assessment of clotting should be performed in patients with severely decreased platelets and/or fibrinogen prior to surgical procedures.

Reproductive Health: Female and Male Potential

- Fertility

  No clinical data are available on the effect of ENSPRYNG on human fertility. Effects on male and female reproductive endpoints have been investigated in monkeys. In 4-week and 26-week repeated-dose toxicity studies conducted in mature cynomolgus monkeys given satralizumab by s.c. injection, males developed testicular atrophy (see NON-CLINICAL TOXICOLOGY).

6.1 Special Populations

6.1.1 Pregnant Women

There are no data from the use of ENSPRYNG in pregnant women. Human IgG is known to cross the placental barrier; therefore, ENSPRYNG may be transmitted from the mother to the developing fetus. Satralizumab was shown to cross the placenta in pregnant cynomolgus monkeys (see NON-CLINICAL TOXICOLOGY).

In an enhanced pre- and postnatal development study, satralizumab administration to pregnant cynomolgus monkeys resulted in reduced immune function in infants (see NON-CLINICAL TOXICOLOGY).

ENSPRYNG is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

6.1.2 Breast-feeding

Breastfeeding is not recommended during treatment with ENSPRYNG as a risk to the nursing infant cannot be excluded. There are no data on the presence of satralizumab in human milk, the effects on the breastfed infant, or the effects on human milk production. However, IgGs are excreted in human milk and satralizumab has been shown to be present in the milk of lactating cynomolgus monkeys (see NON-CLINICAL TOXICOLOGY).

6.1.3 Pediatrics

The safety and efficacy of ENSPRYNG in children younger than 12 years of age have not been established. ENSPRYNG was authorised for use in adolescent patients aged 12 or older based on clinical pharmacology data and extrapolation of efficacy and safety from adult NMOSD patients. (see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment).

6.1.4 Geriatrics

The safety and efficacy of ENSPRYNG have been studied in a limited number of geriatric patients (n=4 aged 65-73). Although there were no apparent age-related differences observed in studies, the number of patients aged 65 and over is not sufficient to determine whether they respond similarly to younger patients (see DOSAGE AND ADMINISTRATION, 3.2

Recommended Dose and Dosage Adjustment; and 9.3 Pharmacokinetics, Special Populations and Conditions).

The safety and efficacy of ENSPRYNG in geriatric patients >74 years of age have not been studied (see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment).

6.1.5 Renal Impairment

The safety and efficacy of ENSPRYNG in patients with moderate to severe renal impairment have not been studied. Patients with mild renal impairment were included in clinical trials. The pharmacokinetics of satralizumab in these patients was not impacted (see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment; and 9.3 Pharmacokinetics, Special Populations and Conditions).

6.1.6 Hepatic Impairment

The safety and efficacy of ENSPRYNG in patients with hepatic impairment have not been studied (see DOSAGE AND ADMINISTRATION, 3.2 Recommended Dose and Dosage Adjustment; and 9.3 Pharmacokinetics, Special Populations and Conditions).

6.1.7 Women of Childbearing Potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment with ENSPRYNG.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety of ENSPRYNG as monotherapy or in combination with IST was evaluated based on data from two phase III randomized, multicenter, double-blind, placebo-controlled clinical trials (BN40900 and BN40898), which included 63 patients exposed to ENSPRYNG monotherapy and 41 patients exposed to ENSPRYNG in combination with IST (see CLINICAL TRIALS). In the double-blind controlled period, patient median exposure to satralizumab was approximately 2 years in both studies BN40900 and BN40898 each. The median exposure to placebo was approximately 1 year.

The most frequently reported adverse drug reactions (ADRs) were headache, arthralgia and injection related reactions (Table 4). Serious drug-related adverse events, including infections, were reported in 2.9% of patients that received ENSPRYNG treatment in the placebo-controlled portion of clinical trials. There were 3.8% of ENSPRYNG-treated patients that discontinued from trials due to adverse events and 22.1% that had dose interruptions due to adverse events (e.g., infections). These rates were comparable to rates seen in placebo-treated patients.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be

compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 4 summarizes the ADRs that have been reported in association with the use of ENSPRYNG as monotherapy or in combination with IST in clinical trials. In both trials, patients in the ENSPRYNG group received doses of 120 mg, injected subcutaneously, at Weeks 0, 2, 4, and every 4 weeks thereafter. Because patients in the ENSPRYNG groups in both clinical studies had a longer treatment period than those in the placebo (or placebo in combination with IST) groups, adverse events after adjustment for exposure are also presented. ADRs from clinical trials are listed by MedDRA system organ class.

Table 4 - Summary of ADRs occurring more commonly in patients receiving ENSPRYNG than in the control group (defined as ≥2% higher proportion of patients and ≥2 events/100 PY) [1]

ADR	BN40898 (in combination with IST)				BN40900 (monotherapy)			
	Number of Patients n (%)		Rate of AE /100PY		Number of Patients n (%)		Rate of AE/100PY	
	Placebo n=42	ENSPRYNG n=41	Placebo (PY=59.5)	ENSPRYNG (PY=78.5)	Placebo n=32	ENSPRYNG n=63	Placebo (PY=40.6)	ENSPRYNG (PY=115.21)
Blood and lymphatic system disorders								
Hypofibrinogenemia	0	1 (2.4%)	0	1.3	0	2 (3.2%)	0	1.7
General disorders and administration site conditions								
Peripheral Edema	0	1 (2.4%)	0	1.3	0	4 (6.3%)	0	3.5
Injury, poisoning and procedural complications								
Injection-Related Reactions	2 (4.8%)	5 (12.2%)	3.4	21.7	5 (15.6%)	8 (12.7%)	17.3	13.9
Investigations								
White blood cell count decreased	4 (9.5%)	7 (17.1%)	21.85	14.01	0	7 (11.1%)	0	9.55
Blood bilirubin increased	0	1 (2.4%)	0	11.46	0	1 (1.6%)	0	0.87
Musculoskeletal and connective tissue disorders								
Arthralgia	0	4 (9.8%)	0	5.1	1 (3.1%)	10 (15.9%)	2.5	8.7
Musculoskeletal stiffness	0	1 (2.4%)	0	1.3	0	4 (6.3%)	0	3.5
Nervous system disorders								
Headache	4 (9.5%)	10 (24.4%)	10.1	28.0	4 (12.5%)	10 (15.9%)	12.3	11.3
Migraine	0	0	0	0	0	4 (6.3%)	0	3.5
Psychiatric disorders								
Insomnia	0	1 (2.4%)	0	1.3	1 (3.1%)	5 (7.9%)	2.5	4.3

