PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSAPHNELO™

anifrolumab for injection

solution, 150 mg / mL, intravenous infusion

Type I interferon (IFN) receptor antagonist

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RECENT MAJOR LABEL CHANGES

Not Applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SAPHNELO (anifrolumab for injection) is indicated in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE).

The safety and efficacy of SAPHNELO have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of SAPHNELO is not recommended in these situations.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Differences in safety or effectiveness between patients ≥ 65 years and younger patients who received anifrolumab in clinical trials have not been determined due to limited clinical trial experience in geriatric patients. See 7.1 Special Populations.

2 CONTRAINDICATIONS

SAPHNELO 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of SAPHNELO is 300 mg, administered as an intravenous (IV) infusion over a 30-minute period, every 4 weeks.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age): Based on population pharmacokinetic (PK) modeling, no dose adjustment is required. There is limited information in geriatric subjects as only 20 patients ≥ 65 years of age were included in the population PK analysis (see Special Populations and Conditions).

Renal Impairment: Based on population PK modeling, no dose adjustment is required. No specific studies with SAPHNELO have been conducted in patients with renal impairment. There is no experience in patients with severe renal impairment or end-stage renal disease (see Special Populations and Conditions).

Hepatic Impairment: Based on population PK modeling, no dose adjustment is required. No specific studies have been conducted in patients with hepatic impairment (see Special Populations and Conditions).

4.3 Reconstitution

SAPHNELO is supplied as a single-dose vial. The solution for infusion should be prepared and administered by a health professional, using aseptic technique as follows:

1. Visually inspect the vial for particulate matter and discolouration. SAPHNELO is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.

2. Withdraw and discard 2.0 mL from an infusion bag containing 50 mL or 100 mL of normal saline (USP).

3. Withdraw 2.0 mL from the vial of SAPHNELO and add it to the infusion bag. Mix the solution by gentle inversion. Do not shake.

4. Each vial is intended for one time use only. Discard any unused portion remaining in the vial.

4.4 Administration

SAPHNELO is for IV use.

Following dilution with normal saline (USP), SAPHNELO is administered as an IV infusion over a 30-minute period by a health professional trained to give infusion therapy. It should not be administered as an IV push or bolus injection.

1. Administer the infusion solution immediately after preparation.

2. If the infusion solution is not administered immediately, store the diluted solution of SAPHNELO at room temperature (15°C to 25°C) for up to 4 hours, or refrigerated (2°C to 8°C) for up to 24 hours. Do not freeze. Protect from light. If the solution for infusion has been stored in a refrigerator (see 11 STORAGE, STABILITY AND DISPOSAL), allow it to reach room temperature prior to administration.

3. Administer the infusion solution intravenously over 30 minutes through an IV line containing a sterile, low-protein binding 0.2 to 15 micron in-line or add-on filter.

4. To ensure the complete dose of SAPHNELO has been administered, flush the infusion set with 25 mL normal saline (USP) at the end of the infusion.

5. Do not co-administer other medicinal products through the same infusion line.

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

Health professionals should be prepared to manage hypersensitivity reactions, including anaphylaxis, and infusion-related reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, immediately interrupt the administration of SAPHNELO and initiate appropriate therapy.

4.5 Missed Dose

If a planned infusion is missed, administer SAPHNELO as soon as possible. A minimum interval of 14 days should be maintained between doses.

5 OVERDOSAGE

In clinical trials, doses of up to 1000 mg have been administered intravenously in patients with SLE with no evidence of dose limiting toxicities.

There is no specific treatment for an overdose with anifrolumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

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

6 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 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Single dose, sterile vial solution of 300 mg anifrolumab / 2.0 mL concentrate solution for infusion	L-Histidine, L-Histidine hydrochloride monohydrate, L-Lysine hydrochloride, Polysorbate 80, Trehalose dihydrate, Water for injection.

Dosage Form Description
SAPHNELO is a sterile, preservative-free, liquid dosage form intended for IV infusion after dilution.

Packaging
2.0 mL of concentrate in a 2R clear type I glass vial closed by a Teflon faced elastomeric stopper sealed with an aluminium overseal. Available in a carton containing one single-dose vial.

7 WARNINGS AND PRECAUTIONS

General

Concomitant Use with Other Biologic Therapies
SAPHNELO has not been studied in combination with other biologic therapies, including B-cell targeted therapies. Therefore, use of SAPHNELO is not recommended for use in combination with biologic therapies.

Carcinogenesis and Mutagenesis

Malignancy
The effect of treatment with SAPHNELO on the development of malignancies is not known. As with other immunomodulating agents, the mechanism of action of SAPHNELO could increase the risk for the development of malignancies. Studies in patients with a history of malignancy have not been conducted.

In controlled 52-week clinical trials, at any dose, malignancies (excluding non-melanoma skin cancers) were observed in 0.7% (5/657) and 0.6% (3/466) of patients receiving SAPHNELO and placebo, respectively. Malignant neoplasm (including non-melanoma skin cancers) was reported for 8/657 (1.2%) patients receiving anifrolumab, compared to 3/466 (0.6%) patients receiving placebo. In patients receiving anifrolumab, breast and squamous cell carcinoma were the malignancies observed in more than one patient.

Immune

Infections
SAPHNELO increases the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been observed). Serious and sometimes fatal infections have occurred in patients receiving SAPHNELO. Overall, the incidence of serious infections in controlled 52-week clinical trials was similar in patients receiving SAPHNELO compared to placebo, whereas fatal infections occurred more frequently in patients receiving SAPHNELO compared with placebo (see 8 ADVERSE REACTIONS).

Studies in patients with a history of primary immunodeficiency have not been conducted.

Due to the mechanism of action, SAPHNELO should be used with caution in patients with a chronic infection, a history of recurrent infections, or known risk factors for infection. Treatment with SAPHNELO should not be initiated in patients with any clinically significant active infection until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms of a clinically significant infection occur. If a patient develops an infection, or is not responding to standard therapy, monitor the patient closely and consider interrupting SAPHNELO therapy until the infection resolves.

