actividad

Concierto de Gala "Danny Rivera en el tiempo" **por 10º Aniversario de Medicare y Mucho Más (MMM) en el Centro de Bellas Artes en Santurce.**

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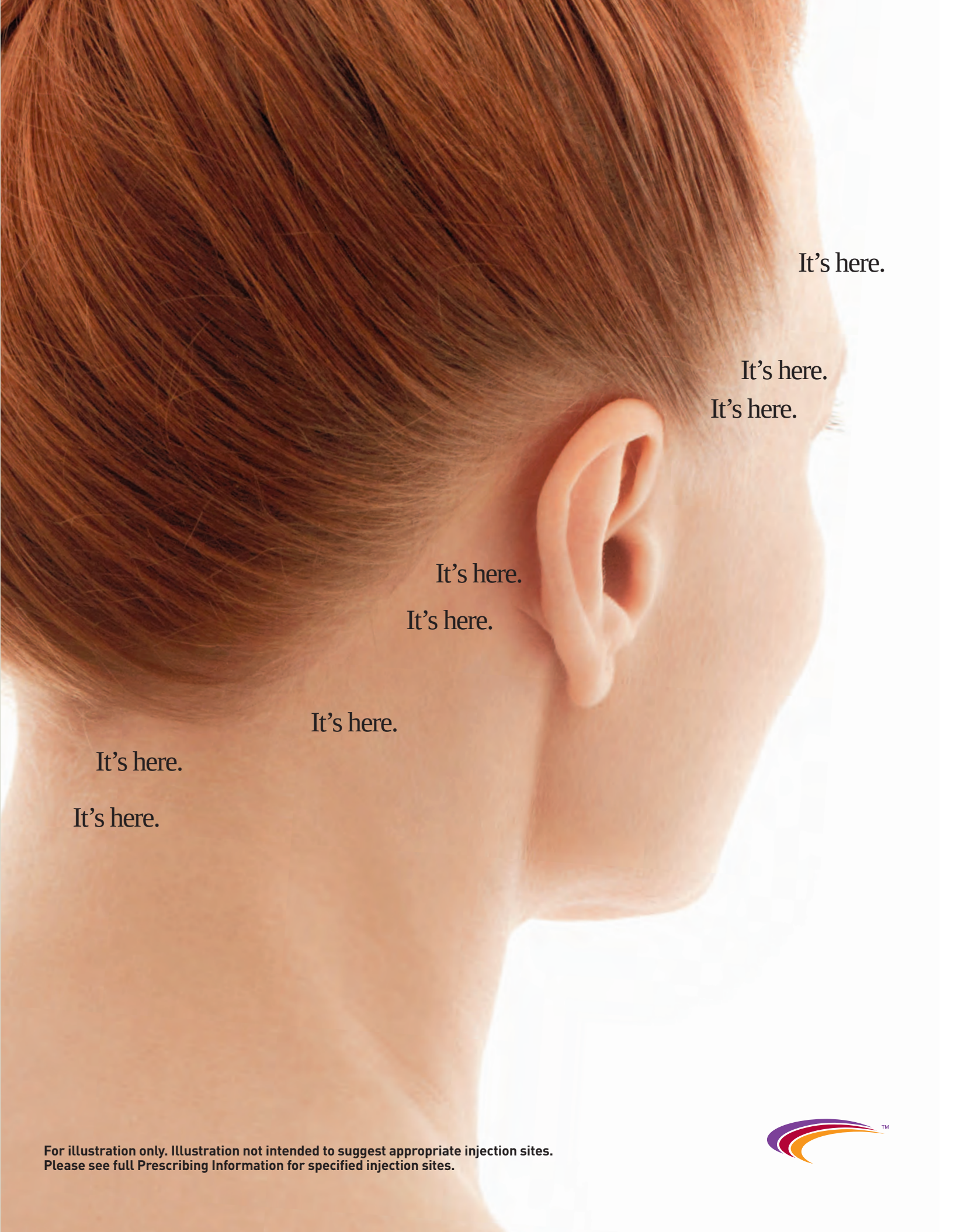

For illustration only. Illustration not intended to suggest appropriate injection sites.
Please see full Prescribing Information for specified injection sites.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

CONTRAINDICATIONS BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for chronic migraine at the labeled doses have been reported.

Hypersensitivity Reactions Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Pre-Existing Neuromuscular Disorders Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®.

Human Albumin and Transmission of Viral Diseases This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

Post Marketing Experience There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS No formal drug interaction studies have been conducted with BOTOX® (onabotulinumtoxinA) for injection. Co-administration of BOTOX® and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

References:
1. BOTOX® Prescribing Information, October 2010. **2.** Aurora SK, Dodick DW, Turkel CC, et al; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30(7):793-803. **3.** Diener HC, Dodick DW, Aurora SK, et al; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30(7):804-814.

