ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 150 mg of anifrolumab*.

One vial of 2.0 ml of concentrate contains 300 mg of anifrolumab (150 mg/ml).

*Anifrolumab is a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

Excipient with known effect

Each vial contains 1 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to opalescent, colourless to slightly yellow, pH 5.9 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of SLE.

Posology

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

In patients with a history of infusion-related reactions, premedication (e.g., an antihistamine) may be administered before an infusion of anifrolumab (see section 4.4).

Missed dose
If a planned infusion is missed, treatment should be administered as soon as possible. A minimum interval of 14 days should be maintained between doses.

Special populations

Elderly
No dose adjustment is required. There is limited information in subjects aged ≥65 years (n=33); no data are available in patients over 75 years of age (see section 5.2).

Renal impairment
No dose adjustment is required. There is no experience in patients with severe renal impairment or end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is required (see section 5.2).

Paediatric population
The safety and efficacy of Saphnelo in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

For intravenous use.

Saphnelo must not be administered as an intravenous push or bolus injection.

Following dilution with sodium chloride 9 mg/ml (0.9%) solution for injection, Saphnelo is administered as an infusion over 30 minutes through an intravenous infusion line containing a sterile, low-protein binding 0.2 to 15 micron in-line or add-on filter.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction.

Upon completion of the infusion, the infusion set should be flushed with 25 ml sodium chloride 9 mg/ml (0.9%) solution for injection to ensure that all of the solution for infusion has been administered.

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

For instructions on dilution of the medicinal product before administration, see section 6.6.

Transitioning between routes of administration
If transitioning a patient from subcutaneous administration to intravenous administration, the first intravenous infusion should be administered approximately 3 to 4 weeks after the last subcutaneous dose.

If transitioning a patient from intravenous administration to subcutaneous administration, the first subcutaneous injection should be administered approximately 2 weeks after the last intravenous dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Patient groups excluded from clinical studies

Anifrolumab has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, treatment with anifrolumab is not recommended in combination with biologic therapies.

Anifrolumab has not been studied in patients with severe active central nervous system lupus or severe active lupus nephritis (see section 5.1).

Hypersensitivity

Serious hypersensitivity reactions including anaphylaxis have been reported following administration of anifrolumab (see section 4.8).

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, serious hypersensitivity reactions (including angioedema) were reported for 0.5% of patients receiving anifrolumab.

In patients with a history of infusion-related reactions and/or hypersensitivity, premedication (e.g., an antihistamine) may be administered before the infusion of anifrolumab (see section 4.2).

If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, administration of anifrolumab should be interrupted immediately, and appropriate therapy initiated.

Infections

Anifrolumab increases the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been observed), see section 4.8. SLE patients also taking immunosuppressants may be at higher risk of herpes zoster infections.

In controlled-clinical trials serious and sometimes fatal infections (including pneumonia) occurred, including in patients receiving anifrolumab.

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

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

The placebo-controlled clinical trials excluded patients with a history of active TB or latent TB in whom an adequate course of treatment could not be confirmed. Anti-tuberculosis (anti-TB) therapy should be considered prior to initiation of anifrolumab in patients with untreated latent TB. Anifrolumab should not be administered to patients with active TB.

Immunisations

Prior to initiating therapy, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Concurrent use of live or attenuated vaccines should be avoided in patients treated with anifrolumab.

Immune responses to non-live vaccines have been assessed in a small number of patients (see section 4.5).

Malignancy

The impact of treatment with anifrolumab on the potential development of malignancies is not known. Studies in patients with a history of malignancy have not been conducted; however, patients with squamous or basal cell skin cancers and uterine cervical cancer that had been fully excised or adequately treated were eligible for enrolment in the SLE clinical trials.

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, malignant neoplasm (including non-melanoma skin cancers) was reported for 1.1% of patients receiving anifrolumab compared to 0.5% patients receiving placebo (exposure-adjusted incidence rate [EAIR]: 1.1 and 0.5 events per 100 patient years [PY], respectively). Malignancies excluding non-melanoma skin cancers were observed in 0.5% and 0.5% of patients receiving anifrolumab and placebo, respectively. In patients receiving anifrolumab, breast and squamous cell carcinoma were the malignancies observed in more than one patient.

Individual benefit-risk should be considered in patients with known risk factors for the development or reoccurrence of malignancy. Caution should be exercised when considering continuing therapy for patients who develop malignancy.

Excipient with known effect

This medicinal product contains 1 mg of polysorbate 80 (E 433) in each vial, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Anifrolumab is not expected to undergo metabolism by hepatic enzymes or renal elimination.

The formation of some CYP450 enzymes is suppressed by increased levels of certain cytokines during chronic inflammation. Anifrolumab modestly suppresses the levels of some cytokines; the impact on CYP450 activity is unknown. In patients who are being treated with other medicines that are CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin), therapeutic monitoring is recommended.

Immune response

Non-live vaccines
Immune response to non-live seasonal influenza vaccine was assessed in a small number of adult patients with moderate to severe SLE in an exploratory study. Humoral antibody responses induced by seasonal influenza virus vaccination were numerically comparable between patients receiving anifrolumab in addition to standard of care and those receiving standard of care alone.

Live vaccines
The concurrent use of anifrolumab with live and live-attenuated vaccines has not been studied (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of Saphnelo in pregnant women.

Animal studies are inconclusive with respect to reproductive toxicity (see section 5.3).

Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

Breast-feeding

It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue from Saphnelo therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans.

Animal studies show no adverse effects of anifrolumab on indirect measures of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during anifrolumab treatment were upper respiratory tract infection (31%), bronchitis (10%), infusion-related reaction (9.4%) and herpes zoster (6.0%). The most common serious adverse reaction was herpes zoster (0.4%).

Tabulated list of adverse reactions

Adverse reactions reported from controlled clinical trials and post-marketing data are classified by MedDRA System Organ Class (SOC), see Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).

Table 1 Adverse reactions

MedDRA SOC	**MedDRA Preferred Term**	**Frequency**
Infections and infestations	Upper respiratory tract infection*	Very common
	Bronchitis*	Very common
	Herpes zoster	Common
	Respiratory tract infection*	Common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic reaction	Uncommon§
Musculoskeletal and connective tissue disorders	Arthralgia	Not known

MedDRA SOC	MedDRA Preferred Term	Frequency
Injury, poisoning and procedural complications	Infusion-related reaction‡	Common

* Grouped terms: Upper respiratory tract infection (including Upper respiratory tract infection, Nasopharyngitis, Pharyngitis); Bronchitis (including Bronchitis, Bronchitis viral, Tracheobronchitis); Respiratory tract infection (including Respiratory tract infection, Respiratory tract infection viral, Respiratory tract infection bacterial).
§ See 'Description of selected adverse reactions' below and section 4.4.
‡ Applies to intravenous infusion route of administration only.

Long-term safety

Patients who completed Trials 1 and 2 (Phase III intravenous trials) through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled long-term extension (LTE) for an additional 3 years (see section 5.1). The overall long-term safety profile of intravenous anifrolumab was consistent with the 52-week trials.

Description of selected adverse reactions

Hypersensitivity
In controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of hypersensitivity reactions was 2.5% in the anifrolumab group and 0.5% in the placebo group. Hypersensitivity reactions were predominantly mild to moderate in intensity. One event of hypersensitivity in the subcutaneous trial led to discontinuation of anifrolumab.

In the intravenous clinical trials of 52-week treatment duration, all hypersensitivity reactions were reported within the first 6 infusions. One serious adverse reaction of hypersensitivity was reported during the patient's first infusion; the patient continued to receive anifrolumab with premedication given for subsequent infusions.

In the SLE development program, anaphylactic reaction was reported in one patient, which occurred following the intravenous administration of 150 mg anifrolumab, the patient was treated and recovered (see section 4.4).

Infusion-related reactions
In the controlled intravenous clinical trials of 52-week treatment duration, the incidence of infusion-related reactions was 9.4% in the anifrolumab group and 7.1% in the placebo group. Infusion-related reactions were mild or moderate in intensity (the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness); none were serious, and none led to discontinuation of anifrolumab. Infusion-related reactions were most commonly reported at the start of treatment, on the first and second infusions, with fewer reports on subsequent infusions.

Respiratory infections
In the controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence rates for anifrolumab compared to placebo were: upper respiratory tract infection (30.9% vs 20.3%), bronchitis (10.2% vs 5.2%) and respiratory tract infection (3.0% vs 1.4%). Infections were predominantly non-serious, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy (see section 4.4).

Herpes zoster
In the controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of herpes zoster infections was 6.0% in the anifrolumab group and 1.4% in the placebo group (see section 4.4). The mean time to onset in patients receiving anifrolumab was 129 days (range 2-351 days).

In the LTE (intravenous administration), incidence rates decreased over time.

Herpes zoster infections were predominantly of localised cutaneous presentation, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy. Cases with multidermatomal involvement and cases of disseminated disease (including central nervous system involvement) have been reported (see section 4.4).

Immunogenicity

In the intravenous Phase III trials, treatment-emergent anti-drug antibodies were detected in 6 out of 352 patients (1.7%) treated with anifrolumab at the recommended dosing regimen during the 60-week study period.

In the LTE (years 2 through 4 on treatment), treatment-emergent anti-drug antibodies were detected in an additional 5 patients treated with anifrolumab.

Due to methodological limitations, the clinical relevance of these findings is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials, doses of up to 1 000 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Monoclonal antibodies, ATC code: L04AG11

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 internalisation 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. Inhibition of type I IFN blocks plasma cell differentiation and normalises peripheral T-cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in SLE.

Pharmacodynamic effects

In adult patients with SLE, administration of anifrolumab at doses ≥300 mg, via intravenous infusion every 4 weeks demonstrated consistent neutralisation (≥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 either maintained or further suppressed 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. Anifrolumab 150 mg intravenous showed <20% suppression of the gene signature at early timepoints, that reached a maximum of <60% by the end of the treatment period.

In SLE patients with positive anti-dsDNA antibodies at baseline, treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time through Week 52.

In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab 300 mg through Week 52.

Clinical efficacy

The safety and efficacy of anifrolumab were evaluated in two 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled, Phase III studies (Trial 1 [TULIP 1] and Trial 2 [TULIP 2]). Patients were diagnosed with SLE according to the American College of Rheumatology (1997) classification criteria.

All patients were ≥18 years of age and had moderate to severe 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, and a Physician's Global Assessment [PGA] score ≥1, despite receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline. With the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol, patients continued to receive their existing SLE therapy at stable doses during the clinical trials. 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. Both studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by intravenous infusion, every 4 weeks.

Trial 1 (N=457) and Trial 2 (N=362) were similar in design.

In Trial 1 the primary endpoint was SLE Responder Index (SRI-4) response, 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 lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS);
- No use of restricted medication beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

In Trial 2 the primary endpoint was British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) response at Week 52, 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 defined as an increase from baseline of >0 points;
- No worsening from baseline in lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No use of restricted medication beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

The secondary efficacy endpoints included in both studies included maintenance of OCS reduction and annual flare rate. Both studies evaluated the efficacy of anifrolumab 300 mg versus placebo.