Immunizations
No data are available on the response to live or attenuated vaccines. Avoid concurrent use of live or attenuated vaccines in patients treated with SAPHNELO.

Prior to initiating therapy with SAPHNELO, consider completion of all appropriate immunizations according to current immunization guidelines.

Reproductive Health: Female and Male Potential

Fertility
There are no data on the effects of anifrolumab on human fertility. See 7.1.1 Pregnant Women.

In the 39-week repeat-dose toxicity study conducted in monkeys administered anifrolumab, one male in each of the high-dose IV and subcutaneous (SC) groups showed altered spermatogenesis and/or seminiferous tubular degeneration. A drug-related effect could not be ruled out (see 16 NON-CLINICAL TOXICOLOGY).

Sensitivity/Resistance

Hypersensitivity
Serious hypersensitivity reactions (including anaphylaxis) and angioedema have been reported following SAPHNELO administration. There was one event of anaphylactic reaction in the SLE development program following administration of anifrolumab (see 8 ADVERSE REACTIONS).

SAPHNELO should be administered by health professionals prepared to manage hypersensitivity reactions, including anaphylaxis, and infusion-related reactions. If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, immediately interrupt administration of SAPHNELO and initiate appropriate therapy.

7.1 Special Populations

7.1.1 Pregnant Women

There is limited data on the use of anifrolumab in pregnant women.

In a pre- and post-natal development study, pregnant cynomolgus monkeys given IV anifrolumab showed an increased incidence of embryo-fetal loss compared to controls (see 16 NON-CLINICAL TOXICOLOGY).

Immunoglobulin G (IgG) antibodies, including anifrolumab, can cross the placenta. SAPHNELO is not recommended during pregnancy and in women of childbearing potential not using contraception.

7.1.2 Breast-feeding

The safety of SAPHNELO for use during lactation has not been established. It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys administered, 30 or 60 mg/kg, intravenously every 2 weeks (see 16 NON-CLINICAL TOXICOLOGY).

A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue SAPHNELO therapy.

7.1.3 Pediatrics

No data were made available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 664 patients with SLE exposed to SAPHNELO in clinical trials, 3% (n=20) were 65 years and over. Patients >70 years of age were not enrolled in clinical trials. Differences in safety or efficacy between these patients and younger patients have not been determined due to limited clinical trial experience in geriatric patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the 52-week controlled clinical trials (studies 1013, 05 and 04) in patients with moderate to

severe, active SLE who received IV anifrolumab 300 mg or placebo every 4 weeks, adverse events were reported in 86.9% of patients receiving anifrolumab and 79.4% of patients receiving placebo. The most commonly reported adverse events (≥ 5%) during anifrolumab treatment, irrespective of causality, were nasopharyngitis (16.3%, placebo: 9.4%), upper respiratory tract infection (15.5%, placebo: 9.7%), urinary tract infection (12.0%, placebo: 13.5%), bronchitis (9.8%, placebo: 4.3%), infusion related reaction (9.4%, placebo: 7.1%), headache (8.1%, placebo: 9.7%), herpes zoster (6.1%, placebo: 1.3%), back pain (5.2%, placebo: 4.3%), sinusitis (5.2%, placebo: 5.2%) and cough (5.0%, placebo: 3.2%).

During the controlled 52-week clinical trials, the proportion of patients with serious adverse events was 11.8% for anifrolumab and 16.7% for placebo.

The proportion of patients who discontinued treatment due to adverse events was 4.1% for anifrolumab and 5.2% for placebo.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of anifrolumab was evaluated through 52 weeks in patients with moderate to severe, active SLE who received 300 mg by IV infusion every 4 weeks (N=459) compared to placebo (N=466) in controlled clinical trials (Studies 1013, 05 and 04). The population studied had a mean age of 41 years (range: 18 to 69), of which 93% were female, 60% White, 13% Black/African American, and 10% Asian.

Adverse events, irrespective of causality that occurred at a frequency greater than or equal to 1% and more frequently in the SAPHNELO group are shown in Table 2.

Table 2 Adverse Events Occurring in ≥ 1% of Patients with Moderate or Severe, Active SLE on SAPHNELO 300 mg and ≥ 1% More Frequently Than in Patients Receiving Placebo at 52 Weeks (Study 1013, Study 05 and Study 04)

	SAPHNELO n = 459 (%)	Placebo n = 466 (%)
Gastrointestinal disorders		
Vomiting	18 (3.9%)	12 (2.6%)
General disorders and administration site conditions		
Edema peripheral	10 (2.2%)	4 (0.9%)
Chest pain	8 (1.7%)	1 (0.2%)
Immune system disorders		
Hypersensitivity	13 (2.8%)	3 (0.6%)
Infections and infestations		
Pharyngitis[a]	89 (19.4%)	56 (12.0%)
Respiratory tract infection[b]	84 (18.3%)	47 (10.1%)
Bronchitis	45 (9.8%)	20 (4.3%)
Herpes Zoster	28 (6.1%)	6 (1.3%)
Oral herpes	17 (3.7%)	12 (2.6%)
Injury, poisoning and procedural complications		
Infusion related reaction	43 (9.4%)	33 (7.1%)
Musculoskeletal and connective tissue disorders		
Arthralgia	22 (4.8%)	9 (1.9%)
Pain in extremity	11 (2.4%)	3 (0.6%)
Psychiatric disorders		
Depression	13 (2.8%)	8 (1.7%)
Respiratory, thoracic and mediastinal disorders		
Cough	23 (5.0%)	15 (3.2%)

All patients received standard therapy.