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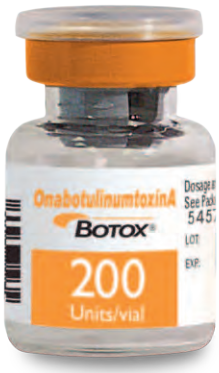

It's here.

The first and only therapy for prophylaxis of headaches in adults with Chronic Migraine

≥ 15 headache days per month with headache lasting 4 hours a day or longer

8 to 9 fewer headache days per month (vs 6 to 7 days with placebo)[1-3]

4% discontinuation rate due to adverse events for BOTOX® vs 1% for placebo (see Adverse Reactions below)[1]

Dosing recommended once every 12 weeks[1]

Indication

Chronic Migraine BOTOX® (onabotulinumtoxinA) for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important Limitations Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning) and Hypersensitivity Reactions (see *Contraindications* and *Warnings and Precautions*).

Chronic Migraine The most frequently reported adverse reactions following injection of BOTOX® for chronic migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX® treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

Please see brief summary of full Prescribing Information on adjacent pages.

BOTOX®
onabotulinumtoxinA

BOTOX® (onabotulinumtoxinA)

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

INDICATION AND USAGE

Chronic Migraine

BOTOX® (onabotulinumtoxinA) for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection.

CONTRAINDICATIONS

Known Hypersensitivity to Botulinum Toxin

BOTOX® is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions]*.

Infection at the Injection Site(s)

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Postmarketing safety data from **BOTOX®** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®**/**BOTOX®** **Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX®** for blepharospasm at the recommended dose (30 Units and below), strabismus, or for chronic migraine at the labeled doses have been reported.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX®** should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *[see Warnings and Precautions]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions and Adverse Reactions]*.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX®** *[see Adverse Reactions]*.

Pulmonary Effects of BOTOX® in Patients with Compromised Respiratory Status Treated for Spasticity

Patients with compromised respiratory status treated with **BOTOX®** for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV_1 40-80% of predicted value and $FEV_1/FVC \leq 0.75$), the event rate in change of Forced Vital Capacity ≥ 15% or ≥ 20% was generally greater in patients treated with **BOTOX®** than in patients treated with placebo (see table below).

Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 postinjection with up to two treatment cycles with BOTOX® or placebo

	BOTOX® 360 Units		BOTOX® 240 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX®** *[see Warnings and Precautions]*.

Corneal Exposure and Ulceration in Patients Treated with BOTOX® for Blepharospasm

Reduced blinking from **BOTOX®** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Retrobulbar Hemorrhages in Patients Treated with BOTOX® for Strabismus

During the administration of **BOTOX®** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with **BOTOX®** (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX®** (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%).

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

The following adverse reactions to **BOTOX®** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions]*
- Hypersensitivity *[see Contraindications and Warnings and Precautions]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions]*

Clinical Studies Experience

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

BOTOX® and **BOTOX® Cosmetic** contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX® Cosmetic** also have the potential to be observed with the use of **BOTOX®** and vice-versa.

In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions]*.

Chronic Migraine

In double-blind placebo controlled chronic migraine pivotal efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the **BOTOX®** treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the **BOTOX®** group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the **BOTOX®** group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of **BOTOX®** for chronic migraine appear in the table below.

Adverse Reactions Reported by ≥ 2% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX® 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections and Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

Other adverse events that occurred more frequently in the **BOTOX®** group compared to the placebo group at a frequency less than 1% and potentially **BOTOX®** related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of **BOTOX®** treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Upper Limb Spasticity

The most frequently reported adverse reactions following injection of **BOTOX®** for adult spasticity appear in the following table, next column.

Adverse Reactions Reported by ≥ 2% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX® 251 Units-360 Units (N=115)	BOTOX® 150 Units-250 Units (N=188)	BOTOX® <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Cervical Dystonia

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX®**, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX®** resulting from the spread of the toxin outside the injected muscles *[see Warnings and Precautions]*.

The most common severe adverse event associated with the use of **BOTOX®** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea *[see Warnings and Precautions]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions]*.

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of **BOTOX®** for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis

The most frequently reported adverse events (3-10% of adult patients) following injection of **BOTOX®** in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to **BOTOX®** 50 Units and 110 patients exposed to **BOTOX®** 75 Units in each axilla.

Blepharospasm

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX®**, the most frequently reported treatment-related adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from **BOTOX®** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus

Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of **BOTOX®**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

Post-Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events, not already addressed elsewhere in the package insert, have been reported since the drug has been marketed: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; paresthesia; pyrexia; radiculopathy; skin rash (including erythema multiforme, and psoriasiform eruption); tinnitus; vertigo; visual disturbances; and vomiting.

Because these events 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 botulinum toxin.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX**® treatment by inactivating the biological activity of the toxin.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of **BOTOX**®, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to **BOTOX**® therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to **BOTOX**® therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), and no patients among 406 migraine patients with analyzed specimens showed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to **BOTOX**® in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX**® with the incidence reported to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that **BOTOX**® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with **BOTOX**® (onabotulinumtoxinA) for injection.

