1. NAME OF THE MEDICINAL PRODUCT

Kesimpta

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kesimpta 20 mg solution for injection in pre-filled pen

Each pre-filled pen contains 20 mg ofatumumab in 0.4 ml solution (50 mg/ml).

Ofatumumab is a fully human monoclonal antibody produced in a murine cell line (NS0) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (Sensoready Pen)

The solution is clear to slightly opalescent, and colourless to slightly brownish-yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of neurological conditions.

Posology

The recommended dose is 20 mg ofatumumab 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 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
Adults over 55 years old
No studies have been performed in MS patients over 55 years old. Based on the limited data available, no dose adjustment is considered necessary in patients over 55 years old (see section 5.2).

Renal impairment
Patients with renal impairment are not expected to require dose modification (see section 5.2).

Hepatic impairment
Patients with hepatic impairment are not expected to require dose modification (see section 5.2).

Paediatric population
Kesimpta is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Kesimpta in children aged 0 to 18 years have not yet been established. No data are available.

Method of administration

This medicinal product 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 should be performed under the guidance of a healthcare professional (see section 4.4).

Comprehensive instructions for administration are provided in the package leaflet.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients in a severely immunocompromised state (see section 4.4).
Severe active infection until resolution (see section 4.4).
Known active malignancy.

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.

Systemic injection-related reactions

Patients should be informed that systemic injection-related reactions (SIRRs) could occur, generally within 24 hours and predominantly following the first injection (see section 4.8). Symptoms most frequently observed in RMS clinical studies include fever, headache, myalgia, chills, fatigue, nausea and vomiting and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening SIRRs reported in RMS clinical studies (see section 4.8).

Additional SIRRs reported in the post-marketing setting include rash, urticaria, dyspnoea and angioedema (e.g. tongue, pharyngeal or laryngeal swelling), and rare cases which were reported as anaphylaxis. While there were some cases which were serious and resulted in discontinuation of ofatumumab treatment, there were also serious cases where patients were able to continue ofatumumab treatment without further incidents.

Some SIRR symptoms may be clinically indistinguishable from Type 1 acute hypersensitivity reactions (IgE-mediated). A hypersensitivity reaction may present during 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 ofatumumab must not be treated with ofatumumab (see section 4.3).

Only limited benefit of premedication with steroids was seen in RMS clinical studies. Injection-related reactions can be managed with symptomatic treatment, should they occur. Therefore, use of premedication is not required.

The first injection should be performed under the guidance of an appropriately trained healthcare professional (see section 4.2).

Local injection-site reactions

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching and pain (see section 4.8).

Infections

It is recommended to evaluate the patient's immune status prior to initiating therapy.

Based on its mode of action and available clinical experience, ofatumumab has the potential for an increased risk of infections (see section 4.8).

Administration should be delayed in patients with an active infection until the infection is resolved.

Ofatumumab must not be given to patients in a severely immunocompromised state (e.g. significant neutropenia or lymphopenia).

Progressive multifocal leukoencephalopathy
Since John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) has been observed in patients treated with anti-CD20 antibodies, other MS therapies, and ofatumumab at substantially higher doses in oncology indications, physicians should be vigilant for medical history of PML and for any clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with ofatumumab should be suspended until PML has been excluded.

Hepatitis B virus reactivation
Hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies, which in some cases resulted in fulminant hepatitis, hepatic failure and death.

Patients with active hepatitis B disease should not be treated with ofatumumab. HBV screening should be performed in all patients before initiation of treatment. As a 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 with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 4.3).

It is not recommended to use other immunosuppressants concomitantly with ofatumumab except corticosteroids for symptomatic treatment of relapses.

Vaccinations

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

Ofatumumab may interfere with the effectiveness of inactivated vaccines.

The safety of immunisation with live or live-attenuated vaccines following ofatumumab 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 4.5). The median time to B-cell recovery to the lower limit of normal (LLN, defined as 40 cells/µl) or baseline value is 24.6 weeks post treatment discontinuation based on data from phase III studies (see section 5.1).