[a] Pharyngitis (nasopharyngitis, pharyngitis)

[b] Respiratory tract infection (upper respiratory tract infection, respiratory tract infection)

Long-term safety

Patients who completed Studies 05 and 04 (Phase III feeder trials) through Week 52 were eligible to continue on treatment in a randomized, double-blind, placebo-controlled LTE for an additional 3 years (study 09). The long-term safety of SAPHNELO was assessed in 257 patients who received anifrolumab 300 mg administered by intravenous infusion once every 4 weeks, compared to 112 patients who received placebo, in both a feeder trial and the LTE. Of these, 177 patients who received SAPHNELO (68.9%) and 52 patients who received placebo (46.4%) completed a total of 4 years on treatment. The overall long-term safety profile of anifrolumab was consistent with the 52-week trials.

Hypersensitivity
There was one report of an anaphylactic reaction in a patient who received 150 mg anifrolumab and four reports of angioedema in patients who received 300 mg anifrolumab in the SLE development program (see 7 WARNINGS AND PRECAUTIONS).

In the 52-week controlled clinical trials, hypersensitivity reactions occurred in 2.8% (13/459) of patients treated with SAPHNELO and 0.6% (3/466) of patients on placebo. Serious hypersensitivity events (including angioedema) were reported for 0.6% (3/459) of patients receiving anifrolumab.

Overall, hypersensitivity reactions were predominantly mild to moderate in intensity and did not lead to discontinuation of anifrolumab.

Infusion-Related Reactions
Infusion-related reactions were mild or moderate in intensity, the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness. Most occurred in the first 24 weeks of treatment.

In the 52-week controlled clinical trials, the incidence of infusion-related reactions was 9.4% (43/459) in patients on treatment with SAPHNELO and 7.1% (33/466) in patients on placebo.

Infections
In the 52-week controlled clinical trials, infections were reported in 69.7% (320/459) of patients while on treatment with SAPHNELO compared to 55.4% (258/466) on placebo.

In the controlled clinical trials, the incidence of serious infections while on treatment was 4.8% (22/459) in patients treated with SAPHNELO compared with 5.6% (26/466) in patients receiving placebo. The most frequent serious infection was pneumonia.

In the controlled clinical trials, fatal infections occurred in 0.4% of patients receiving SAPHNELO and 0.2% of the patients receiving placebo (see 7 WARNINGS AND PRECAUTIONS).

Herpes Zoster
Herpes zoster infections were predominantly of localized cutaneous presentation, mild or moderate in intensity and resolved without discontinuation of anifrolumab.

In the 52-week controlled clinical trials, the incidence of herpes zoster in patients while on treatment with SAPHNELO was 6.1% (28/459) and 1.3% (6/466) in patients on placebo. Of the 28 SAPHNELO treated patients with herpes zoster, 2 experienced disseminated disease requiring hospitalization compared to none among patients who received placebo (see 7 WARNINGS AND PRECAUTIONS).

The incidence rate of herpes zoster was highest in the first year of treatment (52-week controlled clinical trials). Subsequently, in the LTE, the incidence rate of herpes zoster in patients who continued to be treated with SAPHNELO decreased over time.

8.3 Less Common Clinical Trial Adverse Reactions (< 1%)

Adverse events reported in < 1% of patients on SAPHNELO 300 mg treatment group in studies 1013, 05 and 04, and occurring ≥ 0.5% more frequently in anifrolumab than placebo are summarized below.

Eye disorders: vision blurred

Gastrointestinal disorders: food poisoning, hemorrhoidal hemorrhage, hemorrhoids

General disorders and administration site conditions: asthenia

Infections and infestations: abscess limb, appendicitis, candida infection, ear infection, latent tuberculosis, otitis externa, otitis media, tinea versicolour, viral pharyngitis

Injury, poisoning and procedural complications: animal bite, ligament rupture, meniscus injury, skin laceration

Investigations: blood pressure increased

Metabolism and nutrition disorders: diabetes mellitus, hyperglycemia

Musculoskeletal and connective tissue disorders: costochondritis, intervertebral disc protrusion, neck pain

Neoplasms benign, malignant and unspecified (including cysts and polyps): skin papilloma

Nervous system disorders: carpal tunnel syndrome, cervicobrachial syndrome, hypoesthesia, post herpetic neuralgia, restless legs syndrome

Renal and urinary disorders: renal colic, urinary retention

Respiratory, thoracic and mediastinal disorders: pleural effusion, productive cough

Skin and subcutaneous tissue disorders: acne, dermatitis allergic, eczema, ingrowing nail

Vascular disorders: hematoma

9 DRUG INTERACTIONS

9.3 Drug-Behaviour Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

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

In the controlled SLE clinical trials, anifrolumab was administered concomitantly with standard therapies including oral corticosteroids, anti-malarials, immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine), NSAIDs, ACE

inhibitors, and HMG-CoA reductase inhibitors. In a population PK analyses of the Phase III trials, co-administration of these medicines did not significantly affect the PK of anifrolumab. The effect of anifrolumab on the PK of these drugs has not been evaluated.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1) with high specificity and affinity. This binding inhibits type I IFN signalling thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalization of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signalling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes.

Type I IFNs play an important role in the pathogenesis of SLE. Most adult patients with SLE (approximately 60-80%) express elevated levels of type I IFN inducible genes, which are associated with increased disease activity and severity.

10.2 Pharmacodynamics

In adult patients with SLE, administration of anifrolumab at doses ≥ 300 mg, via IV infusion every 4 weeks, demonstrated consistent neutralization (≥ 80%) of a 21 gene type I interferon pharmacodynamic (PD) signature in blood. This suppression occurred as early as 4 weeks post-treatment and was maintained over the 52-week treatment period.

Following withdrawal of anifrolumab at the end of the 52-week treatment period in the SLE clinical trials, the type I IFN PD signature in blood samples returned to baseline levels within 8 to 12 weeks.

In the Phase III trials in SLE patients positive for anti-dsDNA antibodies at baseline, treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies at week 52. In patients with low complement C3 and C4 levels, increases in complement levels were observed in patients treated with anifrolumab through week 52.