ADR	BN40898 (in combination with IST)				BN40900 (monotherapy)			
	Number of Patients n (%)		Rate of AE /100PY		Number of Patients n (%)		Rate of AE/100PY	
	Placebo n=42	ENSPRYNG n=41	Placebo (PY=59.5)	ENSPRYNG (PY=78.5)	Placebo n=32	ENSPRYNG n=63	Placebo (PY=40.6)	ENSPRYNG (PY=115.21)
Respiratory, thoracic and mediastinal disorders								
Rhinitis allergic	0	2 (4.9%)	0	2.6	0	2 (3.2%)	0	1.7
Skin and subcutaneous tissue disorders								
Rash	2 (4.8%)	0	3.4	0	1 (3.1%)	9 (14.3%)	4.9	12.2
Pruritus	1 (2.4%)	0	1.7	0	0	6 (9.5%)	0	6.9

[1]ADRs identified based on medical review of all AEs which were ≥2/100PY higher AND ≥2% higher in the ENSPRYNG group versus the controlled groups
ADRs=Adverse Drug Reactions
IST=Immunosuppressive Therapy
AE=Adverse Events
PY= Patient Years

Description of Selected Adverse Drug Reactions from Clinical Trials

Injection-related Reactions (IRRs)
IRRs reported in patients treated with ENSPRYNG as monotherapy or in combination with IST were predominantly mild to moderate, most occurred within 24 hours after injections. None of the injection related reactions required dose interruption or discontinuation.

Systemic Injection Related Reactions
During the double-blind period, 6.7% of patients receiving ENSPRYNG and 4.1% of patients receiving placebo reported systemic injection related reactions. The most commonly reported systemic symptoms were diarrhea and headache. Severe symptoms include vertigo and hypertension. The rate of systemic injection related reactions occurring in the presence of anti-drug antibodies (ADAs) was 4.96 events per 100 patient-years. In the absence of detectable ADAs, it was 11.41 events per 100 patient-years.

Local Injection Site Reactions
During the double-blind period, 8.7% of patients receving ENSPRYNG and 6.8% of patients receiving placebo reported local injection site reactions. The most commonly reported symptoms were flushing, erythema, pruritus, rash and pain. The rate of local injection site reactions occurring in the presence of ADAs was 6.61 events per 100 patient-years. In the absence of detectable ADAs, it was 11.41 events per 100 patient-years.

Infections and Serious Infections
In the ENSPRYNG monotherapy study, the exposure-adjusted rate of infections was lower in patients treated with ENSPRYNG [99.8 events/100 PY] compared with patients receiving placebo [162.6 events/100 PY]. The rate of serious infections was 5.2 events/100 PY in patients treated with ENSPRYNG compared with 9.9 events/100 PY in patients receiving placebo.

In patients treated with ENSPRYNG in combination with IST, the rate of infections was 132.5 events/100 PY compared with 149.6 events/100 PY in patients receiving placebo in combination

with IST; the rate of serious infections was 2.6 events/100 PY compared with 5.0 events/100 PY in patients receiving placebo in combination with IST.

The overall rates of infections in patients treated with ENSPRYNG who developed anti-drug antibodies were not increased over rates in patients treated with ENSPRYNG that did not develop such antibodies.

Body weight increase
In the double-blinded treatment period, body weight increase ≥ 15% from baseline were observed in 3.8% of patients treated with ENSPRYNG (monotherapy or in combination with IST) as compared with 2.7% of patients receiving placebo (or plus IST).

7.2.1 Clinical Trial Adverse Reactions (Pediatrics)

The safety of ENSPRYNG has been studied in a limited number of pediatric patients ≥12 years of age. Safety results were consistent with those in adults.

7.3 Less Common Clinical Trial Adverse Reactions

Not Applicable.

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 plus IST). The majority of neutrophil decreases were transient or intermittent.

Of the patients in the ENSPRYNG group, 9.6% had neutrophils below 1 x 10^9/L (Grade 3 or Grade 4) as compared with 5.4% in placebo or placebo plus IST, which was 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 (Grade 3).

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 as 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, which 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, normalizing after discontinuation of ENSPRYNG.

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 plus IST; 20.2% of patients receiving ENSPRYNG experienced elevations in triglycerides above 3.42 mmol/L as compared with 10.8% of patients receiving placebo. The elevations in lipid parameters did not require dose interruption.

Fibrinogen
Decreased fibrinogen is a known effect of ENSPRYNG related to its mechanism of action. In the double-blinded treatment period of clinical trials, 71.2% of ENSPRYNG-treated patients and 20.3% of patients receiving placebo had downward shifts from baseline fibrinogen levels. There were no bleeding events among patients with decreased fibrinogen levels.

Complement Factors
Decreases in C3, C4, and CH50 are known effects of ENSPRYNG related to its mechanism of action. In the double-blinded treatment period of clinical trials, decreases in C3, C4 and CH50 occurred in 66.7%, 56.9% and 89.6% of ENSPRYNG-treated patients, respectively, compared with that in 18.2%, 4.1% and 44.4% of patients receiving placebo.

7.5 Post-Market Adverse Reactions

Not applicable.

8 DRUG INTERACTIONS

8.2 Drug Interactions Overview

No formal drug-drug interaction studies have been performed with ENSPRYNG.