Vaccination of infants born to mothers treated with ofatumumab during pregnancy
In infants of mothers treated with ofatumumab during pregnancy live or live-attenuated vaccines should not be administered before it has been confirmed that the B-cell count is within normal range. Depletion of B cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered as indicated before it has been confirmed that the B-cell count is within normal range, 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 4.6).

Excipients with known effect

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Polysorbates

This medicinal product contains 0.08 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed, as no interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters.

Vaccinations

The safety of and the ability to generate a primary or anamnestic (recall) response to immunisation 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 immunisations prior to the start of ofatumumab therapy (see section 4.4).

Other immunosuppressive or immune-modulating therapies

The risk of additive immune system effects should be considered when co-administering immunosuppressive therapies with ofatumumab.

When initiating ofatumumab after other immunosuppressive therapies with prolonged immune effects or initiating other immunosuppressive therapies with prolonged immune effects after ofatumumab, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Kesimpta and for 2 months after the last administration of Kesimpta.

Pregnancy

There is a limited amount of data from the use of ofatumumab in pregnant women. Ofatumumab may cross the placenta and cause foetal B-cell depletion based on findings from animal studies (see section 5.3). No teratogenicity was observed after intravenous administration of ofatumumab to pregnant monkeys during organogenesis.

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 4.4 and 5.1).

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

To help determine the effects of ofatumumab in pregnant women, healthcare professionals are encouraged to report all pregnancy cases and complications that happen during treatment or within 2 months after the last dose of ofatumumab to the registration holder. In addition, all adverse pregnancy events may be reported to the registration holder, Novartis Israel Ltd., at: safetydesk.israel@novartis.com.

Lactation

There are limited data on the use of ofatumumab in women during lactation. There are no data on the effects of ofatumumab on milk production. In humans, excretion of IgG antibodies in

milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

An observational study reported that concentration of ofatumumab in breast milk was generally low, with C_{avg} and C_{max} of less than 0.02 µg/ml in the breast milk of treated lactating women.

In the same observational study, five infants with available B cells had normal levels. Eight infants received live vaccines during/after exposure during breast-feeding with no complications. Infants (up to 24 months of age) did not show abnormalities in infections, antibiotic use, hospitalisations or developmental delays.

Consequently, a risk to the breast-fed child cannot be excluded during the first few days after birth. Afterwards, ofatumumab could be used during breast-feeding if clinically needed. However, if the patient was treated with ofatumumab up to the last few months of pregnancy, breast-feeding can be started immediately after birth.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most important and frequently reported adverse reactions are upper respiratory tract infections (39.4%), systemic injection-related reactions (20.6%), local injection-site reactions (10.9%) and urinary tract infections (11.9%) (see section 4.4 and below subsection "Description of selected adverse reactions" for further details).

Tabulated list of adverse reactions

Adverse reactions that have been reported in association with the use of ofatumumab in pivotal RMS clinical studies and from post-marketing experience are listed by MedDRA system organ class in Table 1. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1 Tabulated list of adverse reactions

Infections and infestations	
Very common	Upper respiratory tract infections[1] Urinary tract infections[2]
Common	Oral herpes
Immune system disorders	
Not known	Hypersensitivity reactions[3]
Gastrointestinal disorders	
Common	Nausea, vomiting[4]
Hepatobiliary disorders	
Common	Hepatic enzymes increased[5]
General disorders and administration site conditions	
Very common	Injection-site reactions (local)
Investigations	
Common	Blood immunoglobulin M decreased
Injury, poisoning and procedural complications	
Very common	Injection-related reactions (systemic)

[1] Grouping of preferred terms (PTs) was considered for ADR frequency determination and includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.
[2] Grouping of preferred terms (PTs) was considered for ADR frequency determination and includes the following: urinary tract infection, cystitis, escherichia urinary tract infection, asymptomatic bacteriuria, bacteriuria.
[3] Reported during post-marketing experience (see section 4.4).
[4] Nausea and vomiting have been reported in association with systemic injection-related reactions (see below and section 4.4)
[5] Grouping of PTs was considered for ADR frequency determination and includes the following: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, transaminases increased, liver function test increased, hepatic function abnormal, liver function test abnormal

Description of selected adverse reactions

Infections
In the RMS phase III clinical studies, the overall rate of infections and serious infections in patients treated with ofatumumab was similar to patients who were treated with teriflunomide (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). Two patients (0.2%) discontinued and 11 patients (1.2%) temporarily interrupted study treatment due to a serious infection.

