1 INDICATIONS AND USAGE

BONSPRI is indicated for the treatment of relapsing forms of multiple sclerosis (RMS), to include relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of BONSPRI

Hepatitis B Virus Screening

Prior to initiating BONSPRI, perform Hepatitis B virus (HBV) screening. BONSPRI is contraindicated in patients with active HBV confirmed by positive results for Hepatitis B surface antigen [HBsAg] and anti-HBV tests. For patients who are negative for HBsAg and positive for Hepatitis B core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with BONSPRI *[see Warnings and Precautions (5.1)]*.

Serum Immunoglobulins

Prior to initiating BONSPRI, perform testing for quantitative serum immunoglobulins *[see Warnings and Precautions (5.3)]*. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with BONSPRI.

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations 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 *[see Warnings and Precautions (5.1)]*.

Liver Function Tests

Prior to initiating BONSPRI, obtain serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, and bilirubin levels *[see Warnings and Precautions (5.4)]*.

2.2 Recommended Dosage

The recommended dosage of BONSPRI is:

- initial dosing of 20 mg by subcutaneous injection at Weeks 0, 1, and 2, followed by
- subsequent dosing of 20 mg by subcutaneous injection once monthly 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.

2.3 Administration Instructions

Administer by subcutaneous injection only.

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

Administer BONSPRI in the abdomen, thigh, or outer upper arm subcutaneously. Do not give injection into moles, scars, stretch marks, or areas where the skin is tender, bruised, red, scaly, or hard.

The first injection of BONSPRI should be performed under the guidance of a healthcare professional *[see Warnings and Precautions (5.2)]*.

BONSPRI syringes are for one-time use only and should be discarded after use. See Instructions for Use for complete administration instructions.

2.4 Preparation of BONSPRI

The BONSPRI "Instructions for Use" for each presentation contains more detailed instructions on the preparation of BONSPRI.

Before administration, remove BONSPRI pre-filled syringe from the refrigerator and allow BONSPRI to reach room temperature for about 15 to 30 minutes. DO NOT remove the needle cover while allowing the pre-filled syringe to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the liquid contains visible particles or is cloudy.

3 DOSAGE FORMS AND STRENGTHS

BONSPRI is a clear to slightly opalescent, and colorless to slightly brownish-yellow solution available as follows:

- Injection: 20 mg/0.4 mL in a single-dose pre-filled syringe

4 CONTRAINDICATIONS

BONSPRI is contraindicated in patients with:

- Active HBV infection *[see Warnings and Precautions (5.1)]*.
- History of hypersensitivity to ofatumumab or life-threatening injection-related reaction to BONSPRI. Hypersensitivity reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Serious, including life-threatening or fatal, bacterial, fungal, and new or reactivated viral infections have been observed during and following completion of treatment with anti-CD20 B-cell depleting therapies.

In Study 1 and Study 2 *[see Clinical Studies (14)]*, the overall rate of infections and serious infections in patients treated with BONSPRI was similar to patients who were treated with teriflunomide (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by BONSPRI-treated patients in the randomized clinical relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay BONSPRI administration in patients with an active infection until the infection is resolved.

<u>Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants</u>

When initiating BONSPRI after an immunosuppressive therapy or initiating an immunosuppressive therapy after BONSPRI, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1)* and *Clinical Pharmacology (12.2)]*. BONSPRI has not been studied in combination with other MS therapies.

<u>Hepatitis B Virus</u>

Reactivation

There were no reports of HBV reactivation in patients with MS treated with BONSPRI. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment) and in patients treated with other anti-CD20 antibodies.

Infection

BONSPRI is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients being treated with ofatumumab for CLL (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). HBV screening should be performed in all patients before initiation of treatment with BONSPRI. At 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. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with BONSPRI. These patients should be monitored and managed following local medical standards to prevent HBV infection or reactivation.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

Although no cases of PML have been reported for BONSPRI in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (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. At the first sign or symptom suggestive of PML, withhold BONSPRI and perform an appropriate diagnostic evaluation. Magnetic resonance imaging (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, treatment with BONSPRI should be discontinued.