Patient demographics were generally similar in both trials; the median age was 41.3 and 42.1 years (range 18-69), 4.4% and 1.7% were ≥65 years of age, 92% and 93% were female, 71% and 60% were White, 14% and 12% were Black/African American, and 5% and 17% were Asian, in Trials 1 and 2 respectively. In both trials, 72% of patients had high disease activity (SLEDAI-2K score ≥10). In Trials 1 and 2 respectively, 48% and 49% had severe disease (BILAG A) in at least 1 organ system and 46% and 47% of patients had moderate disease (BILAG B) in at least 2 organ systems. The most commonly affected organ systems (BILAG A or B at baseline) were the mucocutaneous (Trial 1: 87%, Trial 2: 85%) and musculoskeletal (Trial 1: 89%, Trial 2: 88%) systems.

In Trials 1 and 2, 90% of patients (both trials) were seropositive for anti-nuclear antibodies (ANA), and 45% and 44% for anti-double-stranded DNA (anti-dsDNA) antibodies; 34% and 40% of patients had low C3, and 21% and 26% had low C4.

Baseline concomitant standard therapy medications included oral corticosteroids (Trial 1: 83%, Trial 2: 81%), antimalarials (Trial 1: 73%, Trial 2: 70%) and immunosuppressants (Trial 1: 47%, Trial 2: 48%; including azathioprine, methotrexate, mycophenolate and mizoribine). For those patients taking OCS (prednisone or equivalent) at baseline, the mean daily dose was 12.3 mg in Trial 1 and 10.7 mg in Trial 2. 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.

For BICLA and SRI-4 response, patients who withdrew from treatment prior to Week 52 were considered non-responders. In Trial 1 and 2 respectively, 35 (19%) and 27 (15%) patients receiving anifrolumab, and 38 (21%) and 52 (29%) patients receiving placebo withdrew from treatment prior to Week 52. The results are presented in Table 2.

Table 2 Efficacy results in adults with SLE in Trial 1 and Trial 2

	Trial 1		**Trial 2**	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
BICLA response at Week 52*				
Responder rate, % (n/N)	47.1 (85/180)	30.2 (55/184)	47.8 (86/180)	31.5 (57/182)
Difference % (95% CI)	17.0 (7.2, 26.8)		16.3 (6.3, 26.3)	
Components of BICLA response:				
BILAG improvement, n (%) †	85 (47.2)	58 (31.5)	88 (48.9)	59 (32.4)
No worsening of SLEDAI-2K, n (%) †	121 (67.2)	104 (56.5)	122 (67.8)	94 (51.6)
No worsening of PGA, n (%) †	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)
No discontinuation of treatment, n (%)	145 (80.6)	146 (79.3)	153 (85.0)	130 (71.4)
No use of restricted medication beyond protocol allowed threshold, n (%)	140 (77.8)	128 (69.6)	144 (80.0)	123 (67.6)
SRI-4 response at Week 52*				
Responder rate, % (n/N) †	49.0 (88/180)	43.0 (79/184)	55.5 (100/180)	37.3 (68/182)
Difference % (95% CI)	6.0 (-4.2, 16.2)		18.2 (8.1, 28.3)	

	Trial 1		Trial 2	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
Sustained OCS reduction ‡				
Responder rate, % (n/N) †	49.7 (51/103)	33.1 (34/102)	51.5 (45/87)	30.2 (25/83)
Difference % (95% CI)	16.6 (3.4, 29.8)		21.2 (6.8, 35.7)	
Flare rate				
Annualised flare rate estimate, (95% CI)	0.57 (0.43, 0.76)	0.68 (0.52, 0.90)	0.43 (0.31, 0.59)	0.64 (0.47, 0.86)
Rate ratio estimate (95% CI)	0.83 (0.61, 1.15)		0.67 (0.48, 0.94)	

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; SRI-4: SLE Responder Index.
All patients received standard therapy.

* BICLA and SRI-4 are based on the composite estimand where treatment discontinuation or restricted medication use are part of the response criteria.

† Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders.

‡ Subgroup of patients with OCS ≥10 mg/day at baseline. Responders were defined as patients with OCS reduction to ≤7.5 mg/day at Week 40, maintained through Week 52.

Long-term extension

Patients who completed Trials 1 and 2 (feeder trials) through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled, 3-year LTE. Patients who had received anifrolumab, either 150 mg or 300 mg, in Trials 1 and 2 received anifrolumab 300 mg in the LTE. Patients who had received placebo in Trials 1 and 2 were re-randomised 1:1 to receive either anifrolumab 300 mg or placebo, giving an approximate anifrolumab 300 mg: placebo ratio of 4:1 in the LTE.

Long-term efficacy 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 (0.25) and 4.0 (0.46) in patients who received anifrolumab (n=140) and placebo (n=44) respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with anifrolumab in one or more subset of the paediatric population in treatment of systemic lupus erythematosus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of anifrolumab was studied in adult patients with SLE following intravenous doses ranging from 100 to 1 000 mg administered once every 4 weeks and subcutaneous weekly doses of 120 mg and in healthy volunteers following a single intravenous or subcutaneous dose.

Anifrolumab exhibits nonlinear PK in the dose range of 100 mg to 1 000 mg. PK exposure decreased more rapidly at doses lower than 300 mg every 4 weeks (the recommended intravenous dose).

Absorption

Anifrolumab is administered by intravenous infusion.

Distribution

Based on population PK analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 3.48 L and 1.72 L, respectively for a 68 kg patient.

Biotransformation

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

Due to saturation of IFNAR1-mediated clearance at higher doses, exposure increases are greater-than-dose-proportional.

From population PK modelling the estimated typical systemic clearance (CL) was 0.146 L/day. Following long-term observations, the clearance of anifrolumab was found to be stable in years 2 through 4 on treatment.

Based on population PK analysis, serum concentrations were below detection in the majority (95%) of patients approximately 16 weeks after the last dose of anifrolumab, when anifrolumab has been dosed for one year.

Special populations

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.

Elderly
Based on the population PK analysis, age (range 18 to 70 years) did not impact the clearance of anifrolumab; the population PK dataset included 33 (3%) patients ≥65 years of age.

Renal impairment
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; anifrolumab is not cleared renally.

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

As an IgG1 monoclonal antibody, anifrolumab is principally eliminated via catabolism and is not expected to undergo metabolism via hepatic enzymes, as such changes in hepatic function are unlikely to have any effect on the elimination of anifrolumab. Based on population PK analyses, baseline

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

Interactions

Based on population PK analyses, concomitant use of oral corticosteroids, antimalarials, immunosuppressants (including azathioprine, methotrexate, mycophenolate and mizoribine), NSAIDS, ACE inhibitors, HMG-CoA reductase inhibitors did not significantly influence the PK of anifrolumab.

5.3 Preclinical safety data

Non-clinical

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in cynomolgus monkeys.

Mutagenicity and carcinogenicity

Anifrolumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.

In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown.

Reproductive toxicity

Developmental toxicity
In a pre- and postnatal development study, conducted in cynomolgus monkeys, there was an increased incidence of embryo-foetal loss; the incidence of these findings were within historical control values and were not statistically significant. The relevance of these findings to humans is not known. No maternal, or postnatal developmental effects were observed for exposures up to approximately 28-times the maximum recommended human dose (MRHD) on an AUC basis. Based on the available data, a potential effect of anifrolumab on conception and implantation cannot be excluded.

Fertility
Effects on male and female fertility have not been directly evaluated in animal studies. In the 9-month repeat-dose study, there were no anifrolumab-related adverse effects on indirect measures of male or female fertility, based on semen analysis, spermatogenesis staging, menses cycle, organ weights and histopathological findings in the reproductive organs, in cynomolgus monkeys at approximately 58-times the intravenous MRHD and 52-times the subcutaneous MRHD, on an AUC basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Lysine hydrochloride
Trehalose dihydrate
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

Diluted solution for infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C and for 4 hours at 25 °C.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C.

6.4 Special precautions for storage

Unopened vial

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.
Do not freeze, shake or expose to heat.

Diluted solution for infusion

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2.0 ml of concentrate in a clear type I glass vial with an elastomeric stopper and a gray flip-off aluminium seal.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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

Preparation of solution

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. Dilute 2.0 ml of Saphnelo solution for infusion in an infusion bag to 50 ml or 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection.

3. Mix the solution by gentle inversion. Do not shake.

4. Any concentrate remaining in the vial must be discarded.

5. It is recommended that the solution for infusion should be administered immediately after preparation. If the solution for infusion has been stored in a refrigerator (see section 6.3), allow it to reach room temperature (15 °C – 25 °C) prior to administration.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85
Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 120 mg solution for injection in pre-filled syringe
Saphnelo 120 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 120 mg of anifrolumab* in 0.8 ml.

Each pre-filled pen contains 120 mg of anifrolumab* in 0.8 ml.

*Anifrolumab is a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

Excipient with known effect

Each pre-filled syringe/pre-filled pen contains 0.4 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colourless to slightly yellow, pH 5.9 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of SLE.

A patient may self-inject or the patient caregiver may administer Saphnelo subcutaneously after the healthcare professional determines that it is appropriate. The healthcare professional should provide proper training in subcutaneous injection technique according to the 'Instructions for Use' and education about signs and symptoms of hypersensitivity reactions (see section 4.4).

Posology

The recommended dose is 120 mg administered as a subcutaneous injection every week.

Missed dose
If a subcutaneous dose is missed, instruct the patient to administer Saphnelo as soon as they remember. Thereafter, the patient can start a new weekly schedule from the day that the missed dose

was administered or resume dosing on their usual day of administration providing that a minimum interval of 3 days is maintained between injections.

Special populations

Elderly
No dose adjustment is required. There is limited information in subjects aged ≥65 years (n=33); no data are available in patients over 75 years of age (see section 5.2).

Renal impairment
No dose adjustment is required. There is no experience in patients with severe renal impairment or end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is required (see section 5.2).

Paediatric population
The safety and efficacy of Saphnelo in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

For subcutaneous use.

Saphnelo is administered as a subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If a healthcare professional or caregiver administers the injection, the upper arm can also be used. It should not be injected into areas where the skin is tender, bruised, erythematous or hardened. When injecting in the same region, patients should be advised to use an injection site that is at least 3 cm away from the last injection site.

Comprehensive instructions for subcutaneous administration of Saphnelo in a pre-filled syringe or pre-filled pen are provided in the 'Instructions for Use'.

Transitioning between routes of administration
If transitioning a patient from intravenous administration to subcutaneous administration, the first subcutaneous injection should be administered approximately 2 weeks after the last intravenous dose.

If transitioning a patient from subcutaneous administration to intravenous administration, the first intravenous infusion should be administered approximately 3 to 4 weeks after the last subcutaneous dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Patient groups excluded from clinical studies

Anifrolumab has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, treatment with anifrolumab is not recommended in combination with biologic therapies.

Anifrolumab has not been studied in patients with severe active central nervous system lupus or severe active lupus nephritis (see section 5.1).

Hypersensitivity

Serious hypersensitivity reactions including anaphylaxis have been reported following administration of anifrolumab (see section 4.8).

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, serious hypersensitivity reactions (including angioedema) were reported for 0.5% of patients receiving anifrolumab.

If a serious hypersensitivity reaction (e.g., anaphylaxis) occurs, administration of anifrolumab should be interrupted immediately, and appropriate therapy initiated.

Infections

Anifrolumab increases the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been observed), see section 4.8. SLE patients also taking immunosuppressants may be at higher risk of herpes zoster infections.

In controlled-clinical trials serious and sometimes fatal infections (including pneumonia) occurred, including in patients receiving anifrolumab.