Upper respiratory tract infections
In these 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.

Systemic injection-related reactions (SSIRs)
In the RMS phase III clinical studies, SSIRs were reported in 20.6% of patients treated with ofatumumab.

The incidence of SSRIs was highest with the first injection (14.4%), decreasing significantly with subsequent injections (4.4% with second, <3% from third injection). SSIRs were mostly (99.8%) mild to moderate in severity. Two (0.2%) ofatumumab-treated MS patients reported serious injection-related reactions but not life-threatening. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills and fatigue. Additional reported symptoms included nausea (1.7%) and vomiting (0.6%).

Local injection-site reactions
In the RMS phase III clinical studies, local injection-site reactions were reported in 10.9% of patients treated with ofatumumab.

Local injection-site reactions were very common. They were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2%) included erythema, pain, itching and swelling.

Laboratory abnormalities
Immunoglobulins
During the course of the RMS phase III clinical studies, decrease in mean value of immunoglobulin M (IgM) (30.9% decrease after 48 weeks and 38.8% decrease after 96 weeks) was observed and no association with risk of infections, including serious infections, was shown.

In 14.3% of patients, treatment with ofatumumab resulted in a decrease in IgM that reached a value below 0.34 g/l.

Ofatumumab was associated with a transient decrease of 4.3% in mean immunoglobulin G (IgG) levels after 48 weeks of treatment but an increase of 2.2% after 96 weeks.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il. And to Novartis using the following email address: safetydesk.israel@novartis.com.

4.9 Overdose

Doses up to 700 mg have been administered 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.

Ofatumumab has been previously used in chronic lymphocytic leukaemia (CLL) indications, at doses up to 2,000 mg administered intravenously via infusion. Ofatumumab administered via subcutaneous injection has not been assessed and is not approved for these indications, and must not be used for the treatment of oncology indications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, monoclonal antibodies
ATC code: L04AG12

Mechanism of action

Ofatumumab is a fully human anti-CD20 monoclonal immunoglobulin G1 (IgG1) antibody. 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. A subcutaneous route of administration of ofatumumab and subsequent release/absorption from the tissue allows a gradual interaction with B 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.

Pharmacodynamic effects

B-cell depletion
In the RMS clinical studies using ofatumumab 20 mg every 4 weeks, after an initial dose regimen of 20 mg on days 1, 7, and 14, administration resulted in a rapid and sustained reduction of B cells to below LLN (defined as 40 cells/µl) as early as two weeks after treatment initiation. Before initiation of the maintenance phase starting at week 4, total B-cell levels of <10 cells/µl were reached in 94% of patients, increasing to 98% of patients at week 12, and were sustained for as long as 120 weeks (i.e. while on study treatment).

B-cell repletion
Data from RMS phase III clinical 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 LLN of 23 weeks post treatment discontinuation.

Immunogenicity
In RMS phase III studies, the overall incidence of treatment-induced anti-drug antibodies (ADAs) was 0.2% (2 of 914) in ofatumumab-treated patients and no patients with treatment enhancing or neutralising ADA were identified. The impact of positive ADA titers on PK, safety profile or B-cell kinetics cannot be assessed given the low incidence of ADA associated with ofatumumab.