8.3 Drug-Behavioural Interactions

No studies on the effects on the ability to drive and use of machines have been performed. However, there is no evidence from the available data that ENSPRYNG treatment affects the ability to drive and use of machines (see WARNINGS AND PRECAUTIONS).

8.4 Drug-Drug Interactions

Population PK analyses did not detect any effect of AZA, OC, or MMF on the clearance of ENSPRYNG.

Since the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6 in vitro and in vivo, caution should be exercised when starting or discontinuing satralizumab treatment in patients also receiving

substrates of CYP450 3A4, 1A2, 2C9 or 2C19 particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin & theophylline), and doses adjusted if needed.

8.5 Drug-Food Interactions

Interactions with food have not been established.

8.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

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

IL-6 has been shown to be involved in disease-relevant pro-inflammatory mechanisms. The precise mechanism by which satralizumab exerts its therapeutic effect in NMO and NMOSD is unknown but is presumed to involve reduced production of anti-AQP4 autoantibodies through inhibition of IL-6 signaling.

9.2 Pharmacodynamics

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

9.3 Pharmacokinetics

The pharmacokinetics of ENSPRYNG was studied in healthy subjects and in NMO and NMOSD patients. In healthy subjects, the pharmacokinetics of satralizumab was shown to be non-linear over the dose range of 30 – 240 mg. The pharmacokinetics in NMO and NMOSD patients treated by the recommended dose were characterized using population pharmacokinetic analysis methods based on a database of 154 patients.

Absorption: In adult NMO/NMOSD patients following subcutaneous administration, the absorption half-life was around 3 days at the recommended dose regimen. Steady state were achieved after the dose loading period (8 weeks) with the observed geometric mean (CV) C_{trough} of 19.0 (13.9%) µg/mL. Population pharmacokinetic analysis estimated the absorption rate constant of ENSPRYNG was 0.254 1/day (CV 33.9%) and the bioavailability was 78.5% (CV 7.0%).

Distribution: In NMO/NMOSD patients, ENSPRYNG undergoes biphasic distribution. For a typical 60 kg patient, the estimated central volume of distribution was 3.46 L (95% CI: 3.21-3.97), and the peripheral volume of distribution was 2.07 L (95% CI: 1.78-2.59).

Metabolism: The metabolism of ENSPRYNG has not been directly studied. As a monoclonal antibody, ENSPRYNG is expected to be cleared principally by catabolism.

Elimination: The total clearance of satralizumab is concentration-dependent both linear and target-mediated (Michaelis-Menten) elimination. Bodyweight was shown to be a significant covariate. The clearance and central volume of distribution (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. Population pharmacokinetic analysis estimated thelinear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMO and NMOSD patients) to 0.0679 L/day (CV 27%) and the associated terminal $t_{1/2}$ to be approximately 30 days (range 22-37 days).

Special Populations and Conditions

Population pharmacokinetic analyses in adult patients with NMO or NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab. Body weight and the presence of anti-drug antibody (ADA) was shown to have significant impact on the pharmacokinetics of satralizumab,. In NMOSD patients with either post-treatment ADA positive or higher body weight (75.0-151.0 kg), approximately 2-fold lower exposure was observed as compared to patients with ADA negative or lower body weight (57.3 - 75.0 kg). However, no dose adjustment is recommended, based on the exposure-response relationship analysis.

- ***Pediatrics:*** Based on PK data obtained in 7 adolescent patients [13-17 years] with body weight ranged 40 – 140 kg who received the recommended dosing regimen as combination therapy with OCs, AZA, or MMF, the observed geometric mean (CV) C_{trough} was 17.9 (12.5%) µg/mL at steady state.

- ***Geriatrics:*** 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 including these patients showed that age did not affect the PK of satralizumab.

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

  Renal Insufficiency: 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. The PK in these patients was not significantly impacted based on population pharmacokinetic analysis, and therefore no dose adjustment is required.

10 STORAGE, STABILITY AND DISPOSAL

Store at 2-8°C until ready to use.

ENSPRYNG, if unopened, 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.

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

Do not freeze. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

11 SPECIAL HANDLING INSTRUCTIONS

ENSPRYNG is for single-use only.

Do not inject the medicine if the liquid is cloudy, discoloured, or has particles in it.

Check the PFS + NSD for any damage. Do not use if it is cracked or broken.

Disposal of PFS + NSD
The following points should be strictly adhered to regarding the use and disposal of the PFS + NSD:

- PFS should never be reused.
- Put your used syringe in a sharps disposal container immediately after use.
- Throw away (dispose of) the PFS+NSD in accordance with local requirements or as directed by your healthcare professional.
- Keep the PFS+NSD and all medicines out of the reach of children.

Disposal of Unused/Expired Medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: satralizumab

Structure: Recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the IgG2 subclass. It is comprised of two heavy and two light chains. Each light chain and heavy chain consists of 214 and 443 amino acids, respectively.

Molecular Mass: Approximately 143 kDa

Physicochemical properties: Clear and colorless to slightly yellow solution

Pharmaceutical standard: Professed Standard

Product Characteristics

ENSPRYNG is a recombinant humanized immunoglobulin G2 (IgG2) monoclonal antibody against the human interleukin-6 receptor (IL-6R), produced in Chinese hamster ovary cells by recombinant DNA technology.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The efficacy and safety of ENSPRYNG was evaluated in two pivotal phase III clinical trials (BN40898 and BN40900) in patients with a diagnosis of NMO or with a diagnosis of NMOSD.

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

Study BN40898 was a randomized, multicenter, double-blind, placebo-controlled clinical trial to evaluate the effect of ENSPRYNG in combination with stable IST (oral corticosteroids [OCs] up to 15 mg/day [prednisolone equivalent], azathioprine [AZA] up to 3 mg/kg/day or mycophenolate mofetil [MMF] up to 3000 mg/day; adolescents received a combination of AZA and OCs or MMF and OCs). The study included 83 patients (including 7 adolescents) of which 55 (66.3%) were AQP4-IgG seropositive. 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. A total of 41 patients were randomized to receive ENSPRYNG and 42 were randomized to receive matching placebo.