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

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

The placebo-controlled clinical trials excluded patients with a history of active TB or latent TB in whom an adequate course of treatment could not be confirmed. Anti-tuberculosis (anti-TB) therapy should be considered prior to initiation of anifrolumab in patients with untreated latent TB. Anifrolumab should not be administered to patients with active TB.

Immunisations

Prior to initiating therapy, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Concurrent use of live or attenuated vaccines should be avoided in patients treated with anifrolumab.

Immune responses to non-live vaccines have been assessed in a small number of patients (see section 4.5).

Malignancy

The impact of treatment with anifrolumab on the potential development of malignancies is not known. Studies in patients with a history of malignancy have not been conducted; however, patients with squamous or basal cell skin cancers and uterine cervical cancer that had been fully excised or adequately treated were eligible for enrolment in the SLE clinical trials.

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, malignant neoplasm (including non-melanoma skin cancers) was reported for 1.1% of patients receiving anifrolumab compared to 0.5% patients receiving placebo (exposure-adjusted incidence rate [EAIR]: 1.1 and 0.5 events per 100 patient years [PY], respectively). Malignancies excluding non-melanoma skin cancers were observed in 0.5% and 0.5% of patients receiving anifrolumab and placebo, respectively. In patients receiving anifrolumab, breast and squamous cell carcinoma were the malignancies observed in more than one patient.

Individual benefit-risk should be considered in patients with known risk factors for the development or reoccurrence of malignancy. Caution should be exercised when considering continuing therapy for patients who develop malignancy.

Excipient with known effect

This medicinal product contains 0.4 mg of polysorbate 80 (E 433) in each pre-filled syringe/pre-filled pen, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Anifrolumab is not expected to undergo metabolism by hepatic enzymes or renal elimination.

The formation of some CYP450 enzymes is suppressed by increased levels of certain cytokines during chronic inflammation. Anifrolumab modestly suppresses the levels of some cytokines; the impact on CYP450 activity is unknown. In patients who are being treated with other medicines that are CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin), therapeutic monitoring is recommended.

Immune response

Non-live vaccines
Immune response to non-live seasonal influenza vaccine was assessed in a small number of adult patients with moderate to severe SLE in an exploratory study. Humoral antibody responses induced by seasonal influenza virus vaccination were numerically comparable between patients receiving anifrolumab in addition to standard of care and those receiving standard of care alone.

Live vaccines
The concurrent use of anifrolumab with live and live-attenuated vaccines has not been studied (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of Saphnelo in pregnant women.

Animal studies are inconclusive with respect to reproductive toxicity (see section 5.3).

Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

Breast-feeding

It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue from Saphnelo therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans.

Animal studies show no adverse effects of anifrolumab on indirect measures of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during anifrolumab treatment were upper respiratory tract infection (31%), bronchitis (10%), infusion-related reaction (9.4%) and herpes zoster (6.0%). The most common serious adverse reaction was herpes zoster (0.4%).

Tabulated list of adverse reactions

Adverse reactions reported from controlled clinical trials and post-marketing data are classified by MedDRA System Organ Class (SOC), see Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).

Table 1 Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Infections and infestations	Upper respiratory tract infection*	Very common
	Bronchitis*	Very common
	Herpes zoster	Common
	Respiratory tract infection*	Common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic reaction	Uncommon§
Musculoskeletal and connective tissue disorders	Arthralgia	Not known
Injury, poisoning and procedural complications	Infusion-related reaction‡	Common

* Grouped terms: Upper respiratory tract infection (including Upper respiratory tract infection, Nasopharyngitis, Pharyngitis); Bronchitis (including Bronchitis, Bronchitis viral, Tracheobronchitis); Respiratory tract infection (including Respiratory tract infection, Respiratory tract infection viral, Respiratory tract infection bacterial).

§ See 'Description of selected adverse reactions' below and section 4.4.

‡ Applies to intravenous infusion route of administration only.

Long-term safety:

Patients who completed Trials 1 and 2, the Phase III intravenous trials through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled long-term extension (LTE) for an additional 3 years (see section 5.1). The overall long-term safety profile of intravenous anifrolumab was consistent with the 52-week trials.

Description of selected adverse reactions

Hypersensitivity
In controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of hypersensitivity reactions was 2.5% in the anifrolumab group and 0.5% in the placebo group. Hypersensitivity reactions were predominantly mild to moderate in intensity. One event of hypersensitivity in the subcutaneous trial led to discontinuation of anifrolumab.

In the intravenous clinical trials of 52-week treatment duration, all hypersensitivity reactions were reported within the first 6 infusions. One serious adverse reaction of hypersensitivity was reported during the patient's first infusion; the patient continued to receive anifrolumab with premedication given for subsequent infusions.

In the SLE development program, anaphylactic reaction was reported in one patient, which occurred following the intravenous administration of 150 mg anifrolumab, the patient was treated and recovered (see section 4.4).

Infusion-related reactions
In the controlled intravenous clinical trials of 52-week treatment duration, the incidence of infusion-related reactions was 9.4% in the anifrolumab group and 7.1% in the placebo group. Infusion-related reactions were mild or moderate in intensity (the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness); none were serious, and none led to discontinuation of anifrolumab. Infusion-related reactions were most commonly reported at the start of treatment, on the first and second infusions, with fewer reports on subsequent infusions.

Respiratory infections
In controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence rates for anifrolumab compared to placebo were: upper respiratory tract infection (30.9% vs 20.3%), bronchitis (10.2% vs 5.2%) and respiratory tract infection (3.0% vs 1.4%). Infections were predominantly non-serious, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy (see section 4.4).

Herpes zoster
In the controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of herpes zoster infections was 6.0% in the anifrolumab group and 1.4% in the placebo group (see section 4.4). The mean time to onset in patients receiving anifrolumab was 129 days (range 2-351 days).

In the LTE (intravenous administration), incidence rates decreased over time.

Herpes zoster infections were predominantly of localised cutaneous presentation, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy. Cases with multidermatomal involvement and cases of disseminated disease (including central nervous system involvement) have been reported (see section 4.4).

Immunogenicity

In the intravenous Phase III trials, treatment-emergent anti-drug antibodies were detected in 6 out of 352 patients (1.7%) treated with anifrolumab at the recommended dosing regimen during the 60-week study period.

In the LTE (years 2 through 4 on treatment), treatment-emergent anti-drug antibodies were detected in an additional 5 patients treated with anifrolumab.

Due to methodological limitations, the clinical relevance of these findings is not known.

In the subcutaneous Phase III trial, treatment-emergent anti-drug antibodies were detected in 6 out of 107 patients (5.6%) treated with anifrolumab during the 52-week treatment period, no neutralising antibodies were detected.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials, doses of up to 1 000 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Monoclonal antibodies, ATC code: L04AG11

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 internalisation 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. Inhibition of type I IFN blocks plasma cell differentiation and normalises peripheral T-cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in SLE.

Pharmacodynamic effects

In adult patients with SLE, administration of anifrolumab ≥300 mg intravenous every 4 weeks and 120 mg subcutaneous once weekly, demonstrated consistent neutralisation (≥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 either maintained or further suppressed 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.

Anifrolumab 150 mg (intravenous) showed <20% suppression of the gene signature at early timepoints, that reached a maximum of <60% by the end of the treatment period.

In SLE patients with positive anti-dsDNA antibodies at baseline, intravenous treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time through Week 52.

In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab 300 mg intravenously through Week 52.

Clinical efficacy

Intravenous administration
The safety and efficacy of anifrolumab were evaluated in two 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled, Phase III studies (Trial 1 [TULIP 1] and Trial 2 [TULIP 2]). Patients were diagnosed with SLE according to the American College of Rheumatology (1997) classification criteria.

All patients were ≥18 years of age and had moderate to severe 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, and a Physician's Global Assessment [PGA] score ≥1, despite receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline. With the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol, patients continued to receive their existing SLE therapy at stable doses during the clinical trials. 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. Both studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by intravenous infusion, every 4 weeks.

Trial 1 (N=457) and Trial 2 (N=362) were similar in design.

In Trial 1 the primary endpoint was SLE Responder Index (SRI-4) response, 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 lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS);
- No use of restricted medication beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

In Trial 2 the primary endpoint was British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) response at Week 52, 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 defined as an increase from baseline of >0 points;
- No worsening from baseline in lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No use of restricted medication beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

The secondary efficacy endpoints included in both studies included maintenance of OCS reduction and annual flare rate. Both studies evaluated the efficacy of anifrolumab 300 mg versus placebo.

Patient demographics were generally similar in both trials; the median age was 41.3 and 42.1 years (range 18-69), 4.4% and 1.7% were ≥65 years of age, 92% and 93% were female, 71% and 60% were White, 14% and 12% were Black/African American, and 5% and 17% were Asian, in Trials 1 and 2 respectively. In both trials, 72% of patients had high disease activity (SLEDAI-2K score ≥10). In Trials 1 and 2 respectively, 48% and 49% had severe disease (BILAG A) in at least 1 organ system and 46% and 47% of patients had moderate disease (BILAG B) in at least 2 organ systems. The most commonly affected organ systems (BILAG A or B at baseline) were the mucocutaneous (Trial 1: 87%, Trial 2: 85%) and musculoskeletal (Trial 1: 89%, Trial 2: 88%) systems.

In Trials 1 and 2, 90% of patients (both trials) were seropositive for anti-nuclear antibodies (ANA), and 45% and 44% for anti-double-stranded DNA (anti-dsDNA) antibodies; 34% and 40% of patients had low C3, and 21% and 26% had low C4.

Baseline concomitant standard therapy medications included oral corticosteroids (Trial 1: 83%, Trial 2: 81%), antimalarials (Trial 1: 73%, Trial 2: 70%) and immunosuppressants (Trial 1: 47%, Trial 2: 48%; including azathioprine, methotrexate, mycophenolate and mizoribine). For those patients taking OCS (prednisone or equivalent) at baseline, the mean daily dose was 12.3 mg in Trial 1 and 10.7 mg in Trial 2. 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.

For BICLA and SRI-4 response, patients who withdrew from treatment prior to Week 52 were considered non-responders. In Trial 1 and 2 respectively, 35 (19%) and 27 (15%) patients receiving anifrolumab, and 38 (21%) and 52 (29%) patients receiving placebo withdrew from treatment prior to Week 52. The results are presented in Table 2.

Table 2 Efficacy results in adults with SLE in Trial 1 and Trial 2

	Trial 1		**Trial 2**	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
BICLA response at Week 52*				
Responder rate, % (n/N)	47.1 (85/180)	30.2 (55/184)	47.8 (86/180)	31.5 (57/182)
Difference % (95% CI)	17.0 (7.2, 26.8)		16.3 (6.3, 26.3)	
Components of BICLA response:				
BILAG improvement, n (%) †	85 (47.2)	58 (31.5)	88 (48.9)	59 (32.4)
No worsening of SLEDAI-2K, n (%) †	121 (67.2)	104 (56.5)	122 (67.8)	94 (51.6)
No worsening of PGA, n (%) †	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)
No discontinuation of treatment, n (%)	145 (80.6)	146 (79.3)	153 (85.0)	130 (71.4)
No use of restricted medication beyond protocol allowed threshold, n (%)	140 (77.8)	128 (69.6)	144 (80.0)	123 (67.6)
SRI-4 response at Week 52*				
Responder rate, % (n/N) †	49.0 (88/180)	43.0 (79/184)	55.5 (100/180)	37.3 (68/182)
Difference % (95% CI)	6.0 (-4.2, 16.2)		18.2 (8.1, 28.3)	

	Trial 1		Trial 2	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
Sustained OCS reduction ‡				
Responder rate, % (n/N) †	49.7 (51/103)	33.1 (34/102)	51.5 (45/87)	30.2 (25/83)
Difference % (95% CI)	16.6 (3.4, 29.8)		21.2 (6.8, 35.7)	
Flare rate				
Annualised flare rate estimate, (95% CI)	0.57 (0.43, 0.76)	0.68 (0.52, 0.90)	0.43 (0.31, 0.59)	0.64 (0.47, 0.86)
Rate ratio estimate (95% CI)	0.83 (0.61, 1.15)		0.67 (0.48, 0.94)	

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; SRI-4: SLE Responder Index.
All patients received standard therapy.

