NOVARTIS

Bonspri™

Selective immunosuppressants

ATC code: pending (L04AAxx)

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

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

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 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.

Excipients

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

INDICATIONS

Bonspri is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS).

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended dose is 20 mg Bonspri 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 Bonspri 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 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 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.

Geriatric patients (65 years or above)

No studies have been performed in elderly MS patients. Ofatumumab was studied in patients with RMS aged 18 to 55 years. Results from population pharmacokinetics suggest that dose adjustment is not required in elderly patients (see section CLINICAL PHARMACOLOGY).

Method of administration

Bonspri 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 Bonspri should be performed under the guidance of a healthcare professional (see section WARNING AND PRECAUTIONS).

Comprehensive instructions for administration are provided in section PHARMACEUTICAL INFORMATION.

CONTRAINDICATIONS

None.

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 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. Patients should be informed that injection-related reactions generally occur within 24 hours and predominantly following the first injection. Injection-related reactions can be managed with symptomatic treatment, should they occur.

Only limited benefit of premedication with steroids, antihistamines, or paracetamol 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 Bonspri 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.

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

No cases of progressive multifocal leukoencephalopathy (PML) have been reported for ofatumumab in the RMS clinical studies. However, since John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies, physicians should be vigilant for any clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. If PML is suspected, treatment with Bonspri should be suspended until PML has been excluded.

Hepatitis B Virus Reactivation

No cases of hepatitis B virus (HBV) reactivation were identified in Bonspri 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.

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

Vaccinations

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

Bonspri may interfere with the effectiveness of inactivated vaccines.

The safety of immunization with live or live-attenuated vaccines following Bonspri 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 CLINICAL PHARMACOLOGY).

Vaccination of infants born to mothers treated with Bonspri during pregnancy

In infants of mothers treated with Bonspri 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 PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)

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 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 1 Percentage of patients with adverse drug reactions in ASCLEPIOS I and II

Adverse drug reactions	Ofatumumab 20 mg N=946 %	Teriflunomide 14 mg N=936 %	Frequency category
Infections and infestations			
Upper respiratory tract infection[2]	39.4	37.8	Very common
General disorders and administration site conditions			
Injection site reactions (local)	10.9	5.6 [3]	Very common
Injury, poisoning and procedural complications			
Injection related reactions (systemic)	20.6	15.3 [3]	Very common

[1)] Pooled data from treatment epochs of G2301 and G2302 (safety set)

[2)] Grouping of preferred terms (PTs) was considered for ADR frequency determination

[3)] Teriflunomide group received matching placebo injections

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 WARNINGS AND PRECAUTIONS).

Laboratory abnormalities

Immunoglobulins

During the course of the RMS Phase 3 clinical studies, decrease in mean value of immunoglobulin M (IgM) was observed and was not associated with risk of infections including serious infections. In 14.3% of patients in RMS Phase 3 clinical studies, treatment with Bonspri resulted in a decrease in IgM that reached a value below 0.34 g/L.

There was no decrease in mean values of immunoglobulin G (IgG).

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 Bonspri 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 Bonspri therapy (see section WARNINGS AND PRECAUTIONS).

Other Immunosuppressive or Immune-Modulating Therapies

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

When switching from medicinal products with prolonged immune effects, such as ocrelizumab, cladribine, fingolimod, natalizumab, teriflunomide, mitoxantrone, or dimethyl fumarate, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects when initiating Bonspri.

PREGNANCY, LACTATION, FEMALE AND MALES OF REPRODUCTIVE POTENTIAL

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 area under the curve (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 WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

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.

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 no observed adverse effect level (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.

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 Bonspri 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 Bonspri and any potential adverse effects on the breastfed infant from Bonspri.

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 Bonspri and for 6 months after the last treatment of Bonspri.

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 no observed effect level (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.

OVERDOSAGE

No cases of overdose have been reported in RMS clinical studies.