Study design and baseline characteristics of the study population are presented in Table 5.

Table 5 - 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)*	
Treatment groups, in 1:1 randomization	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 only

Baseline Characteristics and Efficacy in Adolescent Patients (Study BN40898)

The mean age of the 7 adolescent patients enrolled during the double-blind period of study BN40898 was 15.4 (13 - 17) years and the median body weight was 79.6 kg (47.5 - 140.4). The majority of the adolescent patients were females (n=6). Four patients were White, 2 patients were Black/African American, and 1 patient was Asian. Three out of 7 (42.9%) adolescent

patients were AQP4-IgG seropositive at screening (2 in the placebo group and 1 in the ENSPRYNG group).

The primary efficacy endpoint was time to first relapse (TFR), based on a protocol defined relapse (PDR). A PDR was defined as a clinical relapse confirmed as PDR by the CEC clinical endpoint committee (CEC).

Study BN40900 (also known as SA-309JG or SAkuraStar)
Study BN40900 was a randomized, multicenter, double-blind, placebo-controlled clinical trial to evaluate the effect of ENSPRYNG monotherapy compared to placebo. The study included 95 adult patients of which 64 (67.4%) were AQP4-IgG seropositive. 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. A total of 63 patients were randomized to receive ENSPRYNG and 32 were randomized to receive matching placebo.

Study design and baseline characteristics of the study population are presented in Table 6.

Table 6 - 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 randomization of the last enrolled patient, whichever comes first)*	
Treatment groups, in 2:1 randomization	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)

The primary efficacy endpoint was time to first relapse (TFR), based on a protocol defined relapse (PDR). A PDR was defined as a clinical relapse confirmed as PDR by the clinical endpoint committee (CEC).

13.2 Study Results

Primary Efficacy

Treatment with ENSPRYNG resulted in a statistically significant reduction in the risk of experiencing an adjudicated relapse when compared to placebo (Hazard ratio [HR] [95% CI]: 0.38 [0.16-0.88]; p [log rank]=0.0184; Figure 1) when administered in combination with stable IST (Study BN40898). When used as monotherapy ENSPRYNG resulted in a statistically significant reduction in the risk of experiencing an adjudicated relapse when compared to placebo (HR [95% CI]: 0.45 [0.23-0.89]; p [log rank]=0.0184; Figure 2) (Study BN40900) (see Table 7).

Table 7 - Results for the Primary Efficacy Endpoint in Study BN40898 and BN40900

	BN40898		BN40900	
	ENSPRYNG + IST (n=41)	Placebo + IST (n=42)	ENSPRYNG (n=63)	Placebo (n=32)
Number (proportion) of patients with a PDR	8 (19.5%)	18 (42.9%)	19 (30.2%)	16 (50.0%)
HR (95% CI) [1,2]	(HR: 0.38; 95% CI: 0.16, 0.88; p=0.0184)		(HR:0.45; 95% CI: 0.23, 0.89; p=0.0184)	

[1] HR calculated with a cox regression, stratified by the stratification factors at randomization.
[2] p-value calculated with a log-rank test, stratified by the stratification factors at randomization.

Figure 1 - Study BN40898: Kaplan Meier Survival Estimates for Time to First Adjudicated Relapse during the Double-Blind Period (ITT Population)