<u>Cardiac Electrophysiology</u>

Cardiac electrophysiology in the controlled Phase III studies of SAPHNELO administered to patients with moderate to severe, active SLE, detected no patients with QTc > 500 ms or an

increase from baseline in QTc interval > 60 ms, following treatment with SAPHNELO at 300 mg every 4 weeks for 52 weeks (N = 360).

10.3 Pharmacokinetics

The PK of anifrolumab was studied in adult patients with SLE following IV doses ranging from 100 to 1000 mg, once every 4 weeks, and healthy volunteers following a single dose. Consistent with target-mediated drug disposition, anifrolumab exhibits nonlinear PK in the dose range of 100 mg to 1000 mg with more than dose proportional increases in exposure measured with C_{trough} and AUC, and dose proportional increases in exposure measured with C_{max}. Following administration of 300 mg anifrolumab every 4 weeks, steady-state C_{max} and C_{trough} was reached at Day 84. The accumulation ratio was approximately 1.36 for C_{max} and 2.49 for C_{trough}.

Table 3 Population Pharmacokinetic Parameters After Dosing With Anifrolumab 300 mg IV Q4W for 1 year

Pharmacokinetic Parameter[a]	Anifrolumab 300 mg IV Q4W for 1 year
C_{max}, µg/mL	121
AUC_T, µg*day/mL	1152
C_{trough}, µg/mL	19.0
CL, L/day	0.193
Central V_d, L	2.93
Peripheral V_d, L	3.30

[a] Data are for a typical patient with body weight of 69.1 kg.

AUC_T: area under the concentration-time curve from time zero to the end of the dosing period; C_{max}: maximum observed concentration; C_{trough}: trough serum concentration; CL: clearance; V_d: volume of distribution; IV: intravenous; Q4W: administered once every 4 weeks

Absorption: Anifrolumab is administered by IV infusion.

Distribution: Based on the population PK analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 2.93 L (with 26.9% CV inter-individual variability) and 3.3 L, respectively for a 69.1 kg patient.

Metabolism: Anifrolumab is a protein, therefore specific metabolism studies have not been conducted.

Anifrolumab is eliminated by target IFNAR mediated elimination pathway and reticuloendothelial system, where anifrolumab is expected to be degraded into small peptides and individual amino acids by proteolytic enzymes that are widely distributed in the body.

Elimination: Anifrolumab has non-linear elimination kinetics due to IFNAR1-mediated drug clearance.

From population PK modelling the estimated typical systemic clearance (CL) was 0.193 L/day with a 33.0% CV inter individual variability. The median CL decreases slowly over time, with 8.4% after 1 year of treatment. Following long-term observations, the clearance of anifrolumab was found to be stable in years 2 through 4 on treatment.

Special Populations and Conditions

Based on the population PK analysis, there was no clinically meaningful difference in systemic clearance based on age, race, ethnicity, region, gender, IFN status or body weight, that requires dose adjustment.

Geriatrics (≥ 65 years): Based on the population PK analysis, age (range 18 to 69 years) did not impact the clearance of anifrolumab. Limited PK information is available in this population as only 20 (3%) patients ≥ 65 years of age were included in the population PK analysis.

Renal Insufficiency: No specific clinical studies have been conducted to investigate the effect of renal impairment on anifrolumab. Based on population PK analyses, anifrolumab clearance was comparable in SLE patients with mild (60-89 mL/min/1.73 m^2) and moderate decrease in eGFR (30-59 mL/min/1.73 m^2) values and patients with normal renal function (≥ 90 mL/min/1.73 m^2). SLE patients with a severe decrease in eGFR or end stage renal disease (< 30 mL/min/1.73 m^2) were excluded from the clinical trials.

Patients with urine protein/creatinine ratio (UPCR) > 2 mg/mg were excluded from the clinical trials. Based on population PK analyses, increased UPCR did not significantly affect anifrolumab clearance.

Hepatic Insufficiency: No specific clinical studies have been conducted to investigate the effect of hepatic impairment on anifrolumab.

Based on population pharmacokinetic analyses, baseline hepatic function biomarkers (ALT and AST ≤ 2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance.

11 STORAGE, STABILITY AND DISPOSAL

Unopened Vial

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

Diluted solution for infusion

For storage conditions after dilution of the medicinal product, see 4.4 Administration.

Disposal

For disposal, see 4.4 Administration.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: anifrolumab

Chemical name: human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

Molecular formula and molecular mass: Approximately 148 kDa (including oligosaccharides)

Structural formula: Anifrolumab is a human IgG1κ monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). The constant domain of the IgG heavy chain was intentionally modified (three amino acid changes) to eliminate FcγRI, FcγRIIA and FcγRIIB, FcγRIIIA and C1q binding. These mutations also eliminate the potential for antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Physicochemical properties: The extinction coefficient (determined experimentally using amino acid analysis) for anifrolumab is 1.39 $(mg/mL)^{-1}cm^{-1}$ and the isoelectric point (pI) (determined experimentally using capillary isoelectric focusing) is 7.6-8.5.

Product Characteristics: selectively binds to subunit 1 of the type I interferon receptor (IFNAR1), inhibiting type I IFN signaling and blocking the biologic activity of type I IFNs. SAPHNELO is produced in mouse myeloma cells (NS0) by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Systemic lupus erythematosus (SLE)

Trial Design and Study Demographics

Table 4 Summary of Patient Demographics for Clinical Trials in SLE

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex
CD-IA-MEDI-546-1013 'Study 1013' (MUSE)	Phase II, multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group study	SAPHNELO 300 mg,1000 mg or placebo IV, Q4W for 52 weeks (13 doses)	99 (300 mg) 104 (1000 mg) 102 (placebo)	39.1 (300 mg) 39.3 (placebo) 18-65	93.9% Female (SAPHNELO) 91.2% Female (placebo)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex
D3461C00004 'Study 04' (TULIP 2)	Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study	SAPHNELO 300 mg or placebo IV, Q4W for 52 weeks (13 doses).	180 (300 mg) 182 (placebo)	43.1 (300 mg) 41.1 (placebo) 18-69	91.7% female (SAPHNELO) 92.9% female (placebo)
D3461C00005 'Study 05' (TULIP 1)	Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study	SAPHNELO 150 mg, 300 mg, or placebo IV, Q4W for 52 weeks (13 doses)	93 (150 mg) 180 (300 mg) 184 (placebo)	42.0 (300 mg) 41.0 (placebo) 18-69	93.3% female (SAPHNELO) 93.4% female (placebo)

The safety and efficacy of SAPHNELO were evaluated in three 52-week treatment period, multicentre, randomized, double-blind, placebo-controlled studies Study 1013, Study 04 and Study 05. Patients were diagnosed with SLE according to the American College of Rheumatology (1997) classification criteria.

