NOVARTIS

1 KESIMPTA

KESIMPTA® 20 mg/0.4 mL solution for injection

2 Description and composition

Pharmaceutical forms

20 mg/0.4 mL Solution for injection in a pre-filled syringe

20 mg/0.4 mL Solution for injection in a pre-filled pen

The single-use solution for injection is sterile, preservative-free, clear to slightly opalescent, and colorless to slightly brownish-yellow.

Active substance

Each pre-filled syringe and pre-filled pen contains 20 mg ofatumumab solution for injection (0.4 mL of 50 mg/mL solution).

Ofatumumab is a recombinant fully human monoclonal immunoglobulin G1 (IgG1) antibody against human CD20 expressed on B-cells. Ofatumumab is produced in a murine cell line (NS0) by recombinant DNA technology.

Excipients

L-arginine; sodium acetate trihydrate; sodium chloride; polysorbate 80; disodium edetate dihydrate; hydrochloric acid and water for injection.

3 Indications

KESIMPTA is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) (refer to Section 12 Clinical Studies).

4 Dosage regimen and administration

Dosage regimen

The recommended dose is 20 mg KESIMPTA administered by subcutaneous injection with:

- initial dosing at weeks 0, 1 and 2, followed by
- subsequent monthly dosing, starting at week 4.

Missed Doses

If an injection of KESIMPTA is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals.

Special populations

Renal impairment

No specific studies of ofatumumab in patients with renal impairment have been performed.

Patients with mild renal impairment were included in clinical studies. There is no experience in patients with moderate and severe renal impairment. However, as ofatumumab is not excreted via

urine, it is not expected that patients with renal impairment require dose modification (see section 11 Clinical pharmacology).

Hepatic impairment

No studies of ofatumumab in patients with hepatic impairment have been performed.

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification (see section 11 Clinical pharmacology).

Pediatric patients (below 18 years)

The safety and effectiveness in pediatric MS patients below the age of 18 years have not yet been studied.

Adults over 55 years old

No studies have been performed in MS patients over the age of 55 years old. Ofatumumab was studied in patients with RMS aged 18 to 55 years. Based on the limited data available, no dose adjustment is considered necessary in patients over the age of 55 years old (see section 11 Clinical pharmacology).

Method of administration

KESIMPTA is intended for patient self-administration by subcutaneous injection.

The usual sites for subcutaneous injections are the abdomen, the thigh and the upper outer arm.

The first injection of KESIMPTA should be performed under the guidance of a healthcare professional (see section 6 Warning and precautions).

Comprehensive instructions for administration are provided in section 14 Pharmaceutical information.

5 Contraindications

- History of confirmed hypersensitivity to Kesimpta (see section 6 Warnings and precautions)
- Patients who are hypersensitive to ofatumumab or any ingredient in the formulation.
- Patients in a severely immunocompromised state (see section 6 Warnings and Precautions)
- Severe active infection until resolution (see section 6 Warnings and Precautions)
- Known active malignancy

6 Warnings and precautions

Injection-related reactions

Injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain.

Systemic injection-related reactions (SIRRs) observed in clinical studies occurred predominantly with the first injection. Symptoms observed include fever, headache, myalgia, chills and fatigue and were predominantly (99.7%) non-serious and mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies.

Additional SIRRs reported in the post-marketing setting include rash, urticaria, dyspnea, angioedema (e.g., tongue, pharyngeal or laryngeal swelling), and rare cases which were reported as anaphylaxis.

Most of the cases were non-serious and occurred with first injection. While there were some cases which were serious and resulted in discontinuation of Kesimpta treatment, there were also serious cases where patients were able to continue Kesimpta treatment without further incidents.

Some SIRR symptoms may be clinically indistinguishable from Type 1 acute hypersensitivity reactions (IgE-mediated). Patients should be informed that SIRRs generally occur within 24 hours and predominantly following the first injection. SIRRs can be managed with symptomatic treatment, should they occur.

A hypersensitivity reaction may present with any injection, although typically would not present with the first injection. For subsequent injections, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known IgE mediated hypersensitivity to Kesimpta must not be treated with Kesimpta (see section 5 Contraindications).

Only limited benefit of premedication with steroids was seen in RMS clinical studies. Ofatumumab-treated patients who received premedication with methylprednisolone (or an equivalent steroid) experienced fewer symptoms such as fever, myalgia, chills, and nausea. However, the use of steroid premedication increased the occurrence of flushing, chest discomfort, hypertension, tachycardia, and abdominal pain even in the absence of ofatumumab treatment (i.e. in patients receiving placebo injections). Therefore, use of premedication is not required.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional.

Infections

Based on its mode of action, ofatumumab has the potential for an increased risk of infections. Administration should be delayed in patients with an active infection until the infection is resolved.

It is recommended to evaluate the patient's immune status prior to initiating therapy with Kesimpta. Kesimpta must not be given to patients with severe immunosuppression (e.g. significant neutropenia or lymphopenia).

In RMS clinical studies, the proportion of patients with infections was similar in the ofatumumab and the teriflunomide treatment groups. In the Phase 3 pivotal clinical studies, 51.6% of ofatumumab-treated patients experienced at least one infection compared to 52.7% of teriflunomide-treated patients.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (at substantially higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). In addition, JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies, physicians should be vigilant for medical history of PML, any clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. At the first sign or symptom suggestive of PML, withhold KESIMPTA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness

of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is confirmed, discontinue treatment of KESIMPTA.

Hepatitis B Virus Reactivation

Patients with active hepatitis B disease should not be treated with KESIMPTA. HBV screening should be performed in all patients before initiation of treatment with KESIMPTA. At minimum screening should include Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Patients who are negative for HbsAg and positive for Hepatitis B core antibody [HbcAb+] or are carriers of HBV [HbsAg+] should consult liver disease experts before starting and during treatment with Kesimpta.

No cases of hepatitis B virus (HBV) reactivation were identified in Kesimpta RMS clinical studies. However, hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies, which in some cases resulted in fulminant hepatitis, hepatic failure and death.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 5 Contraindications). It is not recommended to use other immunosuppressants concomitantly with KESIMPTA except corticosteroids for symptomatic treatment of relapses.

Vaccinations

All immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines.

KESIMPTA may interfere with the effectiveness of inactivated vaccines.

The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion (see section 11 Clinical pharmacology).