Clinical efficacy and safety

The efficacy and safety of ofatumumab were evaluated in two randomised, double-blind, active-controlled phase III pivotal studies of identical design (Study 1 [ASCLEPIOS I] and Study 2 [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 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 randomised 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 2). 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 annualised 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 included the number of Gd-enhancing T1 lesions per MRI scan, the annualised rate of new or enlarging T2 lesions and the neurofilament light chain (NfL) concentration in serum. Disability-related key secondary endpoints were evaluated in a meta-analysis of combined data from ASCLEPIOS Study 1 and Study 2, as defined in the study protocols.

Table 2 Demographics and baseline characteristics

Characteristics	**Study 1 (ASCLEPIOS I)**		**Study 2 (ASCLEPIOS II)**	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Age (mean ± standard deviation; years)	39±9	38±9	38±9	38±9
Sex (female; %)	68.4	68.6	66.3	67.3
Duration of MS since diagnosis (mean/median; 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
EDSS score (mean/median)	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 with Gd+ T1 lesions (%)	37.4	36.6	43.9	38.6
Number of Gd+ T1 lesions (mean)	1.7	1.2	1.6	1.5

The efficacy results for both studies are summarised in Table 3, Figure 1 and Figure 2.

In both phase III studies, ofatumumab compared to teriflunomide demonstrated a significant reduction in the annualised relapse rate of 50.5% and 58.4%, respectively.

The pre-specified meta-analysis of combined data showed that ofatumumab compared to teriflunomide significantly reduced the risk of 3-month confirmed disability progression (CDP) by 34.3% and the risk of 6-month CDP by 32.4% (see Figure 1).

Ofatumumab compared to teriflunomide significantly reduced the number of Gd-enhancing T1 lesions by 95.9% and the rate of new or enlarging T2 lesions by 83.5% (values represent mean reductions for the combined studies).

Ofatumumab compared to teriflunomide significantly reduced NfL concentrations from the first assessment at 3 months (see Table 3 and Figure 2).

A similar effect of ofatumumab on the key efficacy results compared to teriflunomide was observed across the two phase III studies in exploratory subgroups defined by sex, age, body weight, prior non-steroid MS therapy, and baseline disability and disease activity.

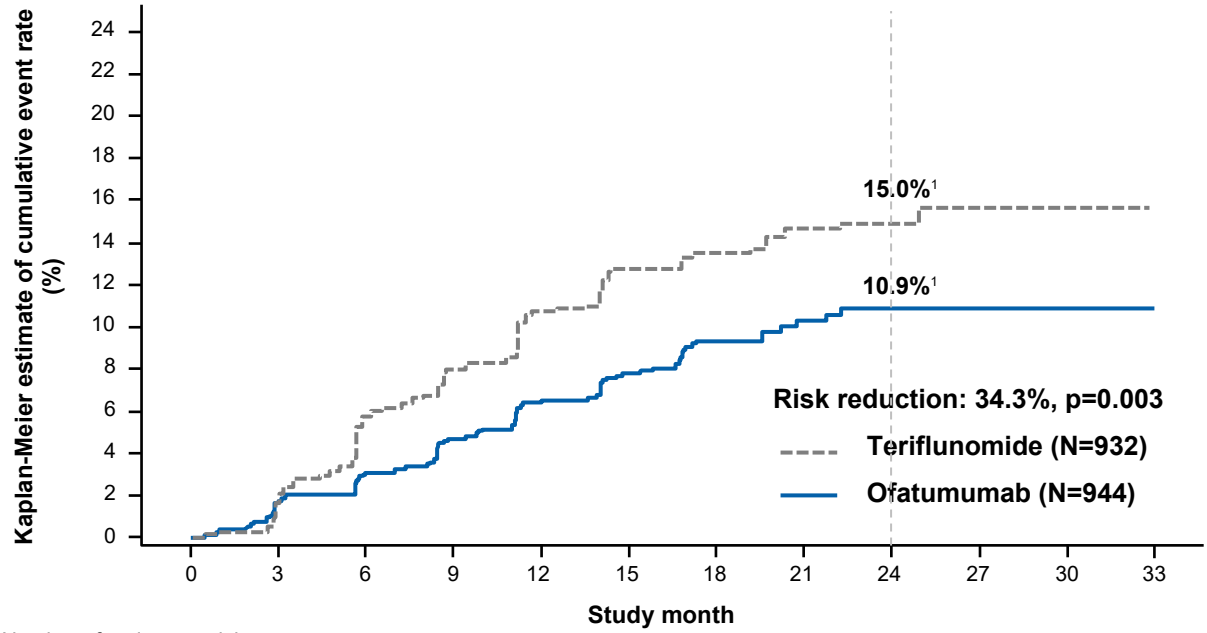
Table 3 Overview of key results from phase III studies in RMS