* BICLA and SRI(4) are based on the composite estimand where treatment discontinuation or restricted medication use are part of the response criteria.

† Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders.

‡ Subgroup of patients with OCS ≥10 mg/day at baseline. Responders were defined as patients with OCS reduction to ≤7.5 mg/day at Week 40, maintained through Week 52.

Long-term extension: Patients who completed Trials 1 and 2 (feeder trials) through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled, 3-year LTE. Patients who had received anifrolumab, either 150 mg or 300 mg, in Trials 1 and 2 received anifrolumab 300 mg in the LTE. Patients who had received placebo in Trials 1 and 2 were re-randomised 1:1 to receive either anifrolumab 300 mg or placebo, giving an approximate anifrolumab 300 mg: placebo ratio of 4:1 in the LTE.

Long-term efficacy 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 (0.25) and 4.0 (0.46) in patients who received anifrolumab (n=140) and placebo (n=44) respectively.

Subcutaneous administration
The safety and efficacy of anifrolumab administered subcutaneously were evaluated in a 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled, Phase III study. All patients were ≥18 years of age, diagnosed with SLE according to the American College of Rheumatology (1997 revised) classification criteria, and had moderate to severe disease, with a SLEDAI-2K score ≥6 points, organ level involvement based on BILAG assessment, and a 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 trial, with the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol. Patients who had severe active lupus nephritis or severe active central nervous system lupus were excluded. Patients were randomised (1:1) to receive 120 mg anifrolumab or placebo by subcutaneous injection once every week.

A pre-specified interim analysis was conducted when 220 randomised patients completed Week 52 or had withdrawn from the trial. Of these, 89% were female, 78% White, 7% Asian and 4% Black/African American. The median age was 43 years (range: 19-70). At baseline, 67% had high disease activity (SLEDAI-2K score ≥10), 45% had severe disease (BILAG A) in at least 1 organ system and 50% had moderate disease (BILAG B) in at least 2 organ systems. The most commonly affected organ systems (BILAG A or B at baseline) were the musculoskeletal (95%) and

mucocutaneous (92%) systems; 2% cardiorespiratory and 2% renal organ domain involvement. At baseline, 95% were seropositive for ANA antibodies and 40% for anti-dsDNA antibodies; 33% of patients had low C3, and 24% low C4. Background SLE standard therapy included OCS (82%; mean daily dose (prednisone or equivalent) 9.8 mg), immunosuppressants (56%), and antimalarials (80%). 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.

Randomisation was stratified by 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).

The primary analyses assessed reduction in overall disease activity as measured by BICLA response at Week 52. At the interim analysis, anifrolumab 120 mg by subcutaneous administration demonstrated a statistically significant and clinically meaningful reduction of overall disease activity compared with placebo.

Table 3 BICLA response rate at Week 52

	Anifrolumab 120 mg	**Placebo**
BICLA response rate		
Responder rate, % (n/N)*	59.4 (65/109)	43.9 (49/111)
Difference % (95% CI)	15.5 (2.3, 28.6)	
Components of BICLA response‡		
BILAG improvement, n (%)	65 (59.5)	49 (44.1)
No worsening of SLEDAI-2K, n (%)	81 (74.3)	80 (71.6)
No worsening of PGA, n (%)	81 (74.4)	82 (73.7)

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
All patients received standard therapy.
* Patients who discontinued treatment or used restricted medications, beyond protocol allowed thresholds, or died are considered non-responders.
‡ Missing data were imputed using multiple imputation.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with anifrolumab in one or more subset of the paediatric population in treatment of systemic lupus erythematosus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of anifrolumab was studied in adult patients with SLE following intravenous doses ranging from 100 to 1 000 mg administered once every 4 weeks and subcutaneous weekly doses of 120 mg and in healthy volunteers following a single intravenous or subcutaneous dose.

Anifrolumab exhibits nonlinear PK in the dose range of 100 mg to 1 000 mg. PK exposure decreased more rapidly at doses lower than 300 mg every 4 weeks (the recommended intravenous dose).

Absorption

Based on population PK analysis, following subcutaneous administration, the estimated bioavailability of anifrolumab was approximately 75%. Steady-state exposure was reached after approximately 16 weeks of subcutaneous administration.

Distribution

Based on population PK analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 3.48 L and 1.72 L, respectively for a 68 kg patient.

Biotransformation

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

Due to saturation of IFNAR1-mediated clearance at higher doses, exposure increases are greater-than-dose-proportional.

From population PK modelling, the estimated typical systemic clearance (CL) was 0.146 L/day. Following long-term observations, the clearance of anifrolumab was found to be stable in years 2 through 4 on treatment.

Based on population PK analysis, serum concentrations were below detection in the majority (95%) of patients approximately 16 weeks after the last dose of anifrolumab, when anifrolumab has been dosed for one year.

Special populations

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.

Elderly
Based on the population PK analysis, age (range 18 to 70 years) did not impact the clearance of anifrolumab; the population PK dataset included 33 (3%) patients ≥65 years of age.

Renal impairment
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; anifrolumab is not cleared renally.

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

As an IgG1 monoclonal antibody, anifrolumab is principally eliminated via catabolism and is not expected to undergo metabolism via hepatic enzymes, as such changes in hepatic function are unlikely to have any effect on the elimination of anifrolumab. Based on population PK analyses, baseline hepatic function biomarkers (ALT and AST ≤2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance.

Interactions

Based on population PK analyses, concomitant use of oral corticosteroids, antimalarials, immunosuppressants (including azathioprine, methotrexate, mycophenolate and mizoribine), NSAIDS, ACE inhibitors, HMG-CoA reductase inhibitors did not significantly influence the PK of anifrolumab.

5.3 Preclinical safety data

Non-clinical

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in cynomolgus monkeys.

Mutagenicity and carcinogenicity

Anifrolumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.

In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown.

Reproductive toxicity

Developmental toxicity
In a pre- and postnatal development study, conducted in cynomolgus monkeys, there was an increased incidence of embryo-foetal loss; the incidence of these findings were within historical control values and were not statistically significant. The relevance of these findings to humans is not known. No maternal, or postnatal developmental effects were observed for exposures up to approximately 28-times the maximum recommended human dose (MRHD) on an AUC basis. Based on the available data, a potential effect of anifrolumab on conception and implantation cannot be excluded.

Fertility
Effects on male and female fertility have not been directly evaluated in animal studies. In the 9-month repeat-dose study, there were no anifrolumab-related adverse effects on indirect measures of male or female fertility, based on semen analysis, spermatogenesis staging, menses cycle, organ weights and histopathological findings in the reproductive organs, in cynomolgus monkeys at approximately 58-times the intravenous MRHD and 52-times the subcutaneous MRHD, on an AUC basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Lysine hydrochloride
Trehalose dihydrate
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 years.

If needed, an unopened carton can be stored at room temperature (20 °C – 25 °C) for up to 7 days. Once the pre-filled syringe/pre-filled pen has been removed from the refrigerator and has reached room temperature (20 °C – 25 °C), it must either be used within 7 days or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.
Do not freeze, shake or expose to heat.

6.5 Nature and contents of container

Pre-filled syringe

0.8 ml of solution in a type I glass syringe with a 27-gauge, 12.7 mm stainless steel needle with a needle cover and a bromobutyl plunger stopper. The pre-filled syringe is assembled with a needle guard, plunger rod and a finger flange.

Pack size of 1 pre-filled syringe.

Pre-filled pen

0.8 ml of solution in a type I glass syringe with a 27-gauge, 12.7 mm stainless steel needle covered with a needle cover and a bromobutyl plunger stopper. The pre-filled pen consists of the syringe and a handheld, mechanical (spring-based) injection device.

Pack size of 1 pre-filled pen.

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

1. Remove carton from the refrigerator and allow the solution for injection to come to room temperature for 60 minutes.

2. Visually inspect the solution for injection for particulate matter and discolouration prior to administration. Discard the pre-filled syringe or pre-filled pen if the solution is cloudy, discoloured or visible particles are observed.

3. Comprehensive instructions for the preparation and administration of Saphnelo using the pre-filled syringe or pre-filled pen are given in the ‘Instructions for Use’.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85
Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/002 pre-filled syringe
EU/1/21/1623/003 pre-filled pen

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC)
633 Research Court
Frederick, Maryland
21703
United States

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

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 300 mg concentrate for solution for infusion
anifrolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 2 ml of concentrate contains 300 mg of anifrolumab (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.
For single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze, shake or expose to heat.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/001 1 vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Saphnelo 300 mg sterile concentrate
anifrolumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

AstraZeneca

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED SYRINGE)

1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 120 mg solution for injection in pre-filled syringe
anifrolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 120 mg of anifrolumab in 0.8 ml.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze, shake or expose to heat.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/002 1 pre-filled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

saphnelo 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Saphnelo 120 mg injection
anifrolumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN)

1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 120 mg solution for injection in pre-filled pen
anifrolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains 120 mg of anifrolumab in 0.8 ml.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze, shake or expose to heat.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/003 1 pre-filled pen

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

saphnelo 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Saphnelo 120 mg injection
anifrolumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 ml

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Saphnelo 300 mg concentrate for solution for infusion
anifrolumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Saphnelo is and what it is used for

What Saphnelo is
Saphnelo contains the active substance anifrolumab, a ‘monoclonal antibody’ (a type of specialised protein that attaches to a specific target in the body).

What Saphnelo is used for
Saphnelo is used to treat **moderate to severe lupus** (systemic lupus erythematosus, SLE) in adults whose disease is not well controlled by standard therapies (‘oral corticosteroids’, ‘immunosuppressants’ and/or ‘antimalarials’).

You will be given Saphnelo as well as your standard therapy for lupus.

Lupus is a disease in which the system that fights infections (the immune system) attacks your own cells and tissues. This causes inflammation and organ damage. It can affect almost any organ in the body, including skin, joints, kidneys, brain and other organs. It can cause pain, rashes, swelling in joints, fevers and make you feel very tired or weak.

How Saphnelo works
People with lupus have high levels of proteins called ‘type I interferons’ which stimulate the activity of the immune system. Anifrolumab attaches to a target (receptor) that these proteins act on, stopping them from working. Blocking their action in this way can reduce the inflammation in your body that causes the signs of lupus.

The benefits of using Saphnelo
Saphnelo may help to reduce your lupus disease activity and reduce the number of lupus flares you have. If you are taking medicines called ‘oral corticosteroids’, using Saphnelo may also allow your doctor to reduce the daily dose of oral corticosteroids that is needed to help control your lupus.