Vaccination of infants born to mothers treated with KESIMPTA during pregnancy

In infants of mothers treated with KESIMPTA during pregnancy, live or live-attenuated vaccines should not be administered before the recovery of B-cell counts has been confirmed. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered as indicated prior to recovery from B-cell depletion, however assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted (see section 9 Pregnancy, lactation, females and males of reproductive potential).

7 Adverse drug reactions

Summary of the safety profile

Approximately 1500 patients with RMS received ofatumumab in clinical studies. In the two Phase 3 pivotal studies, 1882 patients with RMS were randomized, 946 of whom were treated with ofatumumab for a median duration of 85 weeks; 33% of patients receiving ofatumumab were treated for more than 96 weeks (see section 12 Clinical Studies).

The proportion of patients with adverse events (AEs) (83.6% versus 84.2%) and the AEs leading to drug discontinuation (5.7% versus 5.2%) were similar in the ofatumumab and teriflunomide groups.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions that have been reported in pivotal clinical studies are listed by MedDRA system organ class (Table 7-1). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Summary of Adverse Events by System Organ Class, Preferred Term and Frequency categorization based on >=2% in OMB group and >1% higher than TER group (Pool C2)Safety Set

System organ class Preferred term	OMB 20mg N=946 n (%)	TER 14mg N=936 n (%)	Frequency Category for OMB
Gastrointestinal disorders			
Constipation	24 (2.5)	14 (1.5)	common
General disorders and administration site conditions			
Injection site reaction	103 (10.9)	52 (5.6)	very common
Pyrexia	37 (3.9)	26 (2.8)	common
Influenza like illness	21 (2.2)	10 (1.1)	common
Infections and infestations			
Nasopharyngitis	170 (18.0)	156 (16.7)	very common
Urinary tract infection	97 (10.3)	78 (8.3)	very common
Injury, poisoning and procedural complications			
Injection related reaction	195 (20.6)	143 (15.3)	very common
Investigations			
Blood immunoglobulin M decreased	56 (5.9)	21 (2.2)	common
Musculoskeletal and connective tissue disorders			
Back pain	72 (7.6)	58 (6.2)	common
Muscular weakness	23 (2.4)	13 (1.4)	common
Psychiatric disorders			
Anxiety	43 (4.5)	33 (3.5)	common

- A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- Preferred terms are sorted in descending frequency of AEs in the OMB frequency column.
- N is the number of patients in the treatment group, n is the number of patients with at least one event in the treatment group.
- % is calculated by n/N*100.
- MedDRA Version 22.0
- Frequency category is based on the clinical trial database (N) according to the CIOMS III convention: very common (>=1/10); common (>=1/100 to <1/10);

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from postmarketing experience with Kesimpta via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore

categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders	Hypersensitivity reaction

Description of selected adverse drug reactions

Upper Respiratory Tract Infections

A higher proportion of ofatumumab-treated patients experienced upper respiratory tract infections compared to teriflunomide-treated patients. In the RMS clinical studies, 39.4% of ofatumumab-treated patients experienced upper respiratory tract infections compared to 37.8% of teriflunomide-treated patients. The infections were predominantly mild to moderate and mostly consisted of nasopharyngitis, upper respiratory tract infection and influenza.

Injection related reactions and injection site reactions

In patients treated with ofatumumab in the RMS Phase 3 clinical studies, injection related reactions (systemic) and injection-site reactions (local) were reported in 20.6% and 10.9% of patients treated with ofatumumab, respectively.

The incidence of injection-related reactions was highest with the first injection (14.4%), decreasing significantly with subsequent injections (4.4% with second, <3% from third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Only two (0.2%) ofatumumab-treated MS patients reported serious injection-related reactions. There were no life-threatening injection-related reactions. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills, and fatigue.

Local reactions at the administration site were very common. Injection-site reactions were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2%) included erythema, pain, itching, and swelling (see section 6 Warnings and precautions).

Laboratory abnormalities

Immunoglobulins

During the course of the RMS Phase 3 clinical studies, a decrease in mean IgM value of 30.9% after 48 weeks and 38.8% after 96 weeks was noted. In 14.3% of patients, treatment with ofatumumab resulted in a decrease in IgM that reached a value below 0.34 g/L. KESIMPTA was associated with a decrease of 4.3% in mean IgG levels after 48 weeks of treatment and an increase of 2.2% after 96 weeks.

8 Interactions

Ofatumumab does not share a common clearance pathway with chemical drugs that are metabolized by the cytochrome P450 system or other drug metabolizing enzymes. Additionally, there is no evidence that CD20 monoclonal antibodies (mAbs) are involved in the regulation of the expression of drug metabolizing enzymes. Interactions between KESIMPTA and other medicinal products have not been investigated in formal studies.

Vaccinations

The safety of and the ability to generate a primary or anamnestic (recall) response to immunization with live, live-attenuated or inactivated vaccines during ofatumumab treatment has not been investigated. The response to vaccination could be impaired when B-cells are depleted. It is recommended that patients complete immunizations prior to the start of KESIMPTA therapy (see section 6 Warnings and precautions).

Other Immunosuppressive or Immune-Modulating Therapies

The risk of additive immune system effects should be considered when coadministering immunosuppressive therapies with KESIMPTA.

When initiating KESIMPTA after other immunosuppressive therapies with prolonged immune effects, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are limited amount of data from the use of ofatumumab in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies (see Animal data). No teratogenicity was observed after intravenous administration of ofatumumab to pregnant monkeys during organogenesis at doses equivalent to at least 160-fold the therapeutic dose on the basis of AUC.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. The potential duration of B-cell depletion in infants exposed to ofatumumab in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown (see sections 6 Warnings and precautions and 11 Clinical pharmacology).

To help determine the effects of ofatumumab in pregnant woman, healthcare professionals are encouraged to report all pregnancy cases and complications that happen during treatment or within 6 months after the last dose of Kesimpta to the marketing authorization holder, in order to allow monitoring of these patients through the Pregnancy outcomes Intensive Monitoring program (PRIM).

Epidemiologic studies from USA, Canada, major EU countries and South American countries have shown that the risk of birth defects in MS population is similar to that in the general population. For spontaneous abortions and still births, the background risk in the MS population in the US appears to be similar to that in the general US population.