Vaccinations

Administer all immunizations 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 Clinical Pharmacology (12.2)]*.

Vaccination of Infants Born to Mothers Treated with BONSPRI During Pregnancy

In infants of mothers treated with BONSPRI during pregnancy, do not administer live or live-attenuated vaccines before confirming 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, prior to confirming the B-cell count is within normal range, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

5.2 Injection-Related Reactions and Hypersensitivity Reactions

BONSPRI can result in systemic injection-related reactions and hypersensitivity reactions, which may be serious or life-threatening.

In Study 1 and Study 2, systemic and local injection reactions were reported in 21% and 11% of patients treated with BONSPRI compared to 15% and 6% of patients treated with teriflunomide who received matching placebo injections, respectively *[see Adverse Reactions (6.1)* and *Clinical Studies (14)].*

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening injection reactions in the RMS clinical studies.

In the post-marketing setting, additional systemic injection-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, angioedema, pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, dizziness, nausea, and tachycardia. Most cases were non-serious and occurred with the first injection. Most serious cases resulted in permanent discontinuation of BONSPRI.

Symptoms of systemic injection-related reactions may be clinically indistinguishable from acute hypersensitivity reactions. A hypersensitivity reaction may occur with any injection. New or more severe symptoms compared to those experienced with previous injections should prompt consideration of a potential hypersensitivity reaction.

Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of BONSPRI should be performed under the guidance of an appropriately trained healthcare professional. If systemic injection-related reactions occur, initiate appropriate therapy. Patients who experience symptoms of systemic injection-related reactions or hypersensitivity reactions with BONSPRI should be instructed to seek immediate medical attention.

If a hypersensitivity reaction or life-threatening systemic injection-related reaction occurs, immediately and permanently discontinue BONSPRI *[see Contraindications (4)]*. If restarting BONSPRI after a severe (but not life-threatening) systemic injection-related reaction or other event after which rechallenge is considered appropriate, administer the next BONSPRI injection under clinical observation. If a mild to moderate injection-related reaction occurs, consider rechallenge under clinical observation.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain. If local injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7% of patients treated with BONSPRI compared to 3.1% of patients treated with teriflunomide in RMS clinical trials *[see Adverse Reactions (6.1)]*. Treatment was discontinued because of decreased immunoglobulins in 3.4% of patients treated with BONSPRI and in 0.8% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during

treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing BONSPRI therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Liver Injury

Clinically significant liver injury, without findings of viral hepatitis, has been reported in the postmarketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including BONSPRI. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred weeks to months after administration.

Patients treated with BONSPRI found to have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3x the upper limit of normal (ULN) with serum total bilirubin greater than 2x ULN, are potentially at risk for severe drug-induced liver injury.

Obtain liver function tests prior to initiating treatment with BONSPRI *[see Dosage and Administration (2.1)]*, and monitor for signs and symptoms of any hepatic injury during treatment. Measure serum aminotransferases, alkaline phosphatase, and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is present and an alternative etiology is not identified, discontinue BONSPRI.

5.5 Fetal Risk

Based on animal data, BONSPRI can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to BONSPRI *in utero*. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving BONSPRI and for at least 6 months after the last dose *[see Use in Specific Populations (8.1)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Injection-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.3)]*
- Liver Injury *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Approximately 1500 patients with RMS received BONSPRI in clinical studies. In Study 1 and Study 2, 1882 patients with RMS were randomized, 946 of whom were treated with BONSPRI for a median duration of 85 weeks; 33% of patients receiving BONSPRI were treated for up to 120 weeks *[see Clinical Studies (14.1)].* The most common adverse reactions occurring in greater than 10% of patients treated with BONSPRI and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The

most common cause of discontinuation in patients treated with BONSPRI was low immunoglobulin M (3.3%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

Table 1: Adverse Reactions in Patients With RMS With an Incidence of at Least 5% With BONSPRI and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

Adverse reactions	BONSPRI 20 mg N = 946 %	Teriflunomide 14 mg N = 936 %
Upper respiratory tract infections[a]	39	38
Injection-related reactions (systemic)	21	15
Headache	13	12
Injection-site reactions (local)	11	6
Urinary tract infection	10	8
Back pain	8	6
Blood immunoglobulin M decreased	6	2

[a]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.