All patients were ≥ 18 to < 70 years of age and had moderate to severe, active, autoantibody positive disease, with a SLE Disease Activity Index 2000 (SLEDAI-2K) score ≥ 6 points, organ level involvement based on British Isles Lupus Assessment Group (BILAG) assessment (BILAG-2004 level A disease in ≥ 1 organ system or BILAG-2004 level B disease in ≥ 2 organ systems), and a Physician's Global Assessment [PGA] score ≥1, despite receiving standard SLE therapy consisting of either one or any combination of OCS, antimalarials and/or immunosuppressants at baseline. Patients continued to receive their existing SLE therapy at stable doses during the clinical trials, with the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol. Patients who had severe active lupus nephritis and patients who had severe active central nervous system lupus were excluded. The use of other biologic agents and cyclophosphamide were not permitted during the clinical trials; patients receiving other biologic therapies were required to complete a wash-out period of at least 5 half-lives prior to enrolment. All three studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by IV infusion, every 4 weeks.

The efficacy of SAPHNELO is based on assessment of clinical response at Week 52 using the composite endpoints, the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) and the SLE Responder Index (SRI-4).

BICLA response at Week 52, was defined as improvement in all organ domains with moderate or severe activity at baseline:

- Reduction of all baseline BILAG-A to B/C/D and baseline BILAG-B to C/D, and no BILAG worsening in other organ systems, as defined by ≥ 1 new BILAG-A or ≥ 2 new BILAG-B;
- No worsening from baseline in SLEDAI-2K, where worsening is as defined as an increase from baseline of >0 points in SLEDAI-2K;

- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No discontinuation of treatment;
- No use of restricted medication beyond the protocol-allowed thresholds.

SRI-4 response, was defined as meeting each of the following criteria at Week 52 compared with baseline:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K;
- No new organ system affected as defined by 1 or more BILAG-A or 2 or more BILAG-B items compared to baseline;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA visual analogue scale (VAS);
- No discontinuation of treatment;
- No use of restricted medication beyond the protocol-allowed thresholds.

Patient demographics and baseline disease characteristics for Study 1013, Study 05 and Study 04 are presented in Table 5.

Table 5 Patient Demographics and Baseline Disease Characteristics

	Total Population		
	Study 1013 (N = 305)	**Study 05 (N = 457)**	**Study 04 (N = 362)**
Mean Age (years)	40	41	42
Female (%)	93	92	93
White (%)	42	71	60
Black/African American (%)	13	14	12
Asian (%)	7	5	17
Hispanic or Latino (%)	42	19	30
Results of type I IFN gene signature Test – High (%)	75	82	83
Baseline SLEDAI-2K score			
Mean (SD)	10.9 (4.1)	11.3 (3.72)	11.5 (3.76)
≥10 points, n (%)	182 (60)	328 (72)	260 (72)
BILAG organ system scoring (Overall)			
At least one A, n (%)	152 (50)	217 (48)	176 (49)
No A and at least 2 Bs, n (%)	134 (44)	211 (46)	169 (47)
Positive Anti-dsDNA levels, n (%)	185 (77)	207 (45)	159 (44)
Abnormal ANA, n (%)	299 (98)	412 (90)	325 (90)
Abnormal Complement C3 level, n (%)	119 (39)	157 (34)	144 (40)
Abnormal Complement C4 level, n (%)	74 (24)	95 (21)	95 (26)
Baseline SLE treatment			
OCS, n (%)	258 (85)	381 (83)	292 (81)
Antimalarials, n (%)	219 (72)	334 (73)	252 (70)
Immunosuppressants, n (%)	150 (49)	214 (47)	174 (48)

Phase II Study

In Study 1013, 305 patients were randomized (1:1:1) and received anifrolumab, 300 mg or 1000 mg, or placebo. The 1000 mg dose is not recommended. The primary endpoint was a combined assessment of the SLE Responder Index (SRI-4, a composite endpoint) and the sustained reduction in OCS (<10 mg/day and ≤OCS dose at week 1, sustained for 12 weeks) measured at Week 24. BICLA response and SRI-4 response at Week 52 were pre-specified analyses.

Phase III Studies

Study 05 and Study 04 were similar in design. In Study 05, 457 patients were randomized (1:2:2) and received anifrolumab 150 mg or 300 mg, or placebo. In Study 04, 362 patients were randomized (1:1) and received anifrolumab 300 mg or placebo. The primary endpoint was improvement in disease activity evaluated at 52 weeks, measured by SRI-4 (in Study 05) and BICLA (in Study 04). Both studies evaluated the efficacy of anifrolumab 300 mg versus placebo; a dose of 150 mg was also evaluated for dose-response in Study 05. During weeks 8-40, patients with a baseline OCS ≥ 10 mg/day were required to taper their OCS dose to ≤ 7.5 mg/day, unless there was worsening of disease activity. Key secondary efficacy endpoints included in both studies were the maintenance of OCS reduction and annualized flare rate.

The most commonly affected organ systems (BILAG A or B at baseline) were the mucocutaneous (Study 05: 87%, Study 04: 85%) and musculoskeletal (Study 05: 89%, Study 04: 88%) systems.