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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

B-cells play an important role in MS pathogenesis due to production of pro-inflammatory cytokines, release of auto-reactive antibodies and activation of pathogenic T cells. 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 clinical studies indicate B-cell recoveries over the lower limit of normal (LLN) in at least 50% of patients in 24 to 36 weeks post treatment discontinuation. Modelling and

simulation for B-cell repletion corroborates this data, predicting median time to B-cell recovery of 40 weeks post treatment discontinuation.

Immunogenicity

As a fully human monoclonal antibody, ofatumumab has a low potential of inducing anti-drug antibodies (ADA). 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)

Ofatumumab exhibits a long half-life and low volume of distribution similar to that of other monoclonal antibodies. Ofatumumab is eliminated through a non-linear target-mediated route as well as a target-independent route mediated by non-specific endocytosis followed by intracellular catabolism. Higher baseline B-cell count results in greater component of target-mediated elimination clearance and shorter ofatumumab half-life at the start of therapy. Subsequent ofatumumab dosing leads to potent depletion of B-cells resulting in reduced overall clearance.

Absorption

A monthly subcutaneous dose of 20 mg leads to a mean AUCtau of 483 µg·h/mL and a mean maximum plasma (or serum or blood) concentration (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

Overall, ofatumumab steady-state volume of distribution (Vss) values were low (3 to 8 liters), consistent with other monoclonal antibodies. Following two intravenous infusions of ofatumumab (100, 300, or 700 mg in either the first or second treatment period) in patients with relapsing remitting multiple sclerosis (RRMS), geometric mean Vss after the second infusion of ofatumumab ranged from 2.15 to 2.74 liters. Based on pharmacokinetic modelling of the data from the studies using s.c. administration and repeated 20 mg doses, a central volume (Vc) of 2.8 liters was estimated.

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-independent route as with other IgG molecules and a target-mediated route that is related to binding to B-cells. Following a single s.c. administration of 30 to 100 mg in patients with rheumatoid arthritis, ofatumumab geometric mean elimination half-life values ranged from 5.2 to 6.8 days. Based on pharmacokinetic modelling of the data from the studies using s.c. administration and repeated 20 mg doses, an approximate half-life of ofatumumab of 14.9 days in men and 17.1 days in women was estimated.

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.

Geriatric patients (65 years or above)

No studies have been performed in elderly MS patients. Ofatumumab was studied in patients with RMS aged 18 to 55 years. Results from population pharmacokinetics suggest that dose adjustment is not required in elderly patients.

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.

CLINICAL STUDIES

The efficacy and safety of Bonspri 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.

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. 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 G2301 and G2302, as defined in the study protocols.

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

In both Phase 3 studies (G2301 and G2302), Bonspri demonstrated a significant reduction in the annualized relapse rate of 50.5% and 58.5%, respectively (both p<0.001) compared to teriflunomide.

The pre-specified meta-analysis of combined data showed that Bonspri significantly reduced the risk of 3-month confirmed disability worsening (CDW) (risk reduction = 34.4%, p=0.002) and 6-month CDW (risk reduction = 32.5%, p=0.012) compared to teriflunomide (see Figure 1).

Efficacy results were consistent across the two Phase 3 studies (G2301 and G2302) and across subgroups defined based on gender, age, prior MS therapy, baseline and on-study relapse activity, baseline MRI disease activity, baseline EDSS, and RRMS/SPMS diagnosis.