Injection-Related Reactions and Injection-Site Reactions

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4%), decreasing with subsequent injections (4.4% with second, less than 3% with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with BONSPRI reported serious injection-related reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue.

In addition to systemic injection-related reactions, local reactions at the administration site were very common. Local injection-site reactions were all mild to moderate in severity. The most frequently reported symptoms (2% or greater) included erythema, pain, itching, and swelling *[see Warnings and Precautions (5.2)].*

Laboratory Abnormalities

Immunoglobulins

In Study 1 and Study 2, a decrease in the mean level of IgM was observed in BONSPRI-treated patients but was not associated with an increased risk of infections *[see Warnings and Precautions (5.3)].* In 14.3% of patients in Study 1 and Study 2, treatment with BONSPRI resulted in a decrease in a serum IgM that reached a value below 0.34 g/L. BONSPRI 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.

6.2 Immunogenicity

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

the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment-induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) BONSPRI-treated patients; no patients with treatment-enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on pharmacokinetics, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of BONSPRI.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BONSPRI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

Hepatobiliary Disorders: Liver injury *[see Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of BONSPRI with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with BONSPRI.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating BONSPRI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of BONSPRI in pregnant women.

Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies. No teratogenicity was observed after intravenous administration of ofatumumab to pregnant monkeys during organogenesis. However, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels higher than that in humans *(see Data)*.

Although there are no data on ofatumumab, monoclonal antibodies can be actively transported across the placenta, and ofatumumab may cause immunosuppression in the *in utero*-exposed infant (see *Clinical Considerations*).

Clinical Considerations

Fetal/Neonatal adverse reactions

Transport of endogenous IgG antibodies across the placenta is low in the first trimester and increases as pregnancy progresses and peaks during the third trimester. Transient peripheral B-cell depletion and lymphocytopenia have been observed in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to BONSPRI have not been adequately studied in clinical trials. 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. Avoid administering live vaccines to neonates and infants exposed to BONSPRI *in utero* before confirming B-cell count is within normal range *[see Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.2)]*.

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.

Data

Animal Data

In the embryo-fetal development (EFD) study, intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestation days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (C_{avg}) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (C_{avg}) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

In the enhanced pre- and post-natal development (ePPND) study, intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys from gestation day 20 until birth resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose of 100/20 mg/kg. The deaths were considered secondary to B-cell depletion. Plasma exposure (C_{avg}) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose (10/3 mg/kg).

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. 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 or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on animal data, BONSPRI may cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Contraception

Females of childbearing potential should use effective contraception while receiving BONSPRI and for 6 months after the last treatment of BONSPRI.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of BONSPRI did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Ofatumumab is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody that binds to human CD20 expressed on B-cells. Ofatumumab is produced in a murine NS0 cell line and consists of two IgG1 heavy chains and two kappa light chains with a molecular weight of approximately 146 kDa.

BONSPRI (ofatumumab) injection is a sterile, preservative-free solution for subcutaneous use.