2. What you need to know before you are given Saphnelo

You should not be given Saphnelo
- if you are allergic to anifrolumab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor or nurse if you are not sure.

Warnings and precautions
Talk to your doctor or nurse before you are given Saphnelo:
- if you think you have had an **allergic reaction** to this medicine at any time (see below under 'Look out for signs of serious allergic reactions and infections').
- if you get an infection or have symptoms of an **infection** (see below under 'Look out for signs of serious allergic reactions and infections').
- if you have a long-term infection or if you have an infection that keeps coming back.
- if your lupus affects your kidneys or nervous system.
- if you have, or have had, cancer.
- if you have recently had an immunisation (vaccine) or plan to have one. You should not be given certain types of vaccines ('live' or 'live attenuated' vaccines) while being treated with this medicine.
- if you are receiving another biologic medicinal product (such as belimumab for your lupus).

If you are not sure if any of the above applies to you, talk to your doctor or nurse before you are given Saphnelo.

Look out for signs of serious allergic reactions and infections

Saphnelo may cause **serious allergic reactions (anaphylaxis)** see section 4. **Get medical attention immediately** if you think you may be having a serious allergic reaction. Signs may include:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

You may be more at risk of getting an **infection** when you are being treated with Saphnelo. **Tell your doctor or nurse as soon as possible** if you notice signs of any possible infection, including:
- fever or flu-like symptoms
- muscle aches
- cough or feeling short of breath (these may be signs of an infection in your airways, see section 4)
- burning when you urinate or passing urine more often than usual
- diarrhoea or stomach pain
- red skin rash that can cause pain and burning (this may be a sign of shingles, see section 4).

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Saphnelo
- Tell your doctor if you are taking, have recently taken or might take any other medicines.
- Tell your doctor if you have recently had or are going to have a vaccination. You should not be given certain types of vaccines while using this medicine. If you are not sure, talk to your doctor or nurse before and during treatment with Saphnelo.

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

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

Breast-feeding
- **Before you start treatment with Saphnelo, tell your doctor if you are breast-feeding**. It is not known whether this medicine is passed into breast milk. Your doctor will discuss with you whether you should stop treatment with this medicine while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

Saphnelo contains polysorbate
This medicine contains 1 mg of polysorbate 80 (E 433) in each vial, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Saphnelo is used

A nurse or doctor will give you Saphnelo.
- The recommended dose is 300 mg.
- It is given through a drip into a vein (intravenous infusion) over 30 minutes.
- It is given every 4 weeks.

If you miss an appointment to get Saphnelo call your doctor as soon as possible to make another appointment.

Stopping treatment with Saphnelo
Your doctor will decide if you need to stop being treated with this medicine.

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

4. Possible side effects

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

Serious allergic reactions:
Serious allergic reactions (anaphylaxis) are uncommon (may affect up to 1 in 100 people). **Get medical attention immediately, or go to the nearest emergency department,** if you get any of the following signs of a serious allergic reaction:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

Other side effects:
Tell your doctor or nurse if you get any of the following side effects.

Very common (may affect more than 1 in 10 people)
- infections of the nose or throat
- chest infection (*bronchitis*)

Common (may affect up to 1 in 10 people)
- infections of the sinuses or lungs
- shingles (*herpes zoster*) - a red skin rash that can cause pain and burning
- allergic (*hypersensitivity*) reactions
- infusion reactions - can happen at the time of the infusion or shortly after; symptoms may include headache, feeling sick (*nausea*), being sick (*vomiting*), feeling very tired or weak (*fatigue*) and feeling dizzy

Not known (the frequency cannot be estimated from the available data)
- joint pain (*arthralgia*)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Saphnelo

The doctor, nurse or pharmacist is responsible for storing this medicine. The storage details are as follows:

- Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.
- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2 °C – 8 °C).
- Do not freeze, shake or expose to heat.
- Store in the original package to protect from light.

6. Contents of the pack and other information

What Saphnelo contains
- The **active substance** is anifrolumab. Each vial contains 300 mg anifrolumab.
- The **other ingredients** are histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80 (E 433) (see section 2 “Saphnelo contains polysorbate”) and water for injections.

What Saphnelo looks like and contents of the pack
- Saphnelo is supplied as a clear to opalescent, colourless to slightly yellow concentrate solution.
- Saphnelo is available in packs containing 1 vial.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

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

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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

In order to improve the traceability, the name and the batch number of the administered product should be clearly recorded.

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

Preparation of solution

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. Dilute 2.0 ml of the Saphnelo solution for infusion in an infusion bag to 50 ml or 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection.

3. Mix the solution by gentle inversion. Do not shake.

4. Any concentrate remaining in the vial must be discarded.

5. From a microbiological point of view, once diluted the medicinal product should be used immediately. If not used immediately, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C or for 4 hours at room temperature. Discard the diluted solution if not used within that time.

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

Administration

1. It is recommended that the solution for infusion be administered immediately after preparation. If the solution for infusion has been stored in a refrigerator, allow it to reach room temperature (15 °C – 25 °C) prior to administration.

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

3. Upon completion of the infusion, flush the infusion set with 25 ml sodium chloride 9 mg/ml (0.9%) solution for injection to ensure that all of the solution for infusion has been administered.

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

Disposal

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

Package leaflet: Information for the patient

Saphnelo 120 mg solution for injection in pre-filled syringe
anifrolumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

What is in this leaflet

1. What Saphnelo is and what it is used for

What Saphnelo is
Saphnelo contains the active substance anifrolumab, a 'monoclonal antibody' (a type of specialised protein that attaches to a specific target in the body).

What Saphnelo is used for
Saphnelo is used to treat **moderate to severe lupus** (systemic lupus erythematosus, SLE) in adults whose disease is not well controlled by standard therapies ('oral corticosteroids', 'immunosuppressants' and/or 'antimalarials').

You will be given Saphnelo as well as your standard therapy for lupus.

Lupus is a disease in which the system that fights infections (the immune system) attacks your own cells and tissues. This causes inflammation and organ damage. It can affect almost any organ in the body, including skin, joints, kidneys, brain and other organs. It can cause pain, rashes, swelling in joints, fevers and make you feel very tired or weak.

How Saphnelo works
People with lupus have high levels of proteins called 'type I interferons' which stimulate the activity of the immune system. Anifrolumab attaches to a target (receptor) that these proteins act on, stopping them from working. Blocking their action in this way can reduce the inflammation in your body that causes the signs of lupus.

The benefits of using Saphnelo
Saphnelo may help to reduce your lupus disease activity and reduce the number of lupus flares you have. If you are taking medicines called 'oral corticosteroids', using Saphnelo may also allow your doctor to reduce the daily dose of oral corticosteroids that is needed to help control your lupus.

2. What you need to know before you use Saphnelo

Do not use Saphnelo
- if you are allergic to anifrolumab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor or nurse if you are not sure.

Warnings and precautions
Talk to your doctor or nurse before using Saphnelo:
- if you think you have had an **allergic reaction** to this medicine at any time (see below under 'Look out for signs of serious allergic reactions and infections').
- if you get an infection or have symptoms of an **infection** (see below under 'Look out for signs of serious allergic reactions and infections').
- if you have a long-term infection or if you have an infection that keeps coming back.
- if your lupus affects your kidneys or nervous system.
- if you have, or have had, cancer.
- if you have recently had an immunisation (vaccine) or plan to have one. You should not be given certain types of vaccines ('live' or 'live attenuated' vaccines) while being treated with this medicine.
- if you are receiving another biological medicinal product (such as belimumab for your lupus).

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Saphnelo.

Look out for signs of serious allergic reactions and infections
Saphnelo may cause **serious allergic reactions (anaphylaxis)** see section 4. **Get medical attention immediately** if you think you may be having a serious allergic reaction. Signs may include:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

You may be more at risk of getting an **infection** when you are being treated with Saphnelo. **Tell your doctor or nurse as soon as possible** if you notice signs of any possible infection, including:
- fever or flu-like symptoms
- muscle aches
- cough or feeling short of breath (these may be signs of an infection in your airways, see section 4)
- burning when you urinate or passing urine more often than usual
- diarrhoea or stomach pain
- red skin rash that can cause pain and burning (this may be a sign of shingles, see section 4).

Each time you get a new pack of Saphnelo
- Write down the name and the Lot number shown on the outer carton and the label of the pre-filled syringe, and keep this information in a safe place. You may be asked for this information in the future.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Saphnelo
- Tell your doctor if you are taking, have recently taken or might take any other medicines.
- Tell your doctor if you have recently had or are going to have a vaccination. You should not be given certain types of vaccines while using this medicine. If you are not sure, talk to your doctor or nurse before and during treatment with Saphnelo.

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

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

Breast-feeding
- **Before you start treatment with Saphnelo, tell your doctor if you are breast-feeding**. It is not known whether this medicine is passed into breast milk. Your doctor will discuss with you whether you should stop treatment with this medicine while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

Saphnelo contains polysorbate
This medicine contains 0.4 mg of polysorbate 80 (E 433) in each pre-filled syringe, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Saphnelo

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

The recommended dose is 120 mg once a week. Saphnelo is given as an injection under the skin (subcutaneously).

Your doctor or nurse will decide if you can inject this medicine yourself or if your caregiver can do this for you.

Before injecting Saphnelo
- Your doctor or nurse should train you or your caregiver how to use Saphnelo pre-filled syringe in the right way.
- **Carefully read the 'Instructions for Use'**. Do this each time you get a new pack. There may be new information.

If you or your caregiver have any questions, talk to your doctor, nurse or pharmacist.

If you use more Saphnelo than you should
If you have used more Saphnelo than you should talk to your doctor immediately.

If you forget to use Saphnelo
- If you miss your dose of Saphnelo, inject a dose as soon as you remember. Then continue once weekly dosing based on the new day Saphnelo was injected or at your regularly scheduled time as long as there are at least 3 days between the doses.
- If you are not sure when to inject, ask your doctor, nurse or pharmacist.

Stopping treatment with Saphnelo
- Do not stop using Saphnelo without talking to your doctor.
- Your doctor will decide if you need to stop using this medicine.

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

4. Possible side effects

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

Serious allergic reactions:
Serious allergic reactions (*anaphylaxis*) are uncommon (may affect up to 1 in 100 people). **Get medical attention immediately, or go to the nearest emergency department,** if you get any of the following signs of a serious allergic reaction:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

Other side effects:
Tell your doctor or nurse if you get any of the following side effects.

Very common (may affect more than 1 in 10 people)
- infections of the nose or throat
- chest infection (*bronchitis*)

Common (may affect up to 1 in 10 people)
- infections of the sinuses or lungs
- shingles (*herpes zoster*) - a red skin rash that can cause pain and burning
- allergic (*hypersensitivity*) reactions

Not known (the frequency cannot be estimated from the available data)
- joint pain (*arthralgia*)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Saphnelo

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.
Keep this medicine out of the sight and reach of children.
Store in a refrigerator (2 °C – 8 °C).
Store in the original package to protect from light.
Do not freeze, shake or expose to heat.

If needed, an unopened carton can be stored at room temperature (20 °C – 25 °C) for up to 7 days. Once the Saphnelo pre-filled syringe has been removed from the refrigerator and has reached room temperature (20 ºC – 25 ºC) it must either be used within 7 days or thrown away (discarded).