Table 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)		58.5% (p<0.001)	
Mean number of T1 Gd-enhancing lesions per MRI scan	0.0115	0.4523	0.0317	0.5141
Relative reduction	97.5% (p<0.001)		93.8% (p<0.001)	
Number of new or enlarging T2 lesions	0.72	4.00	0.64	4.15
Relative reduction	81.9% (p<0.001)		84.5% (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)	
NfL[2] at month 12 (pg/mL)	7.02	9.62	7.06	9.53
Relative reduction	27% (p<0.001)		26% (p<0.001)	
NfL[2] at month 24 (pg/mL)	6.90	8.99	6.80	8.99
Relative reduction	23% (p<0.001)		24% (p<0.001)	
Endpoints based on pre-specified meta-analyses				
Proportion of patients with 3-month confirmed disability worsening[3] Risk reduction (meta-analysis)	10.9% ofatumumab vs. 15.0% teriflunomide 34.4% (p=0.002)			
Proportion of patients with 6-month confirmed disability worsening[4] Risk reduction (meta-analysis)	8.1% ofatumumab vs. 12.0% teriflunomide			

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)
	32.5% (p=0.012)			

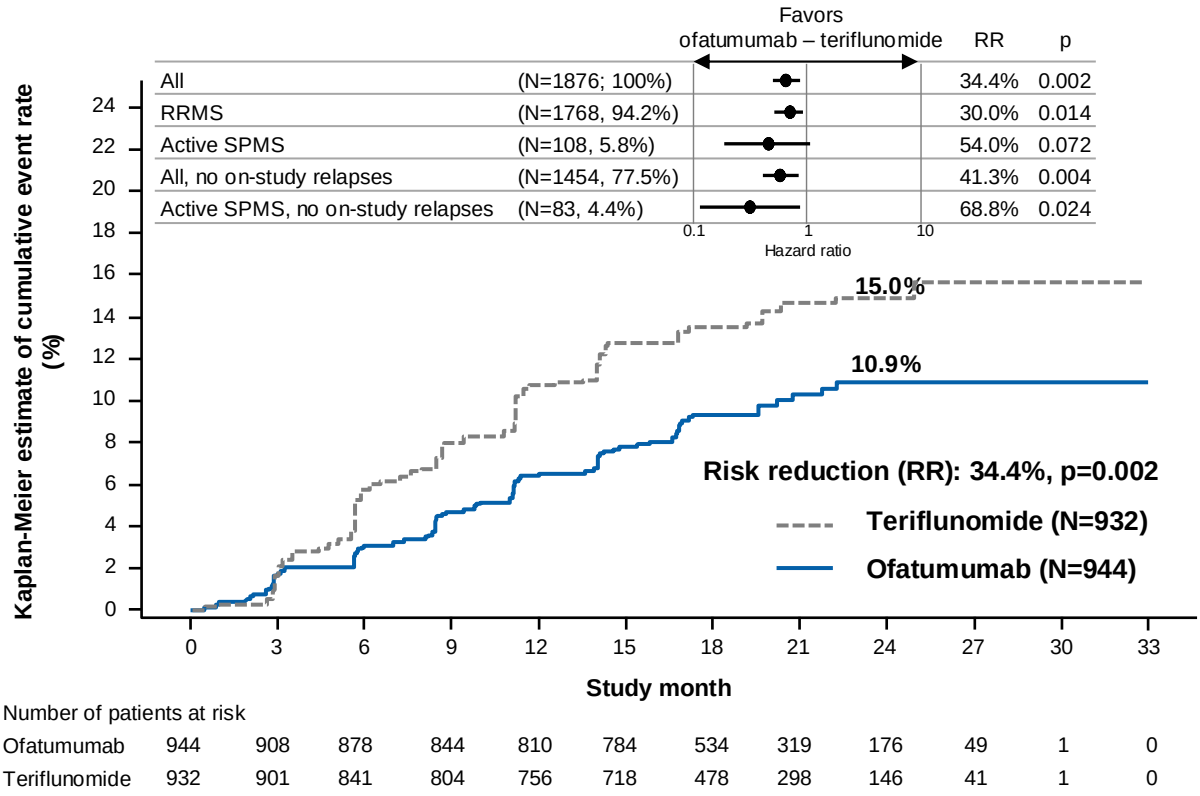
[1] confirmed relapses (accompanied by a clinically relevant change in the EDSS)

[2] in serum

[3] defined as at least a 1-point increase from baseline in EDSS sustained for 3 months (0.5 point increase for patients with baseline EDSS of 5.5 or more and 1.5 point increase for patients with baseline EDSS of 0).