Each 20 mg/0.4 mL BONSPRI pre-filled syringe delivers 0.4 mL of solution. Each 0.4 mL contains 20 mg of ofatumumab, and arginine (4 mg), disodium edetate (0.007 mg), polysorbate 80 (0.08 mg), sodium acetate trihydrate (2.722 mg), sodium chloride (1.192 mg), and Water for Injection, USP with a pH of 5.5. Hydrochloric acid may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which ofatumumab exerts its therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

12.2 Pharmacodynamics

B-cell Depletion

For B-cell counts, assays for CD19+ B-cells are used because the presence of ofatumumab interferes with the CD20 assay. In Study 1 and Study 2, BONSPRI administered as recommended, resulted in a reduction of CD19+ B-cells to below the LLN in 77.0% and 78.8% of patients, respectively, one week after treatment initiation, and in 95.0% and 95.8% of patients, respectively, two weeks after treatment initiation *[see Dosage and Administration (2.2)* and *Clinical Studies (14)]*. In Study 1 and Study 2, at Week 12, 99.3% to 99.5% of patients had CD19+ B-cell counts below LLN. The CD19+ B-cell counts remained below LLN for approximately 97% of patients in Study 1 and 92% of patients in Study 2 from 12 weeks through 120 weeks while on BONSPRI treatment.

In a study of bioequivalence using the same dosing regimen as in Study 1 and Study 2, before initiation of the maintenance phase, total CD19+ B-cell levels below the defined threshold of 10 cells/µL were achieved in 94% of patients starting at Week 4 and 98% of patients at Week 12.

B-cell Repletion

Data from Studies 1 and 2 indicate a median time to B-cell recovery to either LLN or baseline value of 24.6 weeks post-treatment discontinuation. Pharmacokinetics and pharmacodynamics modeling and simulation for B-cell repletion corroborate these data, predicting median time to B-cell recovery to LLN of 23 weeks post-treatment discontinuation.

12.3 Pharmacokinetics

Absorption

A subcutaneous dose of 20 mg every 4 weeks leads to a mean AUC_{tau} of 483 mcg h/mL and a mean C_{max} of 1.43 mcg/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 L following subcutaneous administration of repeated BONSPRI 20 mg dose.

Elimination

Ofatumumab is eliminated by both linear catabolic pathways and a non-linear B-cell mediated pathway, resulting in non-constant elimination half-life. Initially, a higher baseline B-cell count results in greater B-cell-mediated elimination and shorter ofatumumab half-life. As the B-cells are depleted, the catabolic pathway predominates, resulting in a relatively longer ofatumumab half-life compared to earlier in therapy when both elimination pathways were available. Following B-cell depletion, clearance was estimated to be 0.34 L/day following repeated subcutaneous administration of BONSPRI 20 mg injections. The half-life at steady state was estimated to be approximately 16 days following subcutaneous administration of repeated BONSPRI 20 mg dosage.

Metabolism

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

Excretion

Ofatumumab, a monoclonal antibody, is not likely to undergo renal excretion.

Specific Populations

The following population characteristics do not have a clinically meaningful effect on the pharmacokinetics of ofatumumab: body weight, sex, age, race, or baseline B-cell count.

Patients with Renal/Hepatic Impairment

Pharmacokinetics of ofatumumab in patients with renal or hepatic impairment have not been studied.

Drug Interaction Studies

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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies have been conducted to assess the carcinogenic potential of ofatumumab.

Mutagenesis

No studies have been conducted to assess the mutagenic potential of ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA.

Impairment of Fertility

No effects on reproductive parameters, including hormones, menstrual cycle, sperm analysis, or histopathological evaluation of reproductive organs, were observed in male or female monkeys administered ofatumumab for 13 weeks by intravenous injection (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg). Plasma exposures (C_{avg}) at the high dose tested in monkeys are greater than 500 times that in humans at the recommended human maintenance dose of 20 mg/month.

14 CLINICAL STUDIES

The efficacy of BONSPRI was demonstrated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design, in patients with relapsing forms of MS [Study 1 (NCT02792218) and Study 2 (NCT02792231)]. Both studies enrolled patients with at least one relapse in the previous year, 2 relapses in the previous 2 years, or the presence of a T1 gadolinium-enhancing (GdE) lesion in the previous year. Patients were also required to have an Expanded Disability Status Scale (EDSS) score from 0 to 5.5.