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

6. Contents of the pack and other information

What Saphnelo contains

- The **active substance** is anifrolumab. Each pre-filled syringe contains 120 mg of anifrolumab.
- The **other ingredients** are histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80 (E 433) (see section 2 “Saphnelo contains polysorbate”) and water for injections.

What Saphnelo looks like and contents of the pack

- Saphnelo is a clear to opalescent, colourless to slightly yellow solution.
- Saphnelo is available in a pack containing 1 pre-filled syringe.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

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

Instructions for Use

Saphnelo 120 mg solution for injection in pre-filled syringe
anifrolumab

This ‘Instructions for Use’ contains information on how to inject using Saphnelo pre-filled syringe.

Read this Instructions for Use before you start using Saphnelo pre-filled syringe and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you or your caregiver how to use Saphnelo pre-filled syringe the right way. If you or your caregiver have any questions, talk to your healthcare provider. Saphnelo pre-filled syringe is for use under the skin (subcutaneous) only.

Important storage information and warnings

- **Store Saphnelo pre-filled syringe in a refrigerator between 2 °C to 8 °C in the original carton until ready to use.** If needed, an unopened carton can be stored at room temperature between 20 °C to 25 °C for up to 7 days.
- Keep Saphnelo pre-filled syringe in original carton to protect from light.

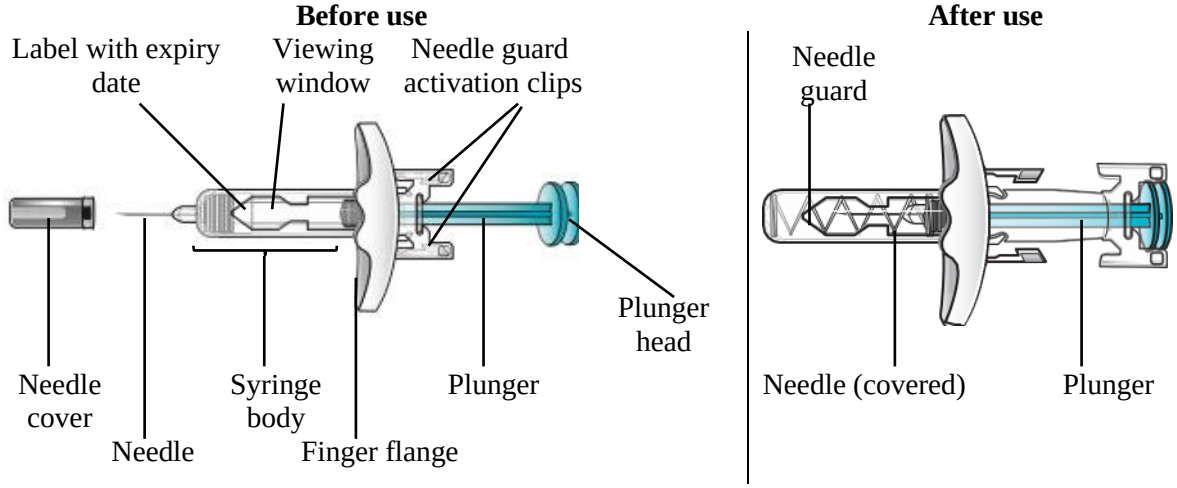
- Each Saphnelo pre-filled syringe contains 1 dose for one time use only. **Do not** share Saphnelo pre-filled syringe with other people.

Do not use Saphnelo pre-filled syringe if it has:

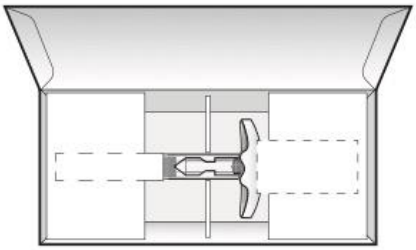
- been frozen or exposed to heat.
- been dropped, damaged, or appears to be tampered with.

Do not shake Saphnelo pre-filled syringe.
If any of the above happens, throw away the pre-filled syringe in a puncture-resistant (sharps) disposal container and use a new pre-filled syringe.
Keep this medicine out of the sight and reach of children.

Saphnelo pre-filled syringe parts
Do not remove the needle cover until right before injecting Saphnelo.
Do not touch the needle guard activation clips. This will keep you from activating the needle guard too soon.



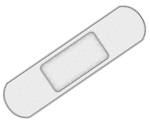
Preparing to inject using Saphnelo pre-filled syringe
Step 1 – Gather supplies for your injection



1 Saphnelo pre-filled syringe from the refrigerator

1 alcohol wipe

1 cotton ball or gauze



1 small bandage

1 sharps disposal container

Not included

See Step 9 for instructions on how to throw away (dispose of) the used Saphnelo pre-filled syringe.

Step 2 – Inspect carton and wait 60 minutes
Select a clean, well-lit, flat work surface, such as a table.
Check the expiry date (EXP) on the carton.
- **Do not** use if the expiry date has passed.

Check the carton for damage.
- **Do not** use if the carton looks damaged.

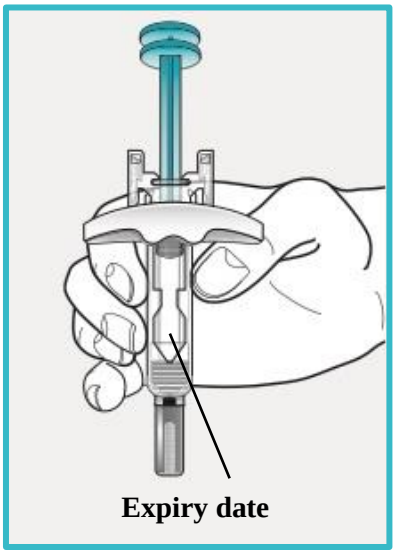
Let Saphnelo pre-filled syringe come to room temperature for 60 minutes before injecting.
- Keep Saphnelo pre-filled syringe in original carton to protect from light.
- **Do not** warm Saphnelo pre-filled syringe in any other way. For example, **do not** warm it in a microwave, hot water, direct sunlight, or near other heat sources.

Step 3 – Remove pre-filled syringe from the carton and inspect
Open the carton and remove Saphnelo pre-filled syringe by holding the middle of the syringe body.
- **Do not** hold or remove by the plunger.

Check the expiry date on the pre-filled syringe.
- **Do not** use if the expiry date has passed.

Check the pre-filled syringe for damage.
- **Do not** use if damaged.

Check the liquid through the viewing window.
- The liquid should be clear and colourless to slightly yellow.
- **Do not** use if the liquid is cloudy, discoloured, or contains visible particles.
- It is normal to see small air bubbles in the liquid. **Do not** try to remove the air bubbles.

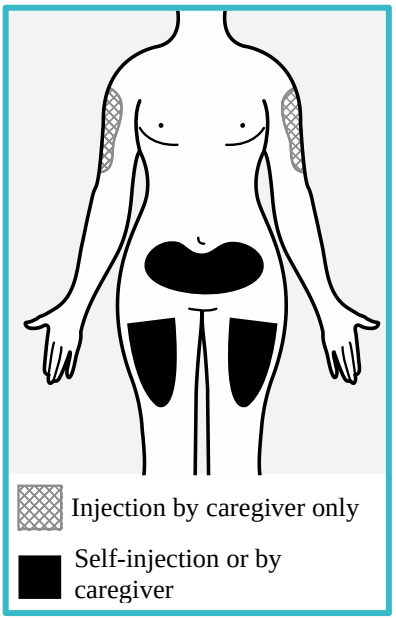


Injecting Saphnelo

Step 4 – Choose an injection site

You or your caregiver can inject in the front of your thigh or the lower part of your stomach (abdomen).
A caregiver may also inject you in your upper arm.
Do not try to inject yourself in the upper arm.
Choose an injection site that is at least 3 cm away from where you last injected.
Do not inject:

- into the 5 cm area around your belly button.
- where the skin is red, warm, tender, bruised, scaly, or hard.
- into scarred, damaged, discoloured, or tattooed skin.
- through clothing.



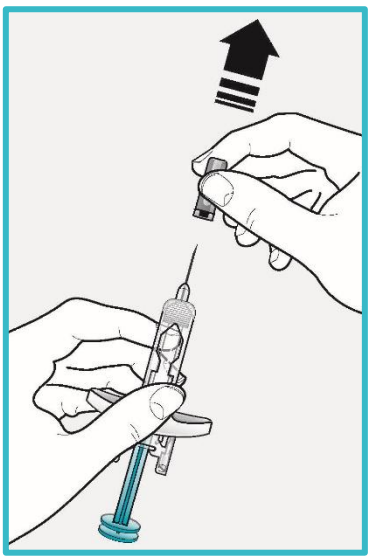
Step 5 – Wash your hands and clean the injection site

Wash your hands well with soap and water.
Clean the injection site with an alcohol wipe or with soap and water. Let the site air dry.

- **Do not** touch the cleaned injection site again or blow on it before injecting.

Step 6 – Pull off the needle cover

Hold the pre-filled syringe body with 1 hand and carefully pull the needle cover straight off with your other hand.

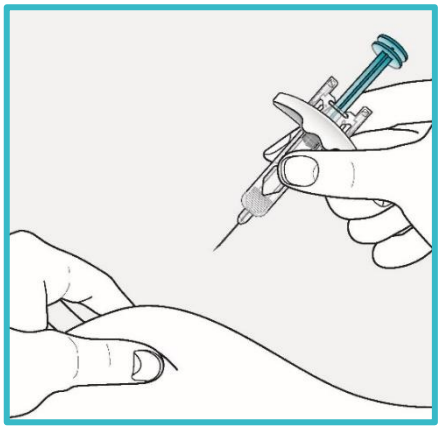


- **Do not** twist or wiggle the needle cover to remove it.
- **Do not** touch or pull the plunger or plunger head while removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- **Do not** recap the needle. Put the needle cover to the side to throw it in the trash later.
- **Do not** touch the needle or let it touch any surface.
- **Do not** use if the needle is damaged or dirty.

Go to Step 7 right away after removing the needle cover.

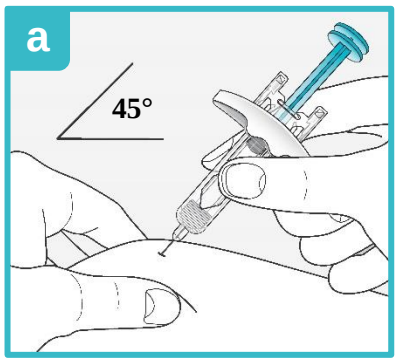
Step 7 – Inject Saphnelo

Hold Saphnelo pre-filled syringe in 1 hand as shown. Use your other hand to gently pinch and hold the cleaned injection site.

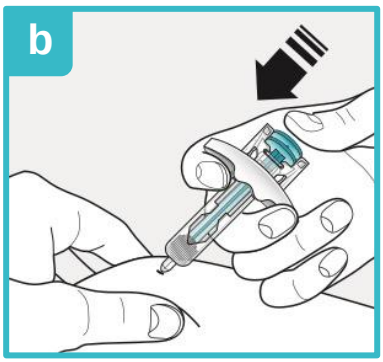


- **Do not** press down on the plunger head until the needle is inserted into the skin.
- **Do not** pull back on the plunger head at any time.