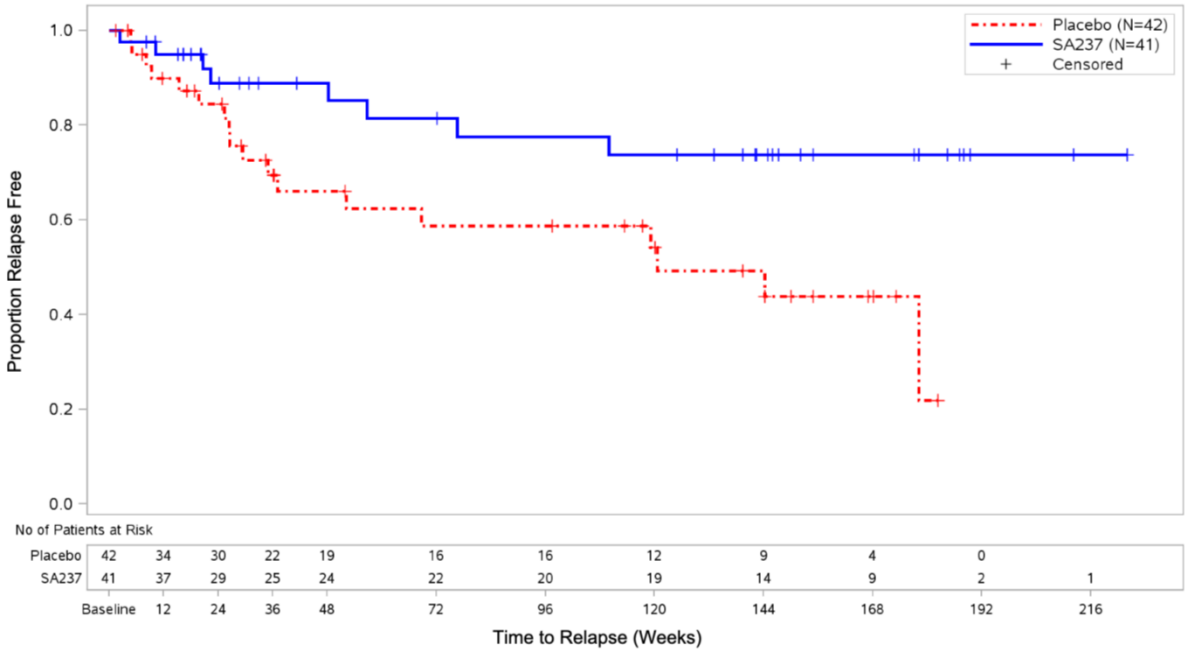
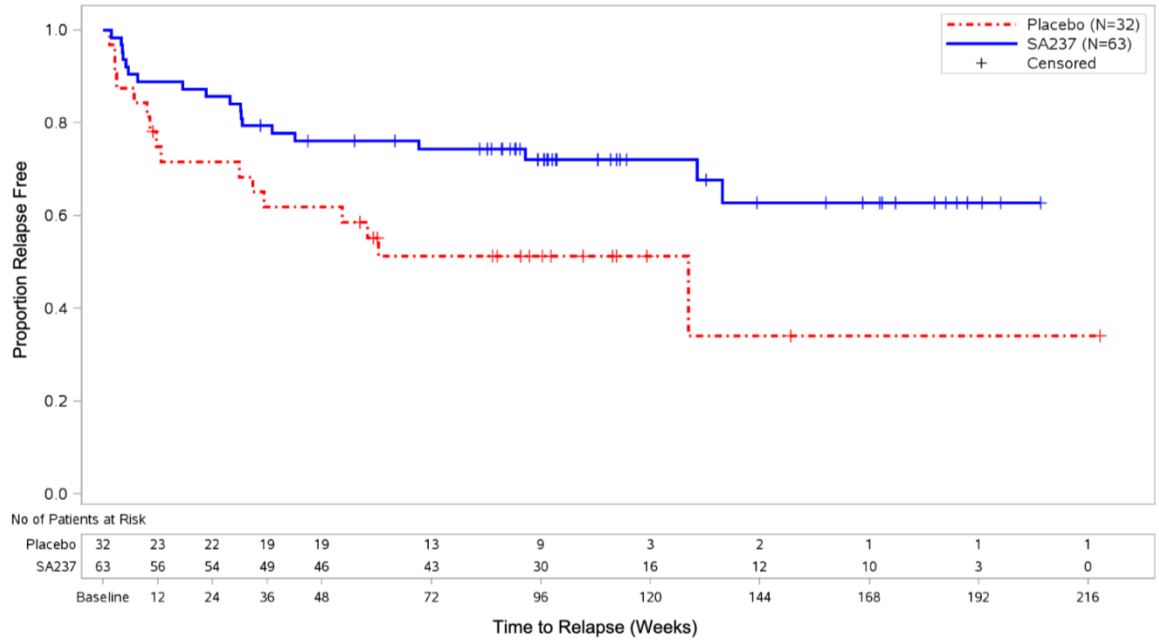


Figure 2 - Study BN40900: Kaplan Meier Survival Estimates for Time to First Adjudicated Relapse during the Double-Blind Period (ITT Population)



Study Results by AQP4-IgG Serostatus

The following results were obtained for the primary endpoint in AQP4-IgG seropositive patients comparing treatment with ENSPRYNG to placebo: when administered in combination with stable IST (Study BN40898) (Hazard ratio [HR] [95% CI]: 0.21 [0.06-0.75]; Figure 3) and when used as monotherapy (Study BN40900)(Hazard ratio [HR] [95% CI]: 0.26 [0.11-0.63]; Figure 4). In AQP4-IgG seronegative patients the following results were obtained compared to placebo: when administered in combination with stable IST (Study BN40898) (Hazard ratio [HR] [95% CI]: 0.66 [0.20-2.23]) and when used as monotherapy (Study BN40900) (Hazard ratio [HR] [95% CI]: 1.19 [0.30-4.78]).

Figure 3 - Study BN40898: Kaplan Meier Survival Estimates for Time to First Adjudicated Relapse during the Double-Blind Period in AQP4-IgG seropositive Patients