Patients were randomized to receive either BONSPRI, 20 mg subcutaneously on Days 1, 7, and 14, followed by 20 mg every 4 weeks thereafter starting at Week 4 with a daily oral placebo, or the active comparator, teriflunomide, at a dose of 14 mg orally once daily with a placebo administered subcutaneously on Days 1, 7, 14, and every 4 weeks thereafter. The treatment duration for an individual patient was variable based on when the end-of-study criteria were met. The maximal duration of treatment for an individual patient was 120 weeks. Neurologic evaluations were performed at baseline, every 3 months during blinded treatment, and at the time of a suspected relapse. Brain MRI scans were performed at baseline, 1 year, and 2 years.

The primary endpoint of both trials was the annualized relapse rate (ARR) over the treatment period. Additional outcome measures included: 1) the time to 3-month confirmed disability progression for the pooled populations, 2) the number of T1 GdE lesions per scan at Weeks 48 and 96, and 3) the annualized rate of new or enlarging T2 MRI lesions. Disability progression was defined as an increase in EDSS of at least 1.5, 1, or 0.5 points in patients with a baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.

In Study 1, a total of 927 patients were randomized to receive BONSPRI (n = 465) or teriflunomide (n = 462). Of those randomized to BONSPRI, 90% completed the study; of those randomized to teriflunomide, 81% completed the study. Demographics and disease characteristics were balanced across treatment arms. The mean age was 38 years, 89% were White, and 69% were female. The mean time since MS diagnosis was 5.7 years and the median EDSS score at baseline was 3.0; 60% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the previous year was 1 and the mean number of T1 GdE lesions on MRI scan was 1.5.

In Study 2, a total of 955 patients were randomized to receive BONSPRI (n = 481) or teriflunomide (n = 474). Of those randomized to BONSPRI, 83% completed the study; of those randomized to teriflunomide, 82% completed the study. Demographics and disease characteristics were balanced across treatment arms. The mean age was 38 years, 87% were White, and 67% were female. The mean time since MS diagnosis was 5.5 years and the median EDSS score at baseline was 2.5; 61% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the previous year was 1.3, and the mean number of T1 GdE lesions on MRI scan was 1.6.

In both studies, BONSPRI significantly lowered the ARR compared to teriflunomide.

BONSPRI significantly reduced the risk of 3-month confirmed disability progression compared to teriflunomide.

BONSPRI significantly reduced the number of T1 GdE lesions and the rate of new or enlarging T2 lesions in both studies.