[4] defined as at least a 1-point increase from baseline in EDSS sustained for 6 months (0.5 point increase for patients with baseline EDSS of 5.5 or more and 1.5 point increase for patients with baseline EDSS of 0).

Figure 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	534	319	176	49	1	0
Teriflunomide	932	901	841	804	756	718	478	298	146	41	1	0

Elevated levels of neurofilament light chain (NfL) in serum are a specific marker of neuronal injury. In both Phase 3 studies (G2301 and G2302), Bonspri significantly reduced NfL concentrations at Month 3 (p=0.011) and in all post-baseline visits compared with teriflunomide (see Table 2).

Furthermore, in both studies higher NfL concentrations at baseline were correlated with higher number of new or enlarging T2 lesions by the end of study, i.e. NfL had prognostic value (p<0.001) for on-study lesion formation. Bonspri reduced the number of on-study lesions, irrespective of the baseline NfL level.

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 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 deoxyribonucleic acid (DNA). For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Bonspri must not be mixed with other medicinal products.

STORAGE

Store between 2°C to 8°C.

Do not freeze.

Store in the original carton to protect from light.

Information might differ in some countries.

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

Instructions for use and handling

Instructions for Use of Bonspri pre-filled syringe

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

Remember:

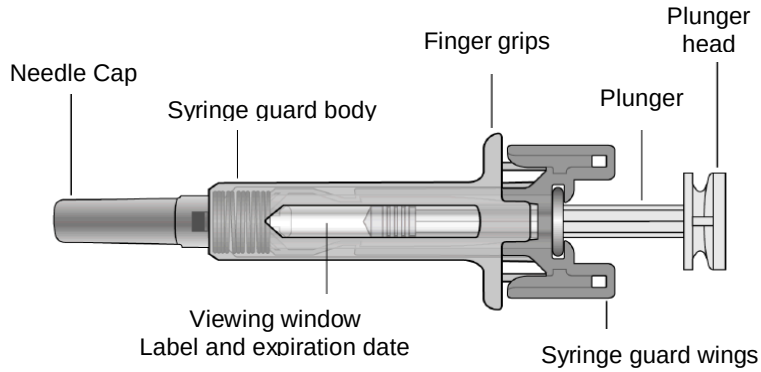
- **Do not use** the Bonspri pre-filled syringe if either the seal on the outer carton or the seal of the blister is broken. Keep the Bonspri pre-filled syringe in the sealed carton until you are ready to use it.
- **Do not shake** the Bonspri pre-filled syringe.
- The pre-filled syringe has a needle 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.
- Throw away (dispose of) the used Bonspri pre-filled syringe right away after use. **Do not re-use a Bonspri pre-filled syringe**. See "**How should I dispose of used Bonspri pre-filled syringe?**" at the end of these "Instructions for Use".

How should I store Bonspri?

- Store your carton of the Bonspri pre-filled syringe in a refrigerator, 2℃ to 8°C (between 36°F to 46°F).
- Keep the Bonspri pre-filled syringe in the original carton until ready to use to protect from light.
- **Do not freeze** the Bonspri pre-filled syringe.

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

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



What you need for your injection:

Included in the carton:

A new Bonspri 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 Bonspri pre-filled syringes?**" at the end of these "Instructions for Use".

Prepare the Bonspri pre-filled syringe

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

Step 2. Take the carton containing the Bonspri 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.

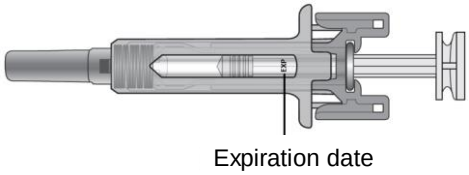
Step 4. Remove the pre-filled syringe from the outer carton and take it out of the blister by holding the syringe guard body.