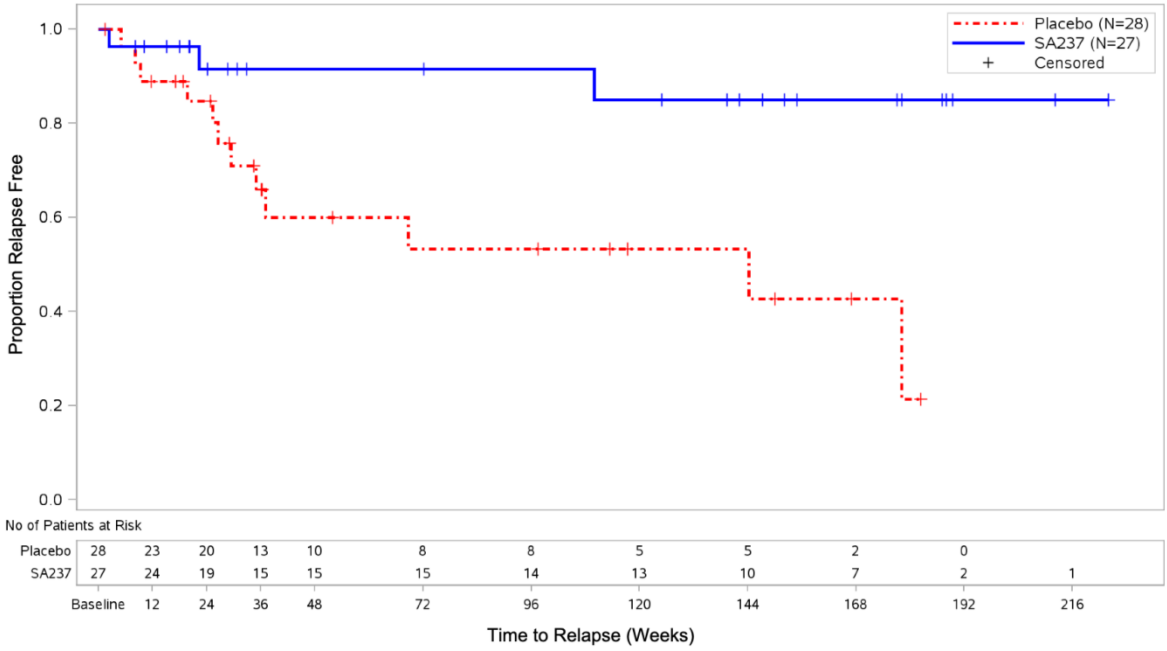
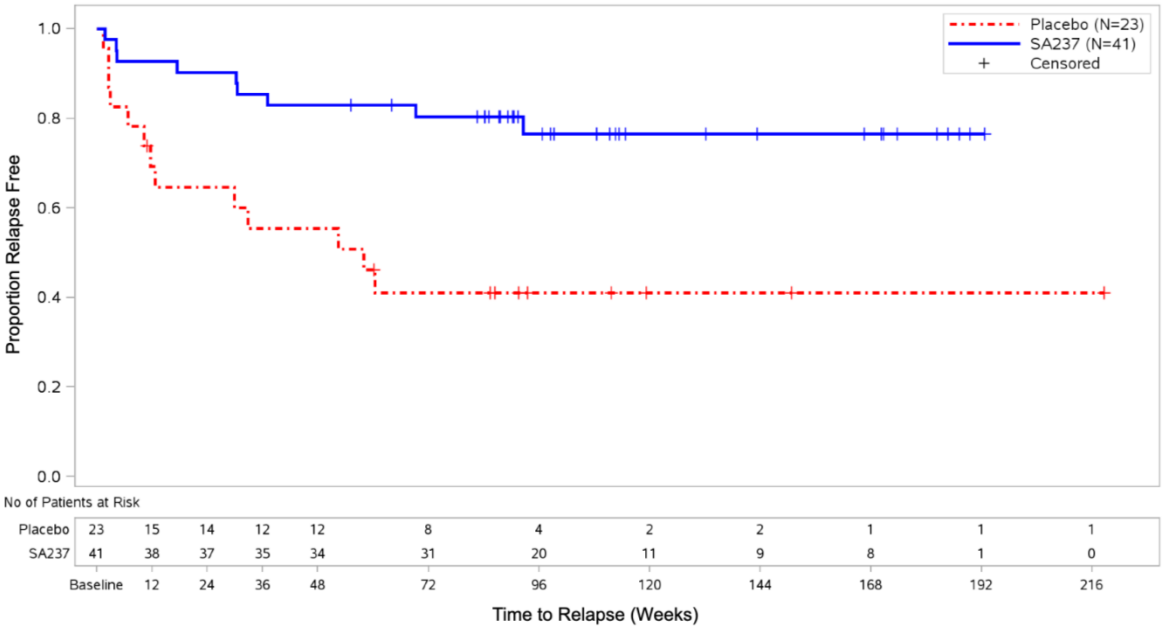


Figure 4 - Study BN40900: Kaplan Meier Survival Estimates for Time to First Adjudicated Relapse during the Double-Blind Period in AQP4-IgG seropositive Patients



13.4 Immunogenicity

In phase III Study BN40898 (combination with IST) and in phase III study BN40900

(monotherapy), anti-drug-antibodies (ADAs) were observed in 41% and 71% of patients receiving ENSPRYNG in the double-blind period, respectively. The ability of these 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.

14 MICROBIOLOGY

No microbiological information is required for this drug product.

15 NON-CLINICAL TOXICOLOGY

15.1 Comparative Non-Clinical Pharmacology and Toxicology

General Toxicology

In the 4-week and 26-week repeated-dose toxicity studies conducted in mature cynomolgus monkeys administered satralizumab at doses of 2, 10, or 50 mg/kg by SC injection once a week (3, 17, and 105 times the human exposure at the maximum recommended dose based on C_{max}). No effects on female reproductive organs have been seen. In male animals, abnormal sperm together with testicular and prostate atrophy, for which a relationship with the test item satralizumab cannot be excluded, have been reported. Animals had increased serum IL-6 levels, which was considered to be the result of the pharmacological action (IL-6R neutralizing 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 did not affect the pharmacological response and did not result in any adverse events. A study no observed adverse effect level (NOAEL) could not be identified due to the testicular atrophy that occurred in males given the lowest dose.

Safety Pharmacology

Safety pharmacology endpoints were incorporated into the 4- and 26-week repeated-dose SC studies, and no adverse effects caused by administration of satralizumab were found up to 50 mg/kg/week.

Local Tolerance

Monkeys administered satralizumab or vehicle showed similarity in terms of local tolerance in that both presented with inflammatory lesions at the injection sites. Except for the injection site reactions, there were no macroscopic or microscopic findings directly attributable to effects of satralizumab.

Carcinogenicity

No rodent carcinogenicity studies have been performed to establish the carcinogenic potential of satralizumab.

Genotoxicity

No studies have been performed to establish the mutagenic potential of satralizumab.

Reproductive and Developmental Toxicology

In an enhanced pre- and postnatal development study, pregnant cynomolgus monkeys were administered satralizumab at doses of 2 or 50 mg/kg by SC injection once per week from gestational day 20 until parturition. Satralizumab was shown to distribute across the placental barrier. Prenatal losses did not differ between maternal monkeys administered satralizumab and those given vehicle control. One neonate in the high-dose group died due to infection. Infants exposed to satralizumab *in utero* also showed reduced and/or delayed IgG and IgM response to keyhole limpet hemocyanin antigen challenge. Satralizumab did not elicit any adverse effects on maternal animals, fetal development, pregnancy outcome or infant development including, learning ability from birth through postnatal day 293. The NOAEL for the developmental toxicity of satralizumab was 2 mg/kg/week (3 times the human exposure at the maximum recommended dose based on C_{max}).

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

Juvenile Toxicity

Testing of a murine analogue of an anti IL-6 receptor monoclonal antibody, structurally similar to satralizumab, i.e. MR16-1, in responder mice did not yield any evidence of harm when dosed at 15 or 50 mg/kg intravenously with treatment every three days from postnatal days 22 to 79.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
Pr ENSPRYNG®
satralizumab injection

Read this carefully before you start taking **ENSPRYNG** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENSPRYNG**.