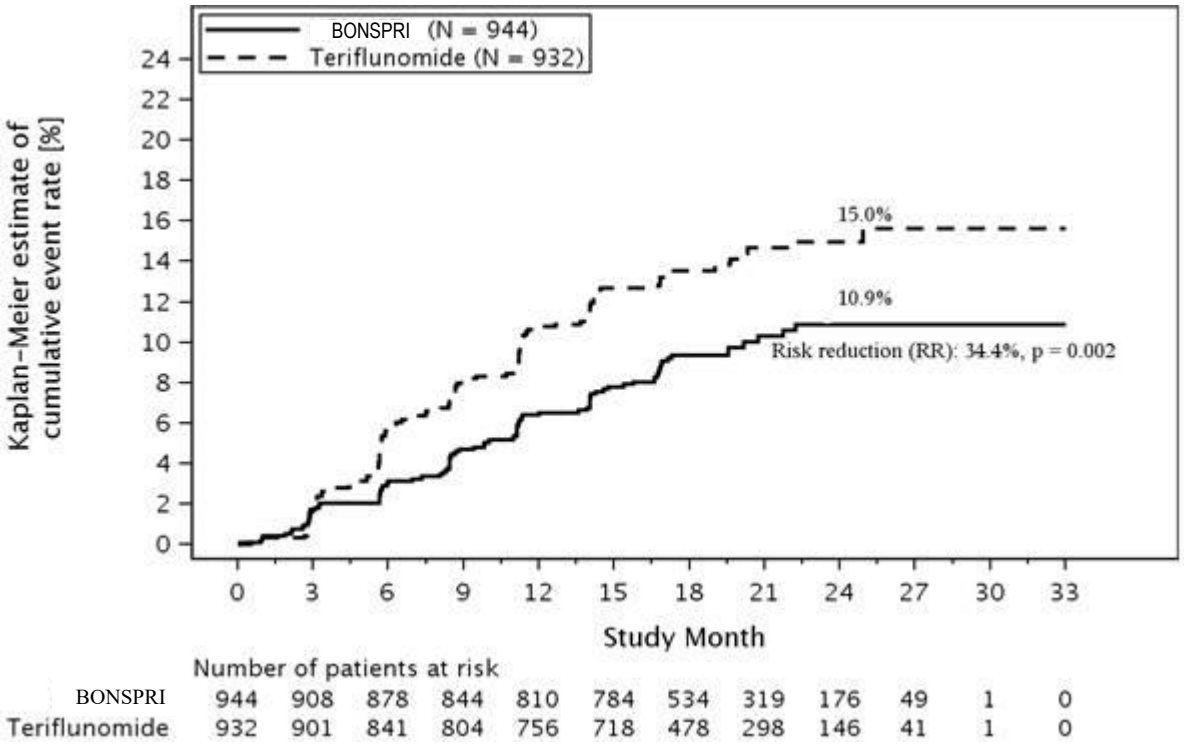
Key results for Study 1 and Study 2 are presented in Table 2 and Figure 1.

Table 2: Key Clinical and MRI Endpoints From Study 1 and Study 2

Endpoints	Study 1		Study 2	
	BONSPRI 20mg (n = 465)	Teriflunomide 14 mg (n = 462)	BONSPRI 20mg (n = 481)	Teriflunomide 14 mg (n = 474)
Clinical Endpoints				
Annualized relapse rate (primary endpoint)	0.11	0.22	0.10	0.25
Relative reduction	51% ($p < 0.001$)		58% ($p < 0.001$)	
Proportion of patients with 3-month confirmed disability progression[a,b]	10.9% BONSPRI vs 15.0% teriflunomide			
Relative risk reduction	34.3% ($p = 0.003$)			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.01	0.46	0.03	0.52
Relative reduction	98% ($p < 0.001$)		94% ($p < 0.001$)	
Number of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.16
Relative reduction	82% ($p < 0.001$)		85% ($p < 0.001$)	

[a]Disability progression was defined as an increase in EDSS of at least 1.5, 1, or 0.5 points in patients with a baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.
[b]Prospective pooled analysis of Studies 1 and 2. Proportion of patients with 3-month confirmed disability progression refers to Kaplan-Meier estimates at Month 24.

Figure 1: Time to First 3-month Confirmed Disability Progression by Treatment Full Analysis Set



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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BONSPRI (ofatumumab) injection is a preservative-free, clear to slightly opalescent and colorless to slightly brownish-yellow solution for subcutaneous administration, which is supplied as follows:

BONSPRI Pre-filled Syringe:

Carton of one 20 mg/0.4 mL single-dose pre-filled syringe

16.2 Storage and Handling

BONSPRI pre-filled syringes must be refrigerated at 2ºC to 8ºC Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake.

If necessary, BONSPRI may be stored for up to 7 days at room temperature, not to exceed 30°C Write the date removed from the refrigerator in the space provided on the carton labeling. If stored below 30°C unused BONSPRI may be returned to the refrigerator and must be used within the next 7 days or discarded after 7 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read patient labeling (Patient Information Leaflet).

Infections

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, or dysuria *[see Warnings and Precautions (5.1)]*.

Advise patients that BONSPRI may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk *[see Warnings and Precautions (5.1)]*.

Advise patients that PML has happened with an intravenous form of ofatumumab administered at a higher intravenous dosage in patients with CLL, as well as with drugs that are similar to BONSPRI, and may happen with BONSPRI. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their healthcare provider if they develop any symptoms suggestive of PML. Inform the patient that 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 *[see Warnings and Precautions (5.1)]*.