Endpoints	**Study 1 (ASCLEPIOS I)**		**Study 2 (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				
Annualised 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 at 3 months (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 progression[2] Risk reduction	10.9% ofatumumab vs. 15.0% teriflunomide 34.3% (p=0.003)			
Proportion of patients with 6-month confirmed disability progression[2] Risk reduction	8.1% ofatumumab vs. 12.0% teriflunomide 32.4% (p=0.012)			

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

[2] Kaplan-Meier estimates at 24 months. 3- and 6-month CDP were assessed based on prospectively planned analysis of the combined data from the two phase III studies and defined as a clinically meaningful increase in the EDSS sustained for at least 3 or 6 months, respectively. A clinically meaningful increase in EDSS is defined as an increase of at least 1.5 points if the baseline EDSS score was 0, an increase of at least 1.0 point if the baseline EDSS score was 1.0–5.0, and an increase of at least 0.5 points if the baseline EDSS score was 5.5 or greater.

Figure 1 Time to first 3-month CDP by treatment (ASCLEPIOS Study 1 and Study 2 combined, full analysis set)

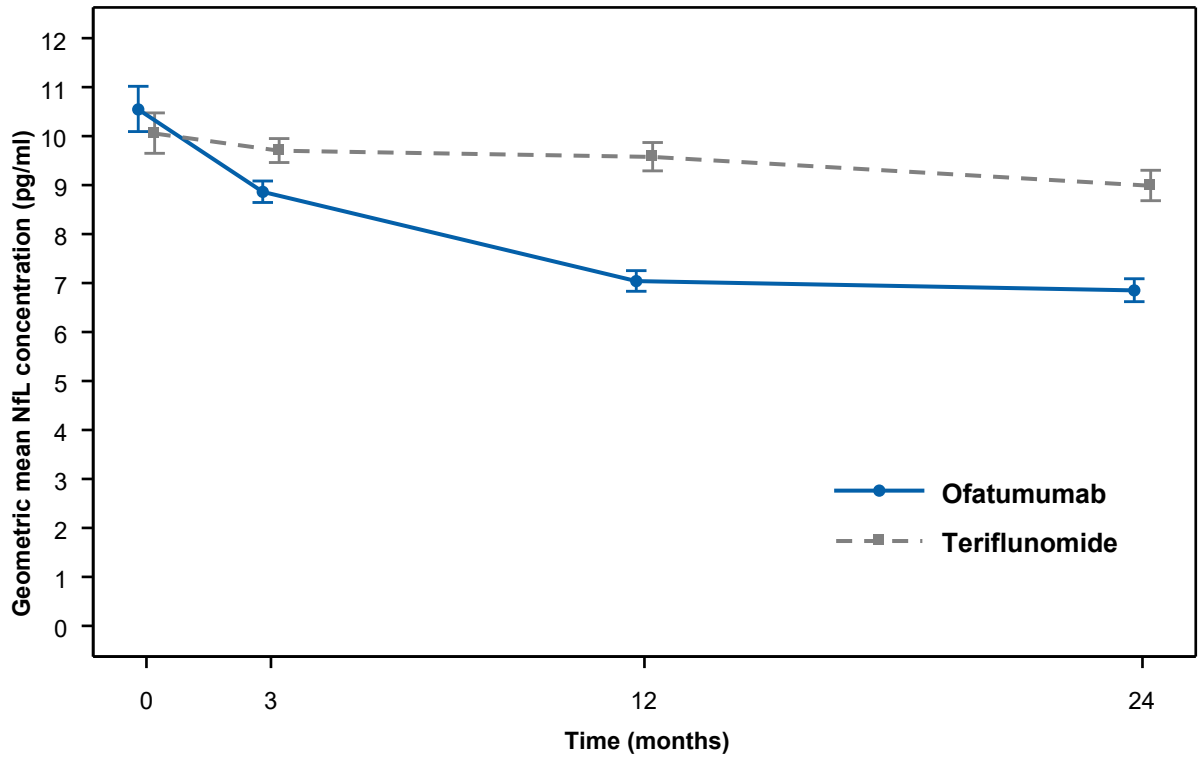


Number of patients at risk

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

[1] The numbers shown on the curves represent Kaplan-Meier estimates of the risk of the event at 24 months (marked by the vertical dashed line).

Figure 2 NfL concentrations in serum by treatment (ASCLEPIOS Study 1 and Study 2 combined, full analysis set)



The line plots represent the adjusted geometric means with 95% CI at each time point which are from Repeated measures model. Geometric means at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of NfL concentrations in serum.

In the phase III studies, the proportion of patients with adverse events (AEs) (83.6% vs 84.2%) and the AEs leading to discontinuation (5.7% vs 5.2%) were similar in the ofatumumab and teriflunomide groups.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous administration, ofatumumab has a prolonged release/absorption profile (T_{max} of 4.3 days) and is predominantly absorbed via the lymphatic system.

A monthly subcutaneous dose of 20 mg leads to a mean AUC_{tau} of 483 µg*h/ml and a mean C_{max} of 1.43 µg/ml at steady state.

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

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 a 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 11 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

Adults over 55 years old
There are no dedicated pharmacokinetic studies of ofatumumab in patients over 55 years old due to limited clinical experience (see section 4.2).

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.

Body weight