Treatment with KESIMPTA should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Animal data

The embryo-fetal development (EFD) and the enhanced pre/postnatal development (ePPND) studies in monkeys showed that exposure to ofatumumab given intravenously during gestation caused no maternal toxicity, no teratogenicity, and no adverse effects on embryo-fetal and pre/post-natal

development. The NOAEL for these parameters leads to AUC-based safety margins of at least 160-fold when compared with human exposure at the therapeutic dose of 20 mg monthly.

In these studies, ofatumumab was detected in the blood of the fetuses and infants, confirming placental transfer and fetal exposure to ofatumumab persisting post-natally (long half-life of the monoclonal antibody). Exposure to ofatumumab during gestation led to the expected depletion of CD20+ B-cells in maternal animals and their fetuses and infants, along with a reduced spleen weight (without histological correlate) in fetuses and a reduced humoral immune response to keyhole limpet haemocyanin (KLH) in infants at high doses. All these changes were reversible during the 6-month postnatal period. In infants, early postnatal mortality was observed at a dose 160 times higher than the therapeutic dose (on AUC basis) and was likely due to potential infections secondary to immunomodulation. The NOAEL related to the pharmacological activity of ofatumumab in infants of the ePPND study leads to an AUC-based safety margin of at least 22-fold when maternal exposure at the NOAEL is compared with human exposure at the therapeutic dose of 20 mg monthly.

9.2 Lactation

Risk summary

The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is transferred into human milk; however, human IgG is present in human milk. There are no data on the effects of KESIMPTA on the breastfed infant or on milk production. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA.

9.3 Females and males of reproductive potential

Contraception

Females of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA.

Fertility

There are no data on the effect of ofatumumab on human fertility.

Non-clinical data did not indicate potential hazards for humans based on male and female fertility parameters assessed in monkeys. The NOEL-related exposure is at least 260-times higher than the human exposure at the therapeutic dose of 20 mg monthly in terms of AUC.

10 Overdosage

Doses up to 700 mg have been administered intravenously in clinical studies with MS patients without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted as necessary.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AG12

Mechanism of action (MOA)

Ofatumumab is a fully human anti-CD20 monoclonal antibody (IgG1). It binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule giving rise to a slow off-rate and high binding affinity. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells.

The binding of ofatumumab to CD20 induces lysis of CD20+ B-cells primarily through complement-dependent cytotoxicity (CDC) and to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.

Pharmacodynamics (PD)

B-cell depletion

In the RMS Phase 3 studies, ofatumumab 20 mg every 4 weeks, after an initial dose regimen of 20 mg on days 1, 7 and 14, resulted in a rapid and sustained reduction of B-cells to below the lower limit of normal as early as two weeks after treatment initiation, and sustained for as long as 120 weeks while on treatment.

Similar results were observed in a study of bioequivalence using the same dosing regimen as in the Phase 3 studies. Before initiation of the maintenance phase starting at week 4, total B-cell levels <10 cells/µL were reached in 94% of patients increasing to 98% of patients at week 12.

B-cell repletion

Data from RMS Phase 3 studies indicate a median time to B-cell recovery to LLN or baseline value of 24.6 weeks post treatment discontinuation. PK-B-cell modelling and simulation for B-cell repletion corroborate this data, predicting median time to B-cell recovery to LNN of 23 weeks post treatment discontinuation.

Immunogenicity

In RMS Phase 3 studies, the overall incidence of ADAs was very low: treatment induced ADA were detected in 2 of 914 ofatumumab treated patients and no patients with treatment enhancing or neutralizing ADA were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient.

Pharmacokinetics (PK)

Absorption

A monthly subcutaneous dose of 20 mg leads to a mean AUCtau of 483 µg·h/mL and a mean Cmax of 1.43 µg/mL at steady state.

After subcutaneous administration, ofatumumab is believed to be predominantly absorbed via the lymphatic system similarly to other therapeutic monoclonal antibodies.

Distribution

The volume of distribution at steady-state was estimated to be 5.42 litres following repeated subcutaneous administration of ofatumumab at a dose of 20 mg.

Biotransformation/metabolism

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Elimination

Ofatumumab is eliminated in two ways: a target mediated route that is related to binding to B cells and a target-independent route mediated by non specific endocytosis followed by intracellular catabolism, as with other IgG molecules. B-cells present at baseline result in greater component of target-mediated clearance of ofatumumab at the start of therapy. Ofatumumab dosing leads to potent depletion of B cells resulting in reduced overall clearance.

The half-life at steady state was estimated to be approximately 16 days following repeated subcutaneous administration of ofatumumab at a dose of 20 mg.

Linearity/non-linearity

Ofatumumab had non-linear pharmacokinetics related to its decreasing clearance over time.

Special populations

Pediatric patients (below 18 years)

The safety and effectiveness in pediatric patients below the age of 18 years have not yet been established.

Adult over 55 years old

There are no dedicated pharmacokinetic studies of ofatumumab in patients over 55 years old due to limited clinical experience.

Gender

Gender had a modest (12%) effect on ofatumumab central volume of distribution in a cross-study population analysis, with higher C_{max} and AUC values observed in female patients (48% of the patients in this analysis were male and 52% were female); these effects are not considered clinically relevant, and no dose adjustment is recommended.

Renal impairment

Ofatumumab is not excreted via urine; therefore, it is not expected that patients with renal impairment require dose modification.

Hepatic impairment

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification.

12 Clinical studies

The efficacy and safety of ofatumumab were evaluated in two randomized, double-blind, active-controlled Phase 3 pivotal studies of identical design (G2301 (ASCLEPIOS I) and G2302 (ASCLEPIOS II)) in patients with relapsing forms of MS (RMS), aged 18 to 55 years, a disability status at screening with an Expanded Disability Status Scale (EDSS) score from 0 to 5.5, and who had experienced at least one documented relapse during the previous year or two relapses during the previous two years or a positive gadolinium (Gd)-enhancing MRI scan during the previous year. Both newly diagnosed patients and patients switching from their current treatment were enrolled.

In the two studies, 927 and 955 patients with RMS, respectively, were randomized 1:1 to receive either ofatumumab 20 mg subcutaneous injections every 4 weeks starting at Week 4 after an initial dosing regimen of three weekly 20 mg doses in the first 14 days (on Days 1, 7 and 14) or teriflunomide 14 mg capsules orally once daily. Patients also received matching placebo corresponding to the other treatment arm to ensure blinding (double-dummy design).