Vaccinations

Advise patients to complete any required live or live-attenuated vaccinations at least 4 weeks and, whenever possible at least 2 weeks, prior to initiation of BONSPRI for inactivated vaccines.

Administration of live-attenuated or live vaccines is not recommended during BONSPRI treatment and until B-cell recovery *[see Warnings and Precautions (5.1)]*.

Injection-Related Reactions and Hypersensitivity Reactions

Inform patients about the signs and symptoms of injection-related reactions and hypersensitivity reactions. Inform patients that injection-related reactions generally occur within 24 hours and predominantly following the first injection. A hypersensitivity reaction may occur with any injection, and any new or worsening symptoms with subsequent BONSPRI injections should prompt consideration of a hypersensitivity reaction. Advise patients to seek immediate medical attention if they experience signs or symptoms of a severe or life-threatening injection-related reaction or hypersensitivity reaction, and to contact their healthcare provider if they experience any signs or symptoms of an injection-related reaction or hypersensitivity reaction *[see Warnings and Precautions (5.2)]*.

Liver Injury

Inform patients that liver injury has been reported with anti-CD20 B-cell depleting therapies, including BONSPRI. Instruct patients treated with BONSPRI to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. A blood test should be obtained before patients start therapy, and during treatment as clinically indicated *[see Warnings and Precautions (5.4)]*.

Contraception

Advise females of childbearing potential to use effective contraception while receiving BONSPRI and for 6 months after the last treatment of BONSPRI *[see Warnings and Precautions (5.5)* and *Use in Specific Populations (8.3)]*.

Pregnancy

Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)]*.

Instruction on Injection Technique

Patients or caregivers should be instructed by a healthcare professional on how to administer BONSPRI *[see Instructions for Use]*.

Instruct patients or caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct patients to inject the full amount of BONSPRI according to the directions provided in the Instructions for Use. Dispose of syringes in a puncture-resistant container.

18 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.

19 INCOMPATIBILITIES

BONSPRI must not be mixed with other medicinal products.

20 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.
- **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 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°C 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.
- If necessary, BONSPRI 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, BONSPRI pre-filled syringe can then be returned to the refrigerator for a maximum of 7 days.

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

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

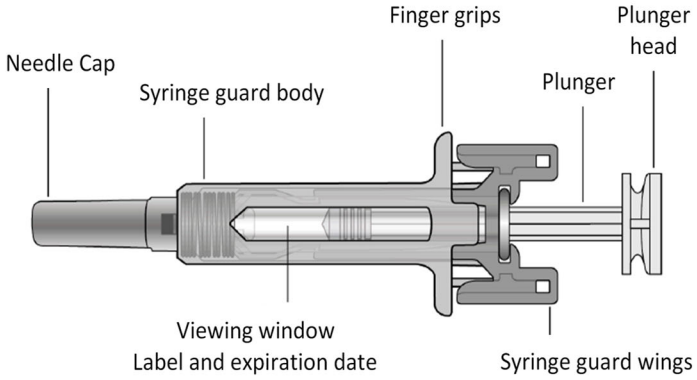


Figure A

What you need for your injection:

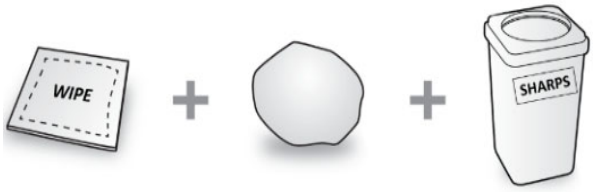
Included in the carton:

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.

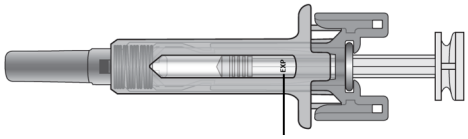
Step 4. Remove the pre-filled syringe from the outer carton and take it out of the blister by holding the syringe guard body.