Based on the results of a cross-study population analysis, body weight was identified as a covariate of exposure (C_{max} and AUC) to ofatumumab in RMS subjects. However, body weight did not affect safety and efficacy measures evaluated in the clinical studies; therefore, dose adjustment is not required.

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.

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.

5.3 Preclinical safety data

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

Neither carcinogenicity nor mutagenicity studies have been conducted with ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA.

The embryo-foetal development (EFD) and the enhanced pre/post-natal 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-foetal and pre/post-natal development.

In these studies, ofatumumab was detected in the blood of the foetuses and infants, confirming placental transfer and foetal 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 foetuses and infants, along with a reduced spleen weight (without histological correlate) in foetuses 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 post-natal period. In infants, early post-natal 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.

In a dedicated monkey fertility study, male and female fertility endpoints were unaffected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Sodium acetate trihydrate
Sodium chloride
Polysorbate 80
Disodium edetate
Hydrochloric acid (for pH adjustment)
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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Kesimpta 20 mg solution for injection in pre-filled pen

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

6.5 Nature and contents of container

Kesimpta 20 mg solution for injection in pre-filled pen

Kesimpta is supplied in a single-use glass syringe, equipped with a stainless steel needle, a plunger stopper and a rigid needle shield. The syringe is assembled into an auto-injector.

Kesimpta is available in unit packs containing 1 pre-filled pen

6.6 Special precautions for disposal and other handling

Instructions for handling of the pre-filled pen

Before injection, the pre-filled pen should be taken out of the refrigerator for about 15 to 30 minutes to allow it to reach room temperature. The pre-filled pen should be kept in the original carton until ready to use, and the cap should not be removed until just before the injection is performed. Prior to use, the solution should be inspected visually by looking through the viewing window. The pre-filled pen should not be used if the liquid contains visible particles or is cloudy.

Comprehensive instructions for administration are given in the package leaflet.

Disposal

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

7. **REGISTRATION HOLDER AND IMPORTER**
Novartis Israel Ltd., POB 9240, Tel-Aviv – Yafo, 6109102

8. REGISTRATION NUMBER
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