The treatment duration for individual patients was variable based on when the end of study criteria were met. Across both studies, the median treatment duration was 85 weeks, 33.0% of patients in the ofatumumab group vs 23.2% of patients in the teriflunomide group were treated more than 96 weeks.

Demographics and baseline characteristics were well-balanced across treatment arms and both studies (see Table 12-1). Mean age was 38 years, mean disease duration was 8.2 years since onset of first symptom, and mean EDSS score was 2.9; 40% of patients had not been previously treated with a disease modifying therapy (DMT) and 40% had gadolinium (Gd)-enhancing T1 lesions on their baseline MRI scan.

The primary efficacy endpoint of both studies was the annualized rate of confirmed relapses (ARR) based on EDSS. Key secondary efficacy endpoints included the time to disability worsening on EDSS (confirmed at 3 months and 6 months), defined as an increase in EDSS of ≥1.5, ≥1, or ≥0.5 in patients with a baseline EDSS of 0, 1 to 5, or ≥5.5, respectively. Further key secondary endpoints were the time to disability improvement on EDSS (confirmed at 6 months), the number of Gd-enhancing T1 lesions per MRI scan, the annualized rate of new or enlarging T2 lesions, the neurofilament light chain (NfL) concentration in serum and the rate of brain volume loss (BVL). Disability-related key-secondary endpoints were evaluated in a meta-analysis of combined data from studies G3201 and G2302, as defined in the study protocols.

Table 12-1 Demographics and baseline characteristics

Characteristics	**Study G2301 (ASCLEPIOS I)**		**Study G2302 (ASCLEPIOS II)**	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Mean age (years)	38.9	37.8	38.0	38.2
Age range (years)	19 - 55	18 - 55	18 - 55	18 - 55
Female (%)	68.4	68.6	66.3	67.3
Mean/Median duration of MS since first symptoms (years)	8.36 / 6.41	8.18 / 6.69	8.20 / 5.70	8.19 / 6.30
Mean/Median duration of MS since diagnosis (years)	5.77 / 3.94	5.64 / 3.49	5.59 / 3.15	5.48 / 3.10
Previously treated with DMTs (%)	58.9	60.6	59.5	61.8
Number of relapses in last 12 months	1.2	1.3	1.3	1.3
Mean/Median EDSS score	2.97 / 3.00	2.94 / 3.00	2.90 / 3.00	2.86 / 2.50
Mean total T2 lesion volume (cm^3)	13.2	13.1	14.3	12.0
Patients free of Gd+ T1 lesions (%)	62.6	63.4	56.1	61.4

Characteristics	Study G2301 (ASCLEPIOS I)		Study G2302 (ASCLEPIOS II)	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Number of Gd+ T1 lesions (mean)	1.7	1.2	1.6	1.5

The efficacy results for both studies are summarized in Table 12-2, Figure 12-1 and Figure 12-2.

In both Phase 3 studies (G2301 and G2302), ofatumumab demonstrated a significant reduction in the annualized relapse rate of 50.5% and 58.4%, respectively (both p<0.001) compared to teriflunomide.

The pre-specified meta-analysis of combined data showed that ofatumumab significantly reduced the risk of 3-month confirmed disability worsening (CDW) (risk reduction = 34.3%, p=0.003) and 6-month CDW (risk reduction = 32.4%, p=0.012) compared to teriflunomide (see Figure 12-1).

Ofatumumab significantly reduced the number of Gd-enhancing T1 lesions and the rate of new or enlarging T2 lesions by 95.9% and 83.5%, respectively (both studies combined).

A consistent effect of ofatumumab compared to teriflunomide on the key efficacy results was observed across the two studies and in exploratory subgroups (see Figure 12-2).

Table 12-2 Overview of results from Phase 3 studies in RMS

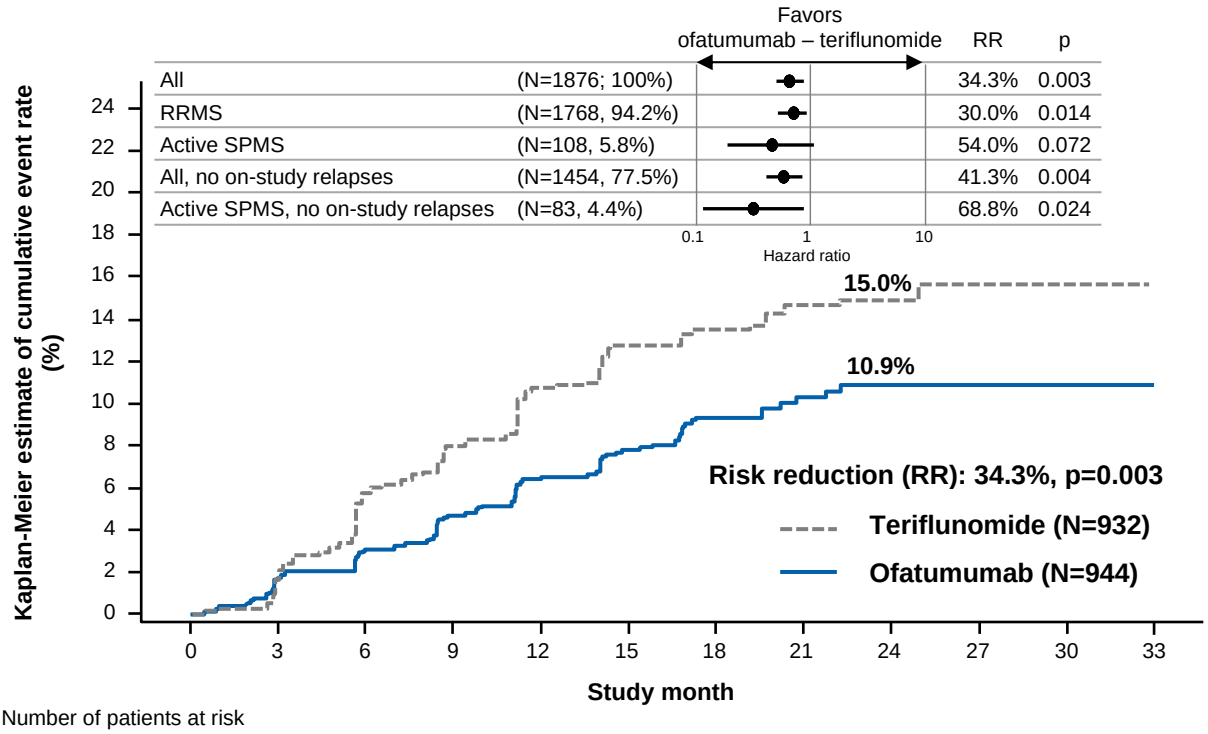
Endpoints	Study G2301 (ASCLEPIOS I)		Study G2302 (ASCLEPIOS II)	
	Ofatumumab 20 mg (n=465)	**Teriflunomide 14 mg (n=462)**	**Ofatumumab 20 mg (n=481)**	**Teriflunomide 14 mg (n=474)**
Endpoints based on separate studies				
Annualized relapse rate (ARR) (Primary Endpoint)[1]	0.11	0.22	0.10	0.25
Rate reduction	50.5% (p<0.001)		58.4% (p<0.001)	
Mean number of T1 Gd-enhancing lesions per MRI scan	0.0115	0.4555	0.0317	0.5172
Relative reduction	97.5% (p<0.001)		93.9% (p<0.001)	
Number of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.16
Relative reduction	81.9% (p<0.001)		84.6% (p<0.001)	
NfL[2] at month 3 (pg/mL)	8.80	9.41	8.92	10.02
Relative reduction	7% (p=0.011)		11% (p<0.001)	
Endpoints based on pre-specified meta-analyses				
Proportion of patients with 3-month confirmed disability worsening[3]	10.9% ofatumumab vs. 15.0% teriflunomide			
Risk reduction	34.3% (p=0.003)			
Proportion of patients with 6-month confirmed disability worsening[3]	8.1% ofatumumab vs. 12.0% teriflunomide			
Risk reduction	32.4% (p=0.012)			