For those patients taking OCS (prednisone or equivalent) at baseline, the mean daily dose was 12.3 mg in Study 05 and 10.7 mg in Study 04.

Randomisation was stratified by disease severity (SLEDAI 2K score at baseline, < 10 vs ≥ 10 points), OCS dose on Day 1 (<10 mg/day vs ≥ 10 mg/day prednisone or equivalent) and interferon gene signature test results (high vs low).

Phase III long-term extension Study

Patients who completed Studies 05 and 04 (feeder trials) were eligible to continue on treatment in a randomized, double-blind, placebo-controlled, 3-year LTE (Study 09). Patients who had received anifrolumab, either 150 mg or 300 mg, in Study 05 and 04 received anifrolumab 300 mg in Study 09. Patients who had received placebo in Study 05 and 04 were re-randomized 1:1 to receive either anifrolumab 300 mg or placebo, giving an approximate anifrolumab 300 mg: placebo ratio of 4:1 in Study 09.

Study Results

Study 1013

Pre-specified analysis of disease activity measured by BICLA response was 53.3% for anifrolumab and 25.1%, placebo at Week 52. Pre-specified analysis of disease activity measured by SRI-4 response was 62.8% for anifrolumab and 38.8% for placebo at Week 52.

Study 05 and Study 04

The BICLA and SRI-4 results are presented in Table 6 and Table 7, respectively.

Table 6 Results of Study 05 and Study 04: BICLA Response Rate at Week 52

	Study 05		Study 04	
Efficacy Parameter	**SAPHNELO 300mg (N=180)**	**Placebo (N=184)**	**SAPHNELO 300mg (N=180)**	**Placebo (N=182)**
BICLA response rate[a]				
Responder, n (%)	85 (47.1)	55 (30.2)	86 (47.8)	57 (31.5)
Difference in Response Rates (95% CI)	17.0 (7.2, 26.8)[b]		16.3 (6.3, 26.3)[c] p-value = 0.001	
Components of BICLA response[a]				
BILAG improvement, n (%) [a]	85 (47.2)	58 (31.5)	88 (48.9)	59 (32.4)
No worsening of SLEDAI-2K, n (%) [a]	121 (67.2)	104 (56.5)	122 (67.8)	94 (51.6)
No worsening of PGA, n (%) [a]	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)

The response rates and associated difference and 95% CI are calculated using a Cochran-Mantel-Haenszel approach adjusted for stratification factors. The reported percentages for the components are unadjusted.

All patients received investigational product in addition to standard therapy.

The most commonly affected organ systems at baseline (BILAG A or B) were mucocutaneous and musculoskeletal.

[a] Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders. For consistency, the results presented for Study 05 represent the post-hoc analysis using the restricted medication thresholds as defined in Study 04.

[b] In Study 05, BICLA was not formally tested in a pre-specified testing scheme

[c] In Study 04, the primary endpoint was amended from SRI-4 response to BICLA response at Week 52 following review of the results from Study 05, which failed to achieve a statistically significant treatment benefit using SRI-4 response (See Table 7)

BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG: British Isles Lupus Assessment Group; PGA: Physician's Global Assessment; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure 1 shows the proportion of BICLA responders over time in Study 04.