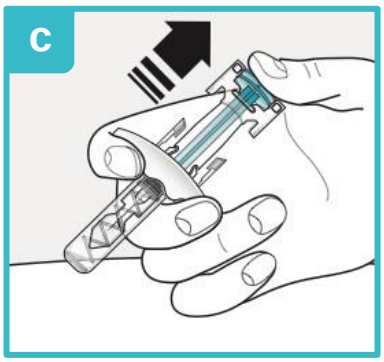
Inject using the pre-filled syringe by following the steps in figures **a, b,** and **c**.



Using a 45-degree angle, fully insert the needle into the pinched skin.
Do not reposition the pre-filled syringe after you insert the needle into the skin.



Use your thumb to push down on the plunger head.
To make sure you inject all the medicine and activate the needle guard, keep pushing firmly on the plunger until it is fully down as far as it will go.

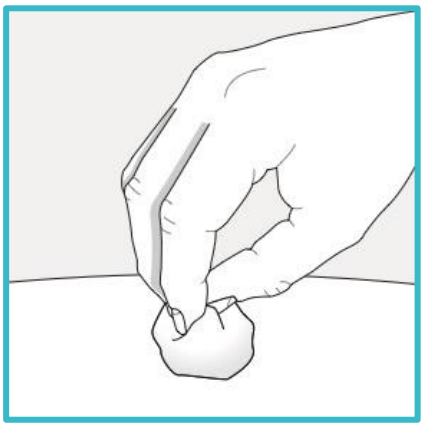


Slowly let go of the plunger until the needle guard covers the needle.
If the needle is not covered, carefully throw away (dispose of) the syringe right away (see Step 9).

Step 8 – Check the injection site

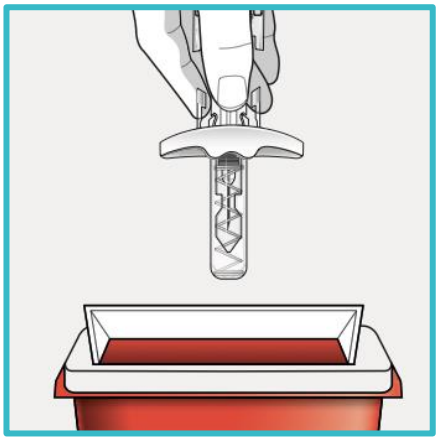
There may be a small amount of blood or liquid at the injection site. This is normal.
If needed, press a cotton ball or gauze on the area and apply a small bandage.

- **Do not** rub the injection site.



Step 9 – Throw away (dispose of) the used Saphnelo pre-filled syringe

Each pre-filled syringe contains 1 single dose of Saphnelo and **cannot be used again. Do not** recap the needle.
Put your used Saphnelo pre-filled syringe in a **sharps disposal container** right away after use.
Do not throw away (dispose of) Saphnelo pre-filled syringe in your household trash.



Disposal guidelines

Dispose of the full container as instructed by your healthcare provider or pharmacist.
Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.
Do not recycle your used sharps disposal container.

Package leaflet: Information for the patient

Saphnelo 120 mg solution for injection in pre-filled pen
anifrolumab

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What Saphnelo is used for
Saphnelo is used to treat **moderate to severe lupus** (systemic lupus erythematosus, SLE) in adults whose disease is not well controlled by standard therapies ('oral corticosteroids', 'immunosuppressants' and/or 'antimalarials').

You will be given Saphnelo as well as your standard therapy for lupus.

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People with lupus have high levels of proteins called 'type I interferons' which stimulate the activity of the immune system. Anifrolumab attaches to a target (receptor) that these proteins act on, stopping them from working. Blocking their action in this way can reduce the inflammation in your body that causes the signs of lupus.

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

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Talk to your doctor or nurse before using Saphnelo:
- if you think you have had an **allergic reaction** to this medicine at any time (see below under 'Look out for signs of serious allergic reactions and infections').
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- if your lupus affects your kidneys or nervous system.
- if you have, or have had, cancer.
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- if you are receiving another biological medicinal product (such as belimumab for your lupus).

If you are not sure if any of the above applies to you, talk to your doctor or nurse before you are given Saphnelo.

Look out for signs of serious allergic reactions and infections
Saphnelo may cause **serious allergic reactions (anaphylaxis)** see section 4. **Get medical attention immediately** if you think you may be having a serious allergic reaction. Signs may include:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

You may be more at risk of getting an **infection** when you are being treated with Saphnelo. **Tell your doctor or nurse as soon as possible** if you notice signs of any possible infection, including:
- fever or flu-like symptoms
- muscle aches
- cough or feeling short of breath (these may be signs of an infection in your airways, see section 4)
- burning when you urinate or passing urine more often than usual
- diarrhoea or stomach pain
- red skin rash that can cause pain and burning (this may be a sign of shingles, see section 4).

Each time you get a new pack of Saphnelo
- Write down the name and the Lot number shown on the outer carton and the label of the pre-filled pen and keep this information in a safe place. You may be asked for this information in the future.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Saphnelo
- Tell your doctor if you are taking, have recently taken or might take any other medicines.
- Tell your doctor if you have recently had or are going to have a vaccination. You should not be given certain types of vaccines while using this medicine. If you are not sure, talk to your doctor or nurse before and during treatment with Saphnelo.

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

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

Breast-feeding
- **Before you start treatment with Saphnelo, tell your doctor if you are breast-feeding**. It is not known whether this medicine is passed into breast milk. Your doctor will discuss with you whether you should stop treatment with this medicine while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

Saphnelo contains polysorbate
This medicine contains 0.4 mg of polysorbate 80 (E 433) in each pre-filled pen, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Saphnelo

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

The recommended dose is 120 mg once a week. Saphnelo is given as an injection under the skin (subcutaneously).

Your doctor or nurse will decide if you can inject this medicine yourself or if your caregiver can do this for you.

Before injecting Saphnelo
- Your doctor or nurse should train you or your caregiver how to use Saphnelo pre-filled pen in the right way.
- **Carefully read the 'Instructions for Use'**. Do this each time you get a new pack. There may be new information.

If you or your caregiver have any questions, talk to your doctor, nurse or pharmacist.

If you use more Saphnelo than you should
If you have used more Saphnelo than you should talk to your doctor immediately.

If you forget to use Saphnelo
- If you miss your dose of Saphnelo, inject a dose as soon as you remember. Then, continue once weekly dosing based on the new day Saphnelo was injected or at your regularly scheduled time as long as there are at least 3 days between the doses.
- If you are not sure when to inject, ask your doctor, nurse or pharmacist.

Stopping treatment with Saphnelo
- Do not stop using Saphnelo without talking to your doctor.

- Your doctor will decide if you need to stop using this medicine.

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

4. Possible side effects

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

Serious allergic reactions:
Serious allergic reactions (*anaphylaxis*) are uncommon (may affect up to 1 in 100 people). **Get medical attention immediately, or go to the nearest emergency department,** if you get any of the following signs of a serious allergic reaction:
- swelling of your face, tongue, or mouth
- breathing difficulties
- feeling faint, dizzy or lightheaded (due to a drop in blood pressure).

Other side effects:
Tell your doctor or nurse if you get any of the following side effects.

Very common (may affect more than 1 in 10 people)
- infections of the nose or throat
- chest infection (*bronchitis*)

Common (may affect up to 1 in 10 people)
- infections of the sinuses or lungs
- shingles (*herpes zoster*) - a red skin rash that can cause pain and burning
- allergic (*hypersensitivity*) reactions

Not known (the frequency cannot be estimated from the available data)
- joint pain (*arthralgia*)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Saphnelo

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.
Keep this medicine out of the sight and reach of children.
Store in a refrigerator (2 °C – 8 °C).
Store in the original package to protect from light.
Do not freeze, shake or expose to heat.

If needed, an unopened carton can be stored at room temperature (20 °C – 25 °C) for up to 7 days. Once the Saphnelo pre-filled pen has been removed from the refrigerator and has reached room temperature (20 ºC – 25 ºC) it must either be used within 7 days or thrown away (discarded).

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

6. Contents of the pack and other information

What Saphnelo contains
- The **active substance** is anifrolumab. Each pre-filled pen contains 120 mg of anifrolumab.
- The **other ingredients** are histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80 (E 433) (see section 2 “Saphnelo contains polysorbate”) and water for injections.

What Saphnelo looks like and contents of the pack
- Saphnelo is a clear to opalescent, colourless to slightly yellow solution.
- Saphnelo is available in a pack containing 1 pre-filled pen.

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Sweden

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

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This leaflet was last revised in

Other sources of information

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

Instructions for Use

Saphnelo 120 mg solution for injection in pre-filled pen
anifrolumab

This ‘Instructions for Use’ contains information on how to inject using Saphnelo pre-filled pen.

Read this Instructions for Use before you start using Saphnelo pre-filled pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you or your caregiver how to use Saphnelo pre-filled pen the right way. If you or your caregiver have any questions, talk to your healthcare provider. Saphnelo pre-filled pen is for use under the skin (subcutaneous) only.

Important storage information and warnings

- **Store Saphnelo pre-filled pen in a refrigerator between 2 °C to 8 °C in the original carton until ready to use.** If needed, an unopened carton can be stored at room temperature between 20 °C to 25 °C for up to 7 days.
- Keep Saphnelo pre-filled pen in original carton to protect from light.

- Each Saphnelo pre-filled pen contains 1 dose for one time use only. **Do not** share Saphnelo pre-filled pen with other people.

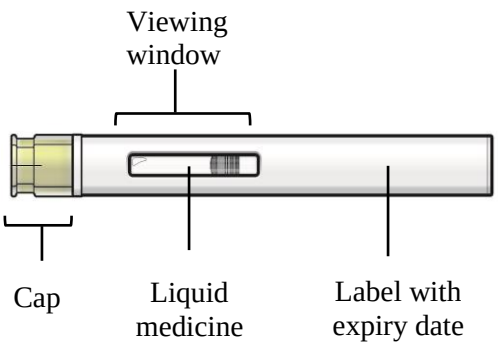
Do not use Saphnelo pre-filled pen if it has:
- been frozen or exposed to heat.
- been dropped, damaged, or appears to be tampered with.

Do not shake Saphnelo pre-filled pen.
If any of the above happens, throw away Saphnelo pre-filled pen in a puncture-resistant (sharps) disposal container and use a new Saphnelo pre-filled pen.
Keep this medicine out of the sight and reach of children.

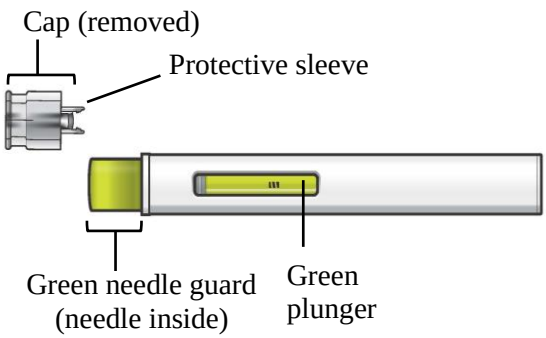
Saphnelo pre-filled pen parts

Do not remove the cap until right before injecting Saphnelo.
Do not touch the green needle guard.