What is ENSPRYNG 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.
- ENSPRYNG reduces the risk of a relapse or attack of NMOSD.

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. This leads 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 does ENSPRYNG work?
ENSPRYNG blocks the action of a protein called 'interleukin-6' (IL-6).
- This protein is involved in swelling in the body.

What are the ingredients in ENSPRYNG?
Medicinal ingredients: satralizumab
Non-medicinal ingredients: L-arginine, L-aspartic Acid, L-histidine, poloxamer 188, and water for injection.

ENSPRYNG comes in the following dosage forms:
Solution, in a single-use, pre-filled syringe of 120 mg/mL.

Do <u>not</u> use ENSPRYNG if:
- You are allergic to ENSPRYNG (satralizumab) or
- You are allergic to any of the other ingredients of this medicine or components of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENSPRYNG. Talk about any health conditions or problems you may have, including if you:
- Have any signs of infection
    - Symptoms could include 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, diarrhea or belly pain.
    - Your doctor will wait until the infection is gone before giving you ENSPRYNG or allowing you to continue to inject ENSPRYNG.

- 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** get 'live' or 'live attenuated' vaccines (for example BCG for tuberculosis or vaccines against yellow fever) while you are taking ENSPRYNG.
    - However, your doctor may recommend that you get a seasonal flu vaccine, since these are usually not 'live' or 'live attenuated.'

- Have increased liver enzymes - see **"*Serious side effects and what to do about them*"** below.
    - Your doctor will do blood tests to check these amounts and monitor how well your liver is working.

- Are pregnant or breast-feeding, or think you may be pregnant or are planning to have a baby.
    - Women of childbearing potential must use effective contraception during and up to 3 months after treatment with ENSPRYNG.
    - Breastfeeding is not recommended during treatment with ENSPRYNG as a risk to the nursing infant cannot be excluded.

Other warnings you should know about:
- 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.
- ENSPRYNG is not likely to affect you being able to drive, cycle or use any tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ENSPRYNG:
Read carefully and follow the enclosed instructions under "**Instructions for Use**" below on how to administer ENSPRYNG.

Always use this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure how to inject it.

- ENSPRYNG is given by injection under the skin (sub-cutaneously).
- Always use the entire contents of the syringe during injection.

Usual dose:
Each injection contains 120 mg of satralizumab. The first injection will be given under the supervision of your healthcare professional.
- 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 right 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.

Instructions for Use

Read these 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** replace talking to your healthcare professional about your condition or treatment.
- Your healthcare professional will decide if you or a caregiver can give you injections of ENSPRYNG at home. They will also show you or a caregiver how to use the syringe before you use it for the first time.
- Talk to your healthcare professional 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.
- Do **not** use the syringe if it has been dropped or damaged.
- Do **not** try to take the syringe apart at any time.
- Do **not** leave the syringe unattended.
- Do **not** re-use the same syringe.

How should I store the ENSPRYNG pre-filled syringe?

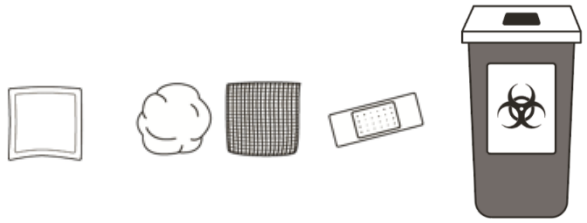
- Keep the unused syringe in the refrigerator between 2 to 8°C until ready to use. Do **not** freeze. Do **not** use the syringe if it has been frozen.
- Keep the syringe and all medicines out of the reach of children.
- Keep the syringe in its original carton away from direct sunlight.
- Always keep the syringe dry.

Supplies needed to give your injection

Each ENSPRYNG carton contains:

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

<u>Not</u> 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:

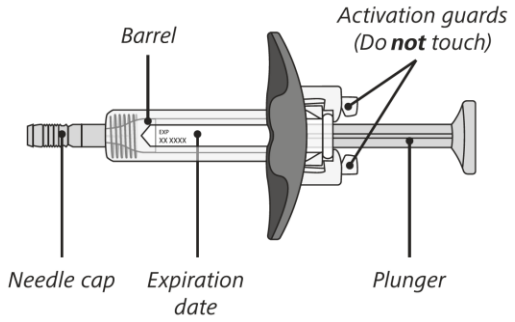


Figure A

After use:

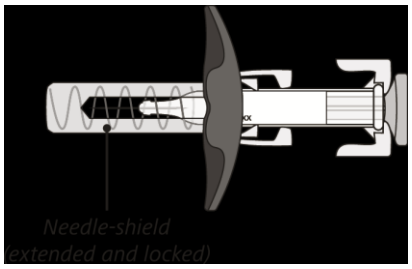


Figure B

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 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. In this case, go to Step 21 "Disposing of ENSPRYNG" and contact your healthcare professional.

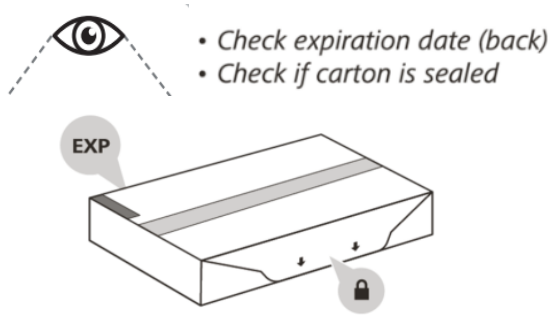


Figure C

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

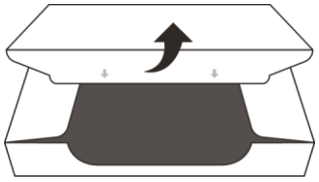


Figure D

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.
- Do **not** touch the activation guards - this may damage the syringe.
- Do **not** hold the plunger or needle cap.