[1] confirmed relapses (accompanied by a clinically relevant change in the EDSS)

[2] Neurofilament light chain concentration in serum (pg/ml): confirmed at month 12 (Study 1: 7.02 vs. 9.62; Study 2: 7.06 vs. 9.53) and month 24 (Study 1: 6.90 vs. 8.99; Study 2: 6.80 vs. 8.99)

[3] Kaplan-Meier estimates at Month 24. Disability worsening was defined as an increase in EDSS of at least 1.5, 1 or 0.5 points in patients with baseline EDSS of 0, 1 to 5, or 5.5 or more respectively.

Figure 12-1 **Time to first 3-month CDW by treatment (G2301 and G2302 combined, full analysis set) and subgroups**

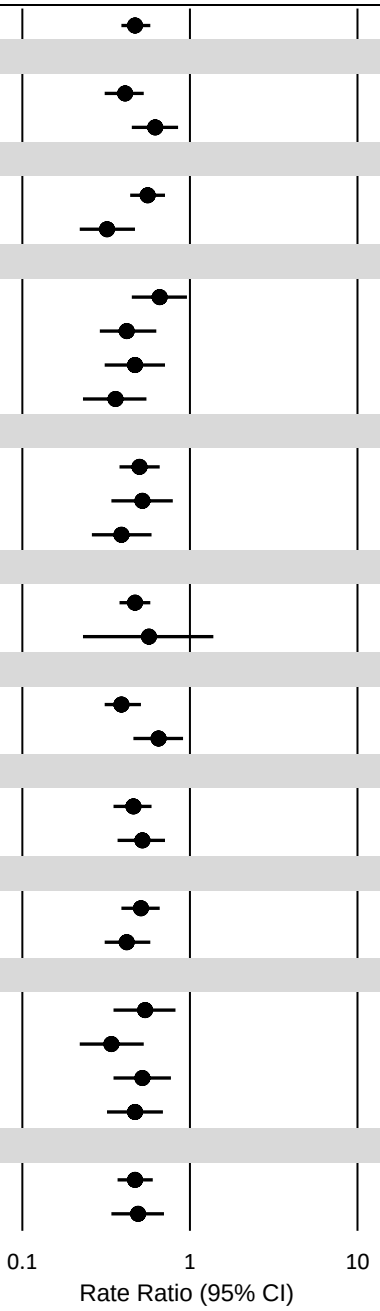


Number of patients at risk

Ofatumumab	944	908	878	844	810	784	533	319	176	49	1	0
Teriflunomide	932	901	841	804	756	718	477	297	146	41	1	0

Figure 12-2 Annualized relapse rates (G2301 and G2302 combined, full analysis set) by subgroup

	% of total population	Rate Ratio (95% CI)	Rate Reduction (%) / p value
Overall	100.0	0.47 (0.39, 0.58)	52.6 / <0.001
Age			
≤ 40	58.1	0.41 (0.31, 0.53)	59.3 / <0.001
> 40	41.9	0.62 (0.45, 0.85)	38.5 / 0.003
Gender			
Female	67.6	0.56 (0.44, 0.71)	43.9 / <0.001
Male	32.4	0.32 (0.22, 0.47)	68.0 / <0.001
Body weight			
< Q1	24.8	0.66 (0.45, 0.96)	34.5 / 0.030
≥ Q1 and < Q2	25.1	0.42 (0.29, 0.63)	57.6 / <0.001
≥ Q2 and < Q3	25.0	0.47 (0.31, 0.71)	53.2 / <0.001
≥ Q3	25.1	0.36 (0.23, 0.55)	64.4 / <0.001
Region			
Europe	51.8	0.50 (0.38, 0.66)	49.9 / <0.001
North America	22.4	0.52 (0.34, 0.79)	48.2 / 0.002
Rest of world	25.9	0.39 (0.26, 0.59)	60.7 / <0.001
MS type			
RRMS	94.3	0.47 (0.38, 0.58)	53.0 / <0.001
Active SPMS	5.7	0.57 (0.23, 1.38)	43.4 / 0.212
Baseline EDSS			
≤ 3.5	71.7	0.39 (0.31, 0.51)	60.7 / <0.001
> 3.5	28.3	0.65 (0.46, 0.91)	35.4 / 0.013
Number of relapses in the previous 2 years			
≤ 2	72.3	0.46 (0.35, 0.59)	54.3 / <0.001
> 2	27.7	0.52 (0.37, 0.71)	48.4 / <0.001
Gd-enhanced T1 lesions at baseline			
0	60.8	0.51 (0.39, 0.66)	49.5 / <0.001
> 0	37.2	0.42 (0.31, 0.58)	57.8 / <0.001
Volume of T2 lesions at baseline			
< Q1	24.8	0.54 (0.35, 0.82)	46.5 / 0.005
≥ Q1 and < Q2	24.8	0.34 (0.22, 0.53)	65.6 / <0.001
≥ Q2 and < Q3	24.7	0.52 (0.35, 0.77)	48.2 / 0.001
≥ Q3	24.8	0.47 (0.32, 0.69)	52.5 / <0.001
Prior MS disease-modifying drug			
Previously treated	60.2	0.47 (0.37, 0.60)	53.1 / <0.001
Treatment-naïve	39.8	0.49 (0.34, 0.70)	50.8 / <0.001



13 Non-clinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints.

In all pivotal repeat dose toxicity studies, the highest dose of 100 mg/kg ofatumumab was defined as the no observed adverse effect level (NOAEL). This corresponds to safety margins of at least 110-fold when compared with the clinical exposure at the therapeutic dose of 20 mg monthly.