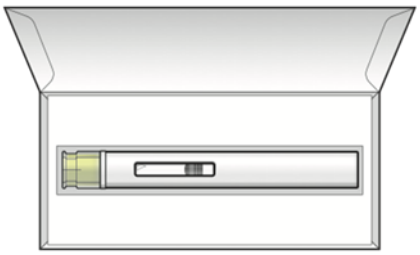
Before use



After use



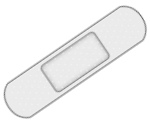
Preparing to inject using Saphnelo pre-filled pen
Step 1 – Gather supplies for your injection



1 Saphnelo pre-filled pen from the refrigerator

1 alcohol wipe

1 cotton ball or gauze



1 small bandage

1 sharps disposal container

Not included

See Step 10 for instructions on how to throw away (dispose of) the used Saphnelo pre-filled pen.

Step 2 – Inspect carton and wait 60 minutes
Select a clean, well-lit, flat work surface, such as a table.
Check the expiry date (EXP) on the carton.

- **Do not** use if the expiry date has passed.

Check the carton for damage.

- **Do not** use if the carton looks damaged.

Let Saphnelo pre-filled pen come to room temperature for 60 minutes before injecting.

- Keep Saphnelo pre-filled pen in original carton to protect from light.
- **Do not** warm Saphnelo pre-filled pen in any other way. For example, **do not** warm it in a microwave, hot water, direct sunlight, or near other heat sources.

Step 3 – Remove Saphnelo from the carton and inspect
Open the carton and remove Saphnelo pre-filled pen by gently grasping the middle of the device.

Check the expiry date on Saphnelo pre-filled pen.

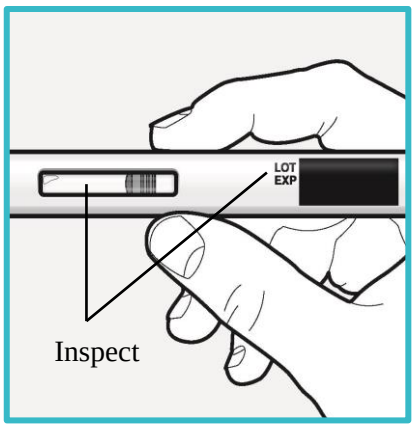
- **Do not** use if the expiry date has passed.

Check Saphnelo pre-filled pen for damage.

- **Do not** use if damaged.

Check the liquid through the viewing window.

- The liquid should be clear and colourless to slightly yellow.
- **Do not** use if the liquid is cloudy, discoloured, or contains visible particles.
- It is normal to see small air bubbles in the liquid. **Do not** try to remove the air bubbles.

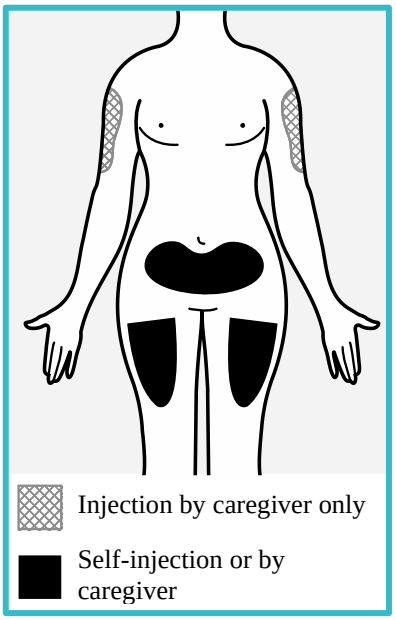


Injecting Saphnelo

Step 4 – Choose an injection site

You or your caregiver can inject in the front of your thigh or the lower part of your stomach (abdomen).
A caregiver may also inject you in your upper arm.
Do not try to inject yourself in the upper arm.
Choose an injection site that is at least 3 cm away from where you last injected.
Do not inject:

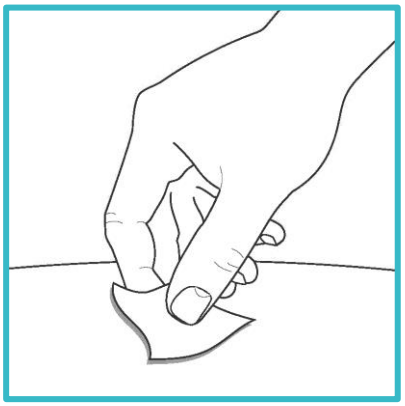
- into the 5 cm area around your belly button.
- where the skin is red, warm, tender, bruised, scaly, or hard.
- into scarred, damaged, discoloured, or tattooed skin.
- through clothing.



Step 5 – Wash your hands and clean the injection site

Wash your hands well with soap and water.
Clean the injection site with an alcohol wipe or with soap and water. Let the site air dry.

- **Do not** touch the cleaned injection site again or blow on it before injecting.



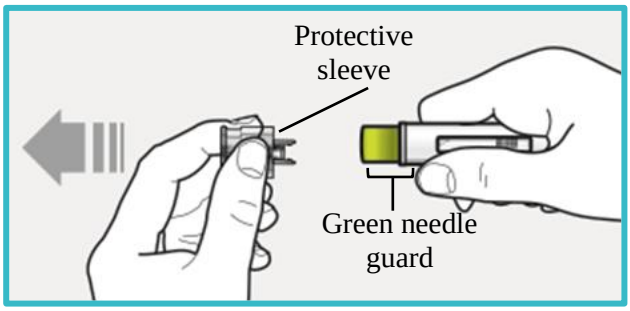
Step 6 – Pull off the cap

Do not remove the cap until you are ready to inject.

Pull off the cap.

- Saphnelo pre-filled pen is now unlocked and ready to inject.
- **Do not** touch the green needle guard or the needle inside.
- **Do not** recap Saphnelo pre-filled pen. This could cause the medicine to come out too soon or damage the pre-filled pen.

Go to Step 7 right away after removing the cap.



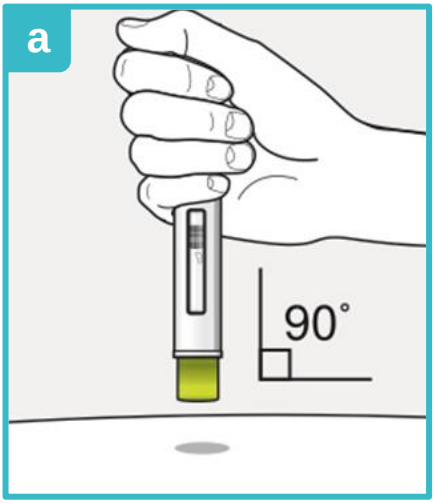
Step 7 – Inject Saphnelo

Inject using Saphnelo pre-filled pen by following the steps in figures **a, b, c, and d**.

To deliver a full dose, **press and hold Saphnelo pre-filled pen for about 15 seconds** until the green plunger fills the viewing window.

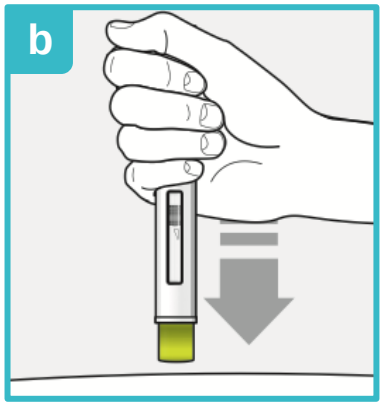
You may hear a **first 'click'** at the start of the injection and a **second 'click'** at the end of the injection.

Do not move or change the position of the pre-filled pen after the injection has started.



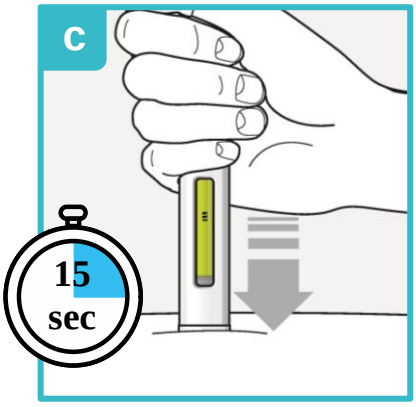
Position Saphnelo pre-filled pen.

- Place the green needle guard flat against the skin (90-degree angle).
- Make sure you can see the viewing window.



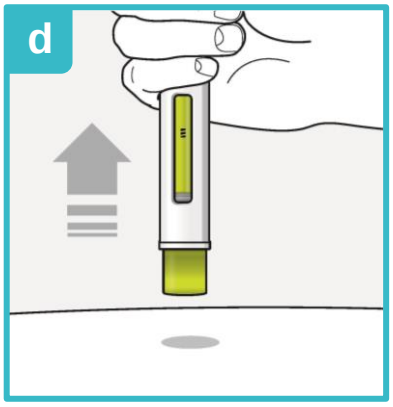
Press down firmly and hold against skin.

- You may hear the **first 'click'** right away. This tells you the injection has started.
- The green plunger will move down in the viewing window.



Hold down firmly for about 15 seconds.

- The green plunger will fill the viewing window.
- You may hear the **second 'click'** at the end of injection.



After you have completed your injection, lift Saphnelo pre-filled pen straight up.

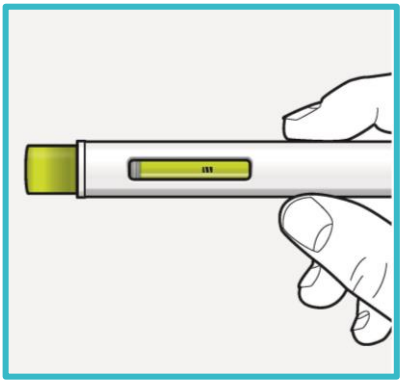
- The green needle guard will slide down and lock into place over the needle.

Step 8 – Check the viewing window

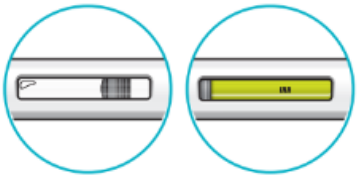
Check the viewing window to make sure all the medicine has been injected.

If the green plunger does not fill the viewing window, you may not have received the full dose.

- If this happens or if you have any other concerns, contact your healthcare provider.



Before injection



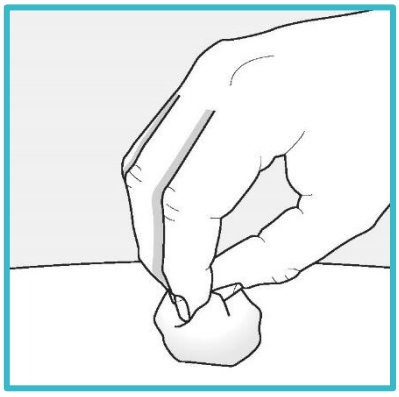
After injection

Step 9 – Check the injection site

There may be a small amount of blood or liquid at the injection site. This is normal.

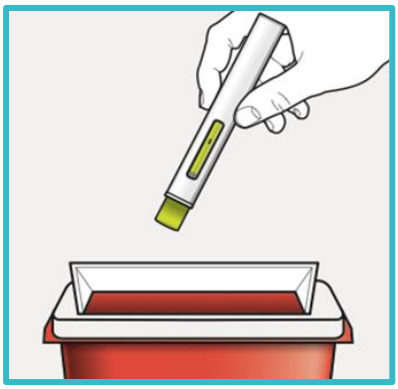
If needed, press a cotton ball or gauze on the area and apply a small bandage.

- **Do not** rub the injection site.



Step 10 – Throw away (dispose of) the used Saphnelo pre-filled pen

Put your used Saphnelo pre-filled pen in a **sharps disposal container** right away after use.
Do not throw away (dispose of) Saphnelo pre-filled pen in your household trash.



Disposal guidelines

Dispose of the full container as instructed by your healthcare provider or pharmacist.
Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.
Do not recycle your used sharps disposal container.