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.

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.

Figure C



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.

Figure D

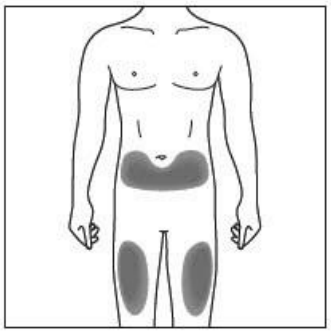
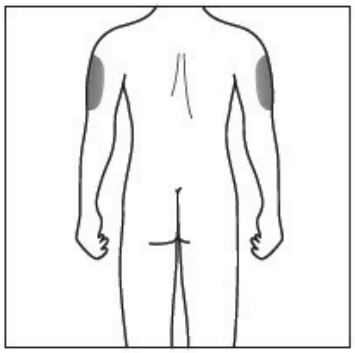


Figure E
(Caregiver and healthcare provider only)



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.

Giving your injection

Figure F

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.

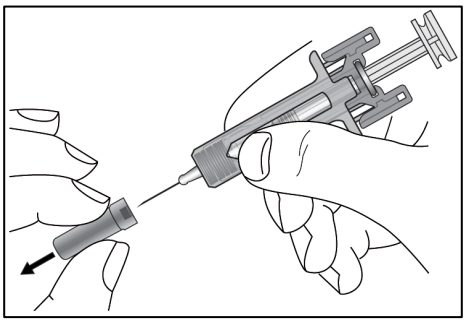


Figure G

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.

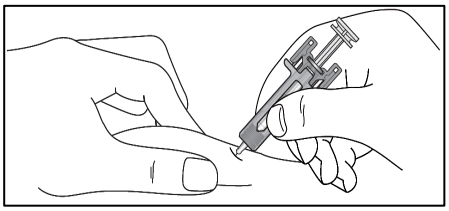
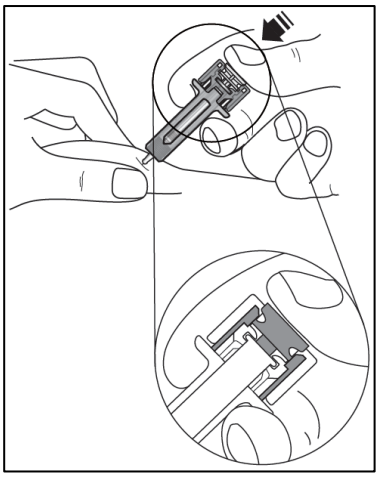


Figure H

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.

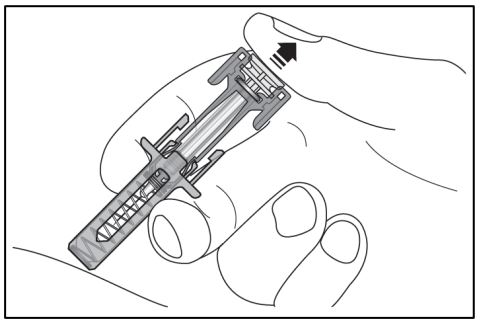
Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.



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

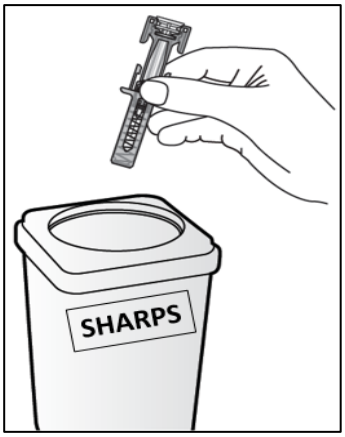
Step 14. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure I



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.

PRODUCT REGISTRATION HOLDER

Novartis Corporation (Malaysia) Sdn. Bhd.

Level 18, Imazium,

No. 8, Jalan SS21/37, Damansara Uptown,

47400 Petaling Jaya, Selangor.

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