Neither carcinogenicity nor mutagenicity studies have been conducted with ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA. For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

This product must not be mixed with other medicinal products.

Special precautions for storage

Store between 2°C to 8°C.

Do not freeze.

Store in the original carton to protect from light.

If necessary, Kesimpta may be stored unrefrigerated for a single period of up to 7 days at room temperature (not above 30°C). If not used during this period, Kesimpta can then be returned to the refrigerator for a maximum of 7 days.

Information might differ in some countries.

KESIMPTA must be kept out of the reach and sight of children.

Manufacturer

See folding box.

Novartis Pharma AG, Basel, Switzerland

Instructions for use and handling

Instructions for Use of KESIMPTA pre-filled syringe

Be sure that you read, understand, and follow these "Instructions for Use" before injecting KESIMPTA. Talk to your healthcare provider if you have any questions before you use KESIMPTA for the first time.

Remember:

- **Do not use** the KESIMPTA pre-filled syringe if either the seal on the outer carton or the seal of the blister is broken. Keep the KESIMPTA pre-filled syringe in the sealed carton until you are ready to use it.
- **Do not shake** the KESIMPTA pre-filled syringe.
- The pre-filled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the pre-filled syringe after injection.
- Do not remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the needle guard to be activated too early.
- **Do not use** if the pre-filled syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- Throw away (dispose of) the used KESIMPTA pre-filled syringe right away after use. **Do not re-use a KESIMPTA pre-filled syringe**. See "**How should I dispose of used KESIMPTA pre-filled syringe?**" at the end of these "Instructions for Use".

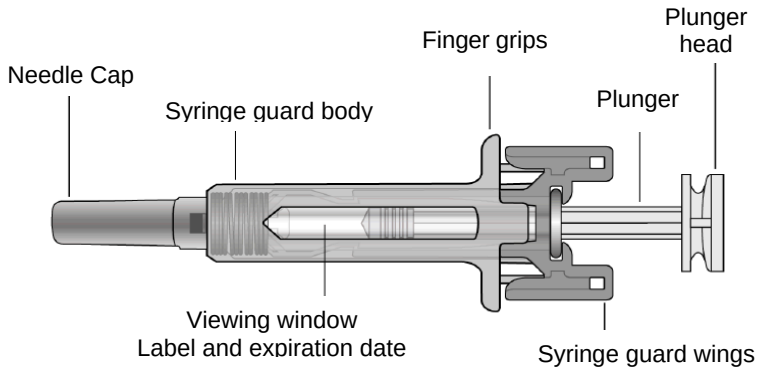
How should I store KESIMPTA?

- Store your carton of the KESIMPTA pre-filled syringe in a refrigerator, 2°C to 8°C (between 36°F to 46°F).
- Keep the KESIMPTA pre-filled syringe in the original carton until ready to use to protect from light.
- **Do not freeze** the KESIMPTA pre-filled syringe.
- **If necessary**, Kesimpta pre-filled syringe can be left out of the refrigerator for a single period of up to 7 days at room temperature (not above 30°C). If not used during this period, Kesimpta pre-filled syringe can then be returned to the refrigerator for a maximum of 7 days.

Keep KESIMPTA and all medicines out of the reach of children.

KESIMPTA pre-filled syringe parts (see Figure A):

Figure A



What you need for your injection:

Included in the carton:

A new KESIMPTA pre-filled syringe.

Not included in the carton (**see Figure B**):

- 1 alcohol wipe
- 1 cotton ball or gauze
- Sharps disposal container

Figure B

See "**How should I dispose of used KESIMPTA pre-filled syringes?**" at the end of these "Instructions for Use".

Prepare the KESIMPTA pre-filled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the KESIMPTA pre-filled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

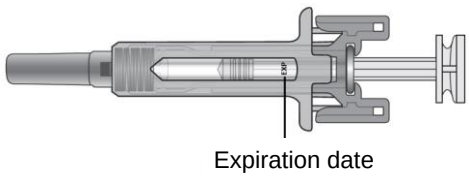
Step 4. Remove the pre-filled syringe from the outer carton and take it out of the blister by holding the syringe guard body.

Step 5. Look through the viewing window on the pre-filled syringe. The liquid inside should be clear to slightly cloudy. You may see a small air bubble in the liquid, which is normal. **Do not use** the pre-filled syringe if the liquid contains visible particles or is cloudy.

Step 6. **Do not use** the pre-filled syringe if it is broken. Return the pre-filled syringe and the package it came in to the pharmacy.

Figure C

Step 7. **Do not use** the pre-filled syringe if the expiration date has passed (**see Figure C**). Return the expired pre-filled syringe and the package it came in to the pharmacy.



Choose and clean the injection site

- Areas of your body that you may use as injection sites include:
  - the front of your thighs (**see Figure D**)
  - the lower stomach-area (abdomen), but not the area five cm (2 inches) around your navel (belly button) (**see Figure D**)
  - your upper outer arms, if a healthcare provider or caregiver is giving you the injection (**see Figure E**).
- Choose a different site each time you inject KESIMPTA.
- **Do not inject** into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.

Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

Figure D

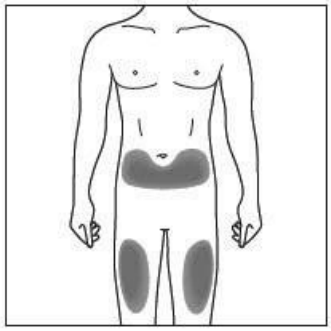
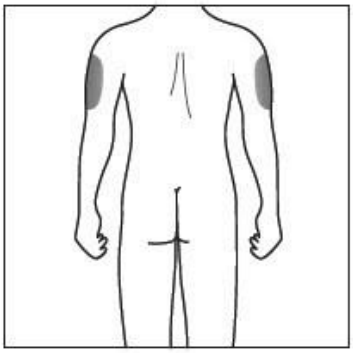


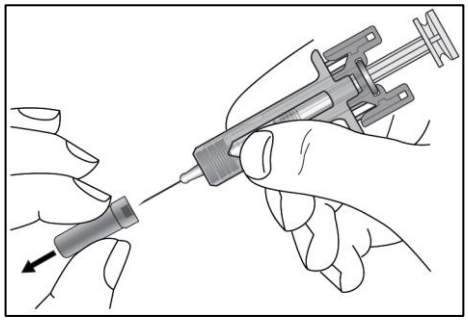
Figure E
(Caregiver and healthcare provider only)



Giving your injection

Step 9. Carefully remove the needle cap from the pre-filled syringe (**see Figure F**). Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure F



Step 10. With one hand, gently pinch the skin at the injection site. With your other hand insert the needle into your skin as shown (**see Figure G**). Push the needle all the way in to make sure that you inject your full dose.

Figure G

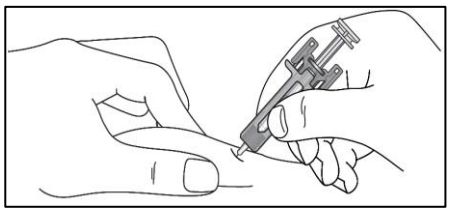


Figure H

Step 11. Hold the pre-filled syringe finger grips as shown (**see Figure H**). Slowly press down on the

plunger as far as it will go, so that the plunger head is completely between the syringe guard wings.

Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

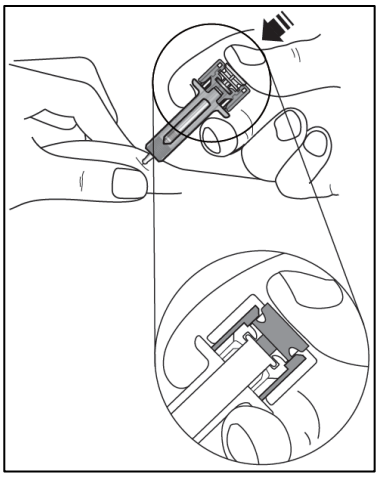
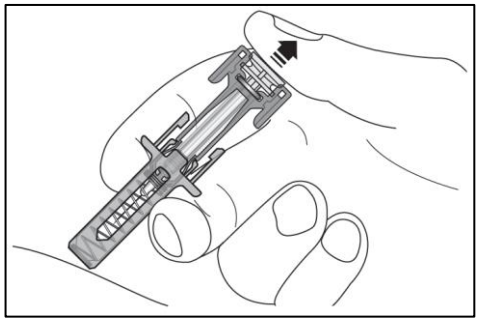


Figure I

Step 13. **Slowly** release the plunger until the needle is covered (**see Figure I**), and then remove the syringe from the injection site.

Step 14. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.



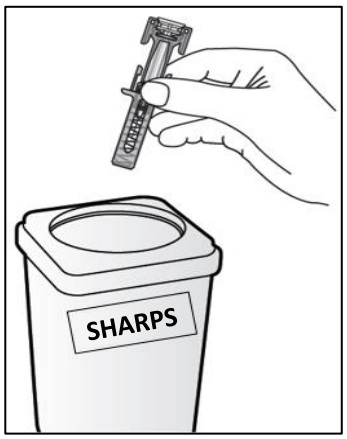
How should I dispose of used KESIMPTA pre-filled syringe?

Figure J

Step 15. Dispose of your used pre-filled syringe:

- Dispose of the used pre-filled syringe in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) (**see Figure J**).
- **Do not throw away (dispose of)** your used pre-filled syringe in your household trash.
- Never try to reuse your pre-filled syringe.

Keep the sharps container out of the reach of children.



Instructions for use and handling

Instructions for use of KESIMPTA pre-filled pen

Be sure that you read, understand, and follow this Instructions for Use before injecting KESIMPTA. Talk to your healthcare provider if you have any questions before you use KESIMPTA for the first time.

Remember:

- **Do not use** the KESIMPTA pen if either the seal on the outer carton or the seal on the pen is broken. Keep the KESIMPTA pen in the sealed outer carton until you are ready to use it.
- **Do not shake** the KESIMPTA pen.
- If you drop your KESIMPTA pen, **do not use** it if the pen looks damaged, or if you dropped it with the cap removed.

Throw away (dispose of) the used KESIMPTA pen right away after use. **Do not re-use a KESIMPTA pen**. See "How should I dispose of used KESIMPTA pen?" at the end of this "Instructions for Use".

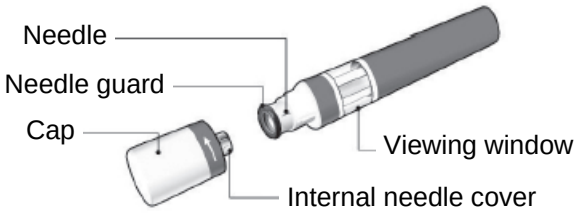
How should I store KESIMPTA?

- Store your carton of KESIMPTA pen in a refrigerator, 2°C to 8°C (between 36°F to 46°F).
- Keep [KESIMPTA] pen in the original carton until ready to use to protect from light.
- **Do not freeze** KESIMPTA pen.
- **If necessary**, Kesimpta pen can be left out of the refrigerator for a single period of up to 7 days at room temperature (not above 30°C). If not used during this period, Kesimpta pen can then be returned to the refrigerator for a maximum of 7 days.

Keep KESIMPTA and all medicines out of the reach of children.

KESIMPTA Sensoready® pen parts (see Figure A):

Figure A

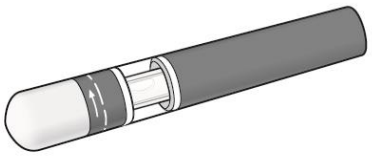


The KESIMPTA pen is shown with the cap removed. **Do not** remove the cap until you are ready to inject.

What you need for your injection:

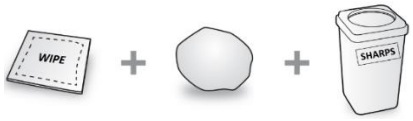
Included in the carton:
A new KESIMPTA pen (**see Figure B**).