Figure 1 Proportion (%) of BICLA Responders Over Time in Study 04

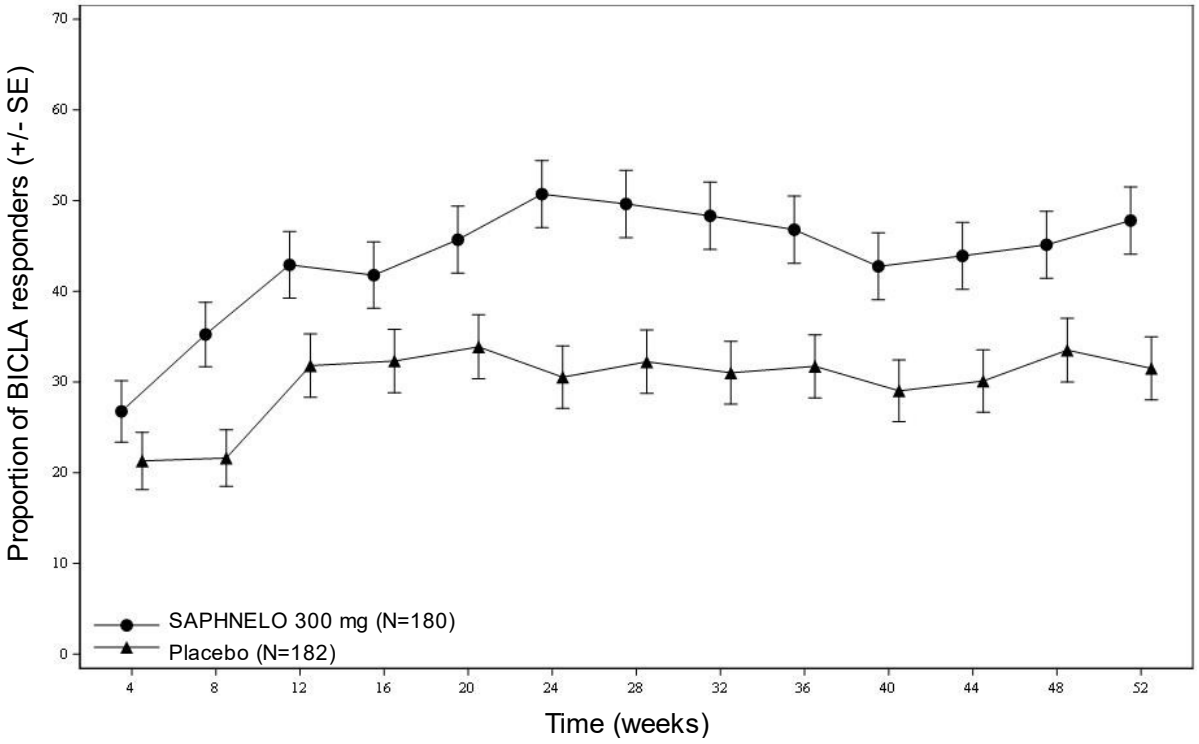

Table 7 Results of Study 05 and Study 04: SRI-4 Response at Week 52

	Study 05		Study 04	
Efficacy Parameter	**SAPHNELO 300 mg (N=180)**	**Placebo (N=184)**	**SAPHNELO 300 mg (N=180)**	**Placebo (N=182)**
SRI-4 Response Rate[a]				
Responder, n (%)	88 (49.0)	79 (43.0)	100 (55.5)	68 (37.3)
Difference in Response Rates (95% CI)	6.0 (-4.2, 16.2)[b]		18.2 (8.1, 28.3)[c]	
Components of SRI-4 Response[a]				
SLEDAI-2K improvement, n (%)	89 (49.4)	80 (43.5)	101 (56.1)	71 (39.0)
No worsening of BILAG, n (%)	119 (66.1)	105 (57.1)	125 (69.4)	94 (51.6)
No worsening of PGA, n (%)	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)

The response rates and associated difference and 95% CI are calculated using a Cochran-Mantel-Haenszel approach adjusted for stratification factors. The reported percentages for the components are unadjusted.

All patients received investigational product in addition to standard therapy.

The most commonly involved SLEDAI-2K organ domains at baseline were mucocutaneous, musculoskeletal and immune

[a] Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders. For consistency, the results presented for Study 05 represent the post-hoc analysis using the restricted medication thresholds as defined in Study 04.

[b] In Study 05, SRI-4 response rate at Week 52 was the pre-specified primary endpoint

[c] In Study 04, SRI-4 response was not formally tested in a pre-specified testing scheme

SRI-4: SLE (systemic lupus erythematosus) Responder Index; BILAG: British Isles Lupus Assessment Group; PGA: Physician's Global Assessment; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

Effect on Concomitant Steroid Treatment: In Study 04, of the 47% (n=170) of patients with a baseline OCS use ≥10 mg/day, 51.5% (45/87) of patients in the SAPHNELO group and 30.2% (25/83) in the placebo group were able to reduce their OCS use to ≤ 7.5 mg/day at Week 40 maintained through to Week 52 (difference 21.2% [95% CI 6.8, 35.7]).

Effect on SLE Flares: Disease flare was defined as severe disease activity (BILAG-A) in one or more new organ system, or moderate disease activity (BILAG-B) in 2 or more new organ systems compared to the previous visit. In Study 04, annualized flare rate was 0.43 in the SAPHNELO group and 0.64 in the placebo group; rate ratio 0.67 [95% CI 0.48, 0.94].

Study 09

The long-term efficacy of anifrolumab was evaluated in patients who received anifrolumab 300 mg or placebo in a feeder trial and continued to receive the same treatment in the LTE (anifrolumab N = 257; placebo N = 112). Of these, 69% of patients who received anifrolumab (177/257) and 46% of patients who received placebo (52/112) completed a total of 4 years on treatment. At Week 208, the mean SLEDAI-2K score (SE) was 3.4 (0.30) and 4.2 (0.47) in patients who received anifrolumab (n=140) and placebo (n=44), respectively.

14.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to anifrolumab in the trials described below with the incidence of antibodies in other trials or to other products may be misleading.

In the Phase III trials and the long-term extension, treatment-emergent anti-drug antibodies were detected in 9 out of 350 (2.6%) patients treated with SAPHNELO at the recommended dosing regimen for up to 4 years. A total of 0.3% (1/332) of patients treated with SAPHNELO developed neutralising antibodies. The clinical relevance of the presence of anti-drug antibodies against anifrolumab is not known.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 9-month repeat-dose toxicity study, cynomolgus monkeys were administered vehicle or anifrolumab at doses of 5 or 50 mg/kg IV once weekly and 15 or 60 mg/kg SC once weekly (5 or 58 times and 14 or 52 times the exposure at the maximum recommended human dose [MRHD] on an AUC basis, respectively). At the end of the 9-month dosing phase, 2 males given 50 mg/kg/dose IV had test article-related inflammation of arteries (arteritis) in multiple organs. At the end of the 12-week recovery period, 3 males had test article-related inflammation of arteries in multiple organs, though less pronounced and less widespread: one each given 5 mg/kg/dose IV, 50 mg/kg/dose IV, and 60 mg/kg/dose SC. Based on the arterial inflammation observed, the no-observable-adverse-effect level (NOAEL) was 15 mg/kg/day for SC anifrolumab and could not be determined for IV anifrolumab.

Carcinogenicity
Carcinogenicity studies have not been conducted with anifrolumab.

Genotoxicity
Genotoxicity studies have not been conducted with anifrolumab.

Reproductive and Developmental Toxicology
Developmental toxicity
In a pre- and postnatal development study, pregnant cynomolgus monkeys were administered anifrolumab at doses of 30 or 60 mg/kg administered intravenously (approximately 12 or 28 times the exposure at the MRHD on an AUC basis) from Gestation Day 20, once every 2 weeks thereafter, throughout gestation to 1 month postpartum (approximately Lactation Day 28). Females given anifrolumab showed an increased incidence of embryo-fetal loss compared to controls (1/16 [6%], 5/17 [29%], and 3/16 [19%] in vehicle, low-, and high-dose groups, respectively). The incidences of these findings were within historical control values. The relevance of these findings to humans is not known. No adverse effects on maternal animals or their offspring were observed.