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 Bonspri.
- **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

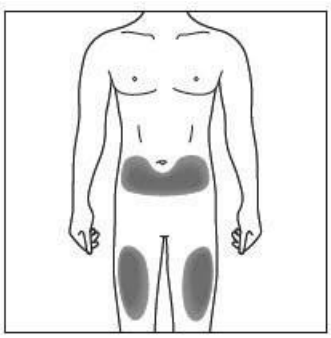
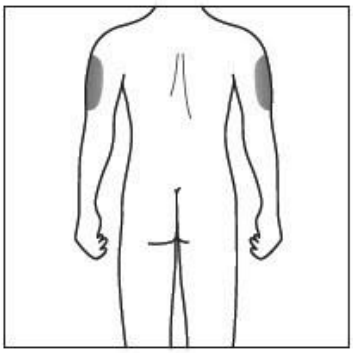


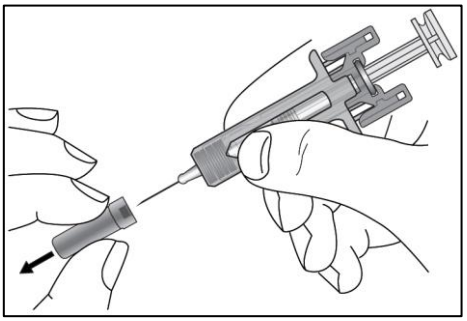
Figure E
(Caregiver and healthcare provider only)



Giving your injection

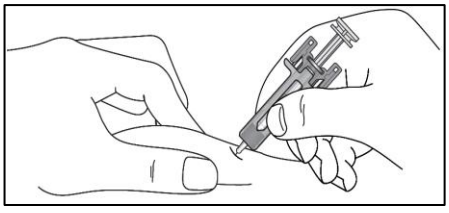
Step 9. Carefully remove the needle cap from the pre-filled syringe (**see Figure F**). Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

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



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 H

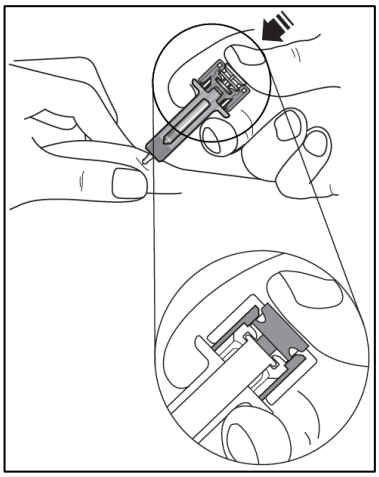
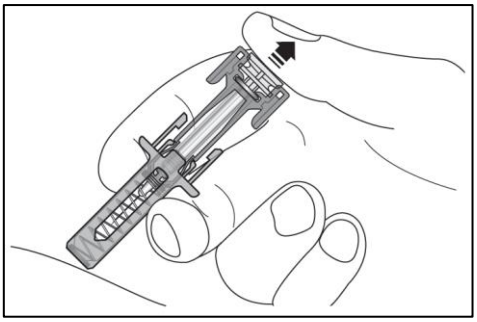


Figure I

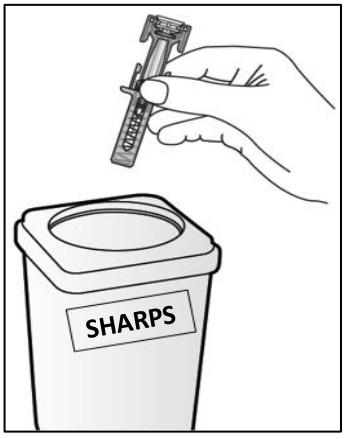


Step 13. **Slowly** release the plunger until the needle is covered (**see Figure I**), and then remove the syringe from the injection site.

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 Bonspri 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.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: Sep 2020 corrected in Dec 2020

TM = Trade Mark

Novartis Pharma AG, Basel, Switzerland