Figure B



Not included in the carton (**see Figure C**):

Figure C



- 1 alcohol wipe
- 1 cotton ball or gauze
- Sharps disposal container

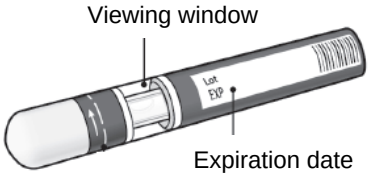
See "**How should I dispose of used KESIMPTA pen?**" at the end of this "Instructions for Use"

Before your injection:

Take the KESIMPTA pen out of the refrigerator **15 to 30 minutes before injecting** to allow it to reach room temperature.

Step 1. Important safety checks before you inject (see Figure D):

Figure D

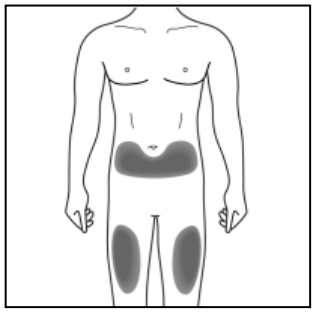


- Look through the viewing window. The liquid should be clear to slightly cloudy.
  Do not use if the liquid contains visible particles or is cloudy.
  You may see a small air bubble, which is normal.
- Look at the **expiration date (EXP)** on your KESIMPTA pen. **Do not use** your pen if the expiration date has passed.

Contact your pharmacist or healthcare provider if your pen fails any of these checks

Step 2. Choose your injection site:

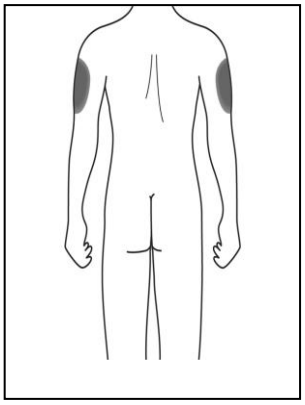
Figure E



- The recommended site is the front of the thighs. You may also use the lower stomach area (lower abdomen), but **not** the area five cm (2 inches) around the navel (belly button) (**see Figure E**).
- Choose a different site each time you inject KESIMPTA.
- Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your upper outer arm (**see Figure F**).

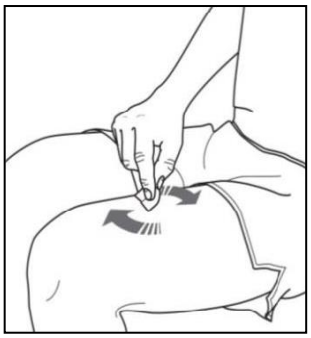
Figure F
(Caregiver and healthcare provider only)



Step 3. Clean your injection site:

- Wash your hands with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting (**see Figure G**).
- Do not touch the cleaned area again before injecting.

Figure G



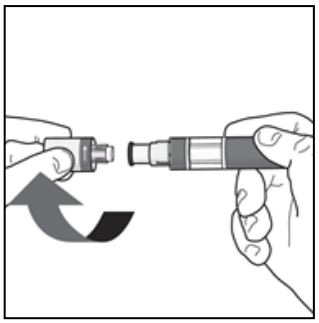
Your injection:

Step 4. Remove the cap:

- Only remove the cap when you are ready to use the pen.
- Twist off the cap in the direction of the arrow (**see Figure H**).
- Throw away the cap. **Do not try to re-attach the cap.**
- Use the pen within 5 minutes of removing the cap.

You may see a few drops of medicine come out of the needle. This is normal.

Figure H



Step 5. Hold your KESIMPTA pen:

- Hold the pen at 90 degrees to the cleaned injection site (**see Figure I**).

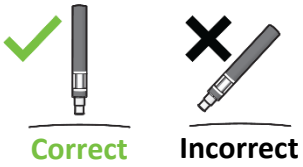
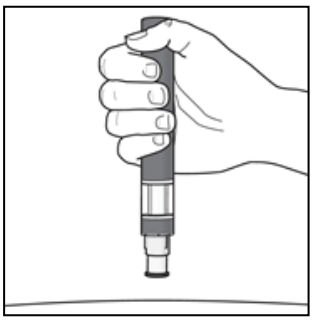


Figure I



Important: **During the injection** you will hear **2 loud clicks**:

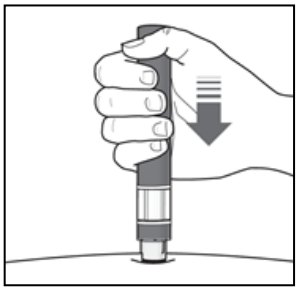
- The **1st click** indicates that **the injection has started**.
- A **2nd click** will indicate that **the injection is almost complete**.

You must keep holding the KESIMPTA pen firmly against your skin until the **green indicator** fills the window and stops moving.

Step 6. Start your injection:

- Press the pen firmly against the skin to start the injection (**see Figure J**).
- The **1st click** indicates the injection has started.
- **Keep holding** the pen firmly against your skin.
- The **green indicator** shows the progress of the injection

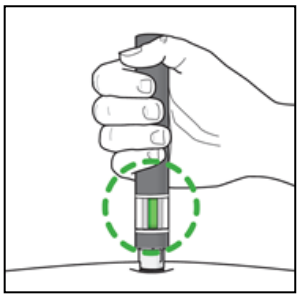
Figure J



Step 7. Complete your injection:

- Listen for the **2nd click**. This indicates that the injection is **almost** complete.
- Check to see if the **green indicator** fills the window and has stopped moving (**see Figure K**).
- The pen can now be removed (**see Figure L**).

Figure K



After your injection:

- In case the green indicator does not fill the window, it means the medicine has not been delivered. Contact your healthcare provider if the green indicator is not visible.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure L

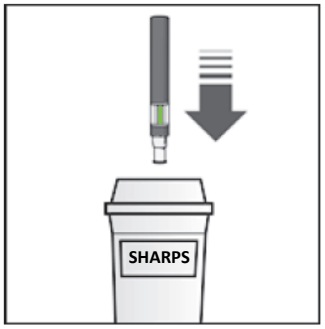
How should I dispose of used KESIMPTA pens?

Step 8. Dispose of your KESIMPTA pen:

- Dispose of the used pen in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) (**see Figure M**).
- Never try to reuse your pen.

Keep the sharps container out of the reach of children.

Figure M



Special precautions for disposal

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