Fertility
Effects on male and female fertility have not been directly evaluated in animal studies. In the 9-month repeat-dose toxicity study, indirect measures of male or female fertility were assessed based on semen analysis, spermatogenesis staging, menses cycle, organ weights and histopathological findings in the reproductive organs, in cynomolgus monkeys administered anifrolumab at doses up to 50 mg/kg IV or 60 mg/kg SC once weekly. One male in each of the high-dose IV and SC groups showed altered spermatogenesis and/or seminiferous tubular degeneration, a drug-related effect could not be ruled out.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSAPHNELO™
anifrolumab for injection, intravenous infusion

Read this carefully before you start taking **SAPHNELO** and each time you get an infusion. 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 **SAPHNELO**.

What is SAPHNELO used for?

SAPHNELO is used for the treatment of:

- active lupus (systemic lupus erythematosus, SLE) in adults whose disease is not well controlled by other standard therapies (oral corticosteroids and/or immunosuppressants and/or antimalarials) they are also receiving. You will be given SAPHNELO as well as your standard therapy for lupus.

Lupus is a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation and organ damage. It can affect almost any organ in the body, including skin, joints, kidneys, brain and other organs, and can cause pain, rashes, fatigue, swelling in joints, and fevers.

How does SAPHNELO work?

SAPHNELO contains anifrolumab, a monoclonal antibody (a type of specialized protein) that blocks the action of a group of proteins called Type I Interferons (IFN). Type I Interferons are found at high levels in people with lupus and blocking them can reduce the inflammation in your body that causes the signs and symptoms of lupus.

SAPHNELO may help to reduce your lupus disease activity and the number of lupus flares you are experiencing. If you are taking medicines called 'oral corticosteroids', using SAPHNELO may also allow your healthcare professional to reduce your daily dose of the oral corticosteroids that are needed to help control your lupus.

What are the ingredients in SAPHNELO?

Medicinal ingredients: anifrolumab
Non-medicinal ingredients: L-Histidine, L-Histidine hydrochloride monohydrate, L-Lysine hydrochloride, Polysorbate 80, Trehalose dihydrate, Water for injection.

SAPHNELO comes in the following dosage forms:

150 mg/mL concentrate solution for infusion. Each 2.0 mL vial contains 300 mg anifrolumab. There is 1 vial in each pack.

Do not use SAPHNELO if:

- you are allergic to anifrolumab or to any ingredients in SAPHNELO. If you are not sure, talk to your healthcare professional before you are given SAPHNELO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before or while you are taking SAPHNELO. Talk about any health conditions or problems you may have, including if you:

- think you have had an allergic reaction to this medicine at any time
- get an infection or have symptoms of an infection
- have a long-term (chronic) infection or if you have an infection that keeps coming back.
- have, or have had, cancer.
- have recently received or plan to receive an immunization (vaccine). You should not be given certain types of vaccines while using SAPHNELO.

Other warnings you should know about:
Infections

- You may be at more risk of getting an infection when you are being treated with SAPHNELO, including infection of the airways and shingles.
- Signs of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; diarrhea or stomach pain; shingles (a red skin rash that can cause pain and burning). Tell your healthcare professional as soon as possible if you notice any signs indicating a possible infection.

Pregnancy

- Before you start treatment with SAPHNELO, tell your healthcare professional if you are pregnant or think you may be pregnant. Your healthcare professional will decide if you can be given SAPHNELO.
- Talk to your healthcare professional if you plan to become pregnant while on SAPHNELO. It is not known if SAPHNELO can harm your unborn baby.
- If you become pregnant while being treated with SAPHNELO, tell your healthcare professional. They will discuss with you whether you should stop treatment with SAPHNELO.

Breast-feeding

- Before you start treatment with SAPHNELO, tell your healthcare professional if you are breast-feeding. It is not known whether SAPHNELO is passed into breast milk. Your healthcare professional will discuss with you whether you should stop treatment with SAPHNELO while you are breast-feeding, or if you should stop breast-feeding.

Children and adolescents

- SAPHNELO should not be used in children and adolescents below 18 years of age.

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

The following may interact with SAPHNELO:

- certain types of vaccines. If you are not sure, talk to your healthcare professional before and during the use of SAPHNELO.

How to take SAPHNELO:
A healthcare professional will give you SAPHNELO, through a drip in your vein (intravenous infusion) over 30 minutes, every 4 weeks. The recommended dose is 300 mg.

Your healthcare professional will decide if you need to stop being given SAPHNELO. If you

have any further questions on the use of this medicine, ask your healthcare professional.

Usual dose:
The recommended dose is 300 mg, administered as an intravenous infusion over a 30 minute period, every 4 weeks.

Overdose:

If you think you, or a person you are caring for, have taken too much SAPHNELO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss an appointment to get SAPHNELO, call your healthcare professional as soon as possible to reschedule your appointment.

What are possible side effects from using SAPHNELO?
These are not all the possible side effects you may have when taking SAPHNELO. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects in SAPHNELO studies include joint pain and pain in the arms or legs. Uncommon side effects include neck pain, weakness and fatigue.

SAPHNELO can cause a reaction to the infusion or an allergic (*hypersensitivity*) reaction. In most cases these reactions are mild, but occasionally the reaction can be severe, such as anaphylaxis (uncommon, affecting up to 1 in 100 people).

Tell your healthcare professional immediately, or go to the emergency department of your nearest hospital, if you get any of the following symptoms of a serious allergic reaction (anaphylaxis):
- swelling of your face, tongue, or mouth
- and/or breathing difficulties
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)

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**	
COMMON			
Allergic (hypersensitivity) reactions which may include: • Wheezing • Itching • Rash • Hives • Nausea • Headache • Dizziness		✓	
Chest Pain		✓	

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**	
Depression: • New or worse depression • New or worse anxiety • Trouble sleeping (insomnia) • Other unusual changes in your behaviour or mood		✓	
Other infections, which may become serious: • Fever • Chills • Cough • Pain or burning with urination or urinating often • Vomiting, abdominal pain and/or diarrhea • Earache • Warm, red, or painful skin		✓	
Shingles (herpes zoster)		✓	
Swelling of limbs	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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:
Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month. Store at 2 to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Keep out of reach and sight of children.

If you want more information about SAPHNELO:

- 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4

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