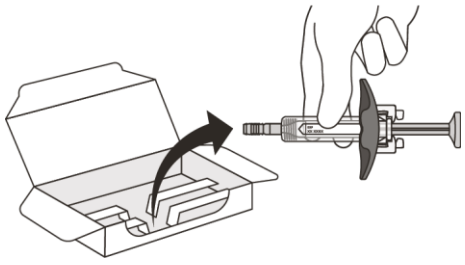


Figure E

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 colorless to pale 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.

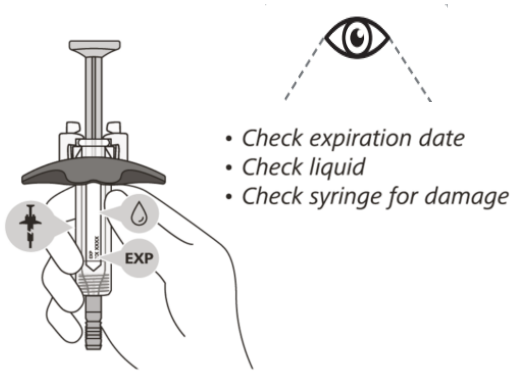


Figure F

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

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 warm up slowly. Injecting cold solution may feel uncomfortable and make it harder to push out.

   - Do **not** speed up the warming process in any way. Do **not** use a microwave or place the syringe in warm water.
   - Do **not** 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)**.

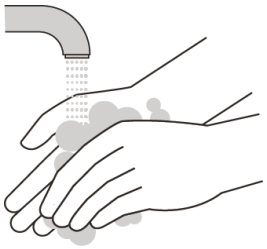


Figure H

Choose the injection site

11. Choose your injection site in either:
    - The lower part of your stomach (abdomen) or
    - The front middle of your thighs **(See Figure I)**.

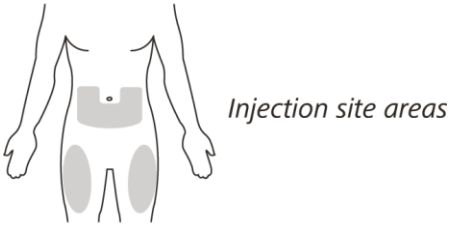


Figure I

- **Do not** select the 5 cm area around your belly button.
- **Do not** select areas with moles, scars, bruises, or areas where the skin is tender, red, hard or broken.

Choose a different injection site for **each new injection. Each new injection should be 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.
- Do **not** touch the injection site again before you give the injection.

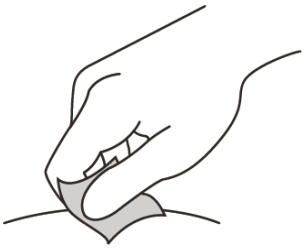


Figure J

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.
    - Do **not** put the needle cap back on once it has been removed as this may damage the needle.
    - Do **not** touch the needle or let it touch any surfaces after removing the needle cap.

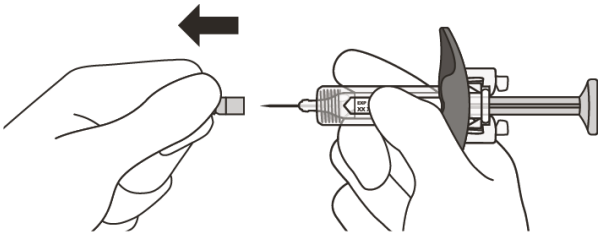


Figure K

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.
    - Do **not** change the angle of the injection.
    - Do **not** insert the needle again.

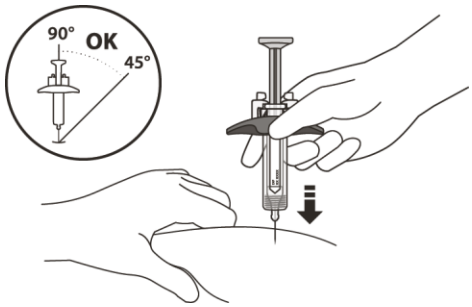


Figure L

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)**.

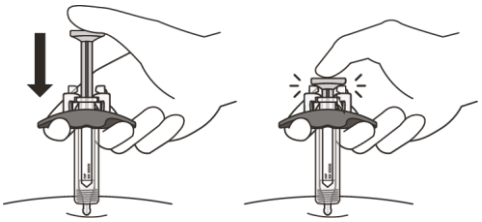


Figure M

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)**.

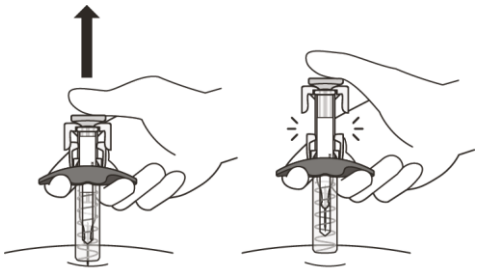


Figure N

- **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 professional 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 professional.
- Do **not** dispose of your used sharps disposal container in your household waste.
- Do **not** recycle your used sharps disposal container.

Overdose:
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 healthcare professional.

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 think you have taken too much ENSPRYNG, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

If your healthcare professional is giving your injections and you miss an appointment, make another one right 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 healthcare professional if you are not sure.

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 healthcare professional.

What are possible side effects from using ENSPRYNG?

These are not all the possible side effects you may feel when taking ENSPRYNG. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of ENSPRYNG include:

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 right 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 sick to your stomach or vomiting
- diarrhea
- fast heart rate, fluttering or pounding heart (heart palpitations)

You may experience the following other side effects:

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 levels of fibrinogen, a type of blood clotting protein shown in tests
- low levels of white blood cells as shown in blood tests
- high levels of bilirubin, a yellowish substance formed in the liver, as shown in a blood test

Your doctor may also test your blood to check for other abnormal test results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver enzyme increase: • yellowing of the skin and the whites of the eyes (jaundice) • dark coloured urine • feeling sick to your stomach or vomiting		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- 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 to 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.

If you want more information about ENSPRYNG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

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