Co-administration of **BOTOX**® and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Use of anticholinergic drugs after administration of **BOTOX**® may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX**®.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. **BOTOX**® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When **BOTOX**® (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 1½ times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

When **BOTOX**® was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on Units/kg.

Nursing Mothers

It is not known whether **BOTOX**® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX**® is administered to a nursing woman.

Pediatric Use

Prophylaxis of Headaches in Chronic Migraine

Safety and effectiveness in patients below the age of 18 years have not been established.

Spasticity

Safety and effectiveness in patients below the age of 18 years have not been established.

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Axillary Hyperhidrosis

Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use

Clinical studies of **BOTOX**® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE

Excessive doses of **BOTOX**® (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis *[see Boxed Warning and Warnings and Precautions]*. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc.
2525 Dupont Dr.
Irvine, CA 92612

U.S. Patents 6,974,578; 6,683,049; and 6,896,886
Based on 71580US11B revised 10/2010

APC46GE11

eventos

Dr. Eddy Ríos, con su esposa, Zilka, y su hija, Liza Ivette.

Dr. Edward Nieves, Presidente entrante de la AEUCCEM.

La Asociación de Egresados de la Escuela de Medicina de la Universidad Central del Caribe llevó a cabo su 15ª Convención Anual en el Sheraton Old San Juan.

Dr. Milton Pérez y su esposa Josefina Durán.

Dr. José I. Russe y Dr. Raúl Marcial Rojas rodean al Dr. Milton A. Pérez Ruiz, quien recibió el “Premio Dr. Raúl Marcial Rojas”.

Dr. José I. Russe (pasado Presidente), Dr. Eddy Ríos Olivares, a quien se le dedicó la convención y Dr. Eric González.

Grupo de egresados con miembros de la nueva Directiva de la Asociación de Egresados de la UCCEM.

eventos

La Sociedad de Endocrinología y Diabetología de Puerto Rico realizó el *SPED-AACE Annual Meeting* en el Ritz Carlton Hotel de Isla Verde.

Dr. Harry Jiménez y esposa Sra. Myrna Ramos; Dr. Ángel Comulada y Sra. Sonia Ortiz; Dr. Francis Baco y Dr. Carlos Pacheco.

Dr. Rodríguez Vigil, Dr. Rafael Rivera, Dr. Julián Vázquez, Sra. Vilma Vicenti de Vázquez, Dra. Lillian Haddock, Sra. Marita Vázquez.

Sr. Agustín Irizarry; Sra. Rebecca Passapera; Sra. Marisol Barzana; Sr. Harry Román Dr. Alejandro Martino y su esposa Sra. Rosa González.

Dra. Carmen Ana Sáenz, Dr. Ángel Comulada, Dr. Adolfo Pérez Comas.

Dr. José Riestra y su esposa, Sra. Margarita Riestra.

Sra. Elba Mc Faline, Dr. Alejandro Martino y su esposa Sra. Rosa González; Dr. Jorge Rohena y esposa Sra. Glorilis Ortiz; Dra. Mariela Nieves, Dr. Carlos Montalvo y Dra. Yanira Marrero.

Dr. Francis Baco, Sra. Karine, Sr. Khalil Baco, Sra. María Viera, y Sr. Wadih Baco.

Dr. Efraín Rodríguez, Sra. Ana Hilda Aguiló, Sr. Amílcar Cintrón, Sra. Claudette Becerra, Sr. Ismael Rodríguez.

Dra. María de Lourdes Miranda; Dr. Francisco Nieves, Dra. Horidel Febo; Dr. Francis Baco; Dr. Ángel L. Comulada.

Dra. Ana Medina, Dr. Jorge De Jesús; Sra. Mary Padilla; Dr. Harry Jiménez y Lcda. Myrna Ramos.

Dr. Efraín Meléndez, Dra. Gloria Rodríguez, Sr. Antonio Vélez y Sra. Frances Torres; Sr. Gabino Irizarry; Dr. Jorge De Jesús; Dra. Taty Medina; Dr. Juan Otero y su esposa Lucy.

eventos

Con el propósito de recaudar fondos para fines benéficos, la Fundación Dr. García Rinaldi (FDGR) realizó su 19º Torneo de Golf en Dorado Beach and Golf Club.

El Presidente de la Junta de Directores de la Fundación el Lcdo. Miranda Daleccio, la Directora ejecutiva de la Fundación Dra. Maura Tapia, Julio Torres, Daniel Roquette, Norman Roquette, Salvador Pons y el Presidente del comité de Golf Mr. Teale.

Lcdo. Miranda Daleccio, Pedro A. Jimenez, María A. Santienes, el Dr. García Rinaldi , Lcdo. Malave, José Ortiz, Dra. Maura Tapia, y Mr. Teale.

El Lcdo. Miranda Daleccio y el Dr. Raúl García Rinaldi junto a jugadores del Torneo de Golf en el momento de las premiaciones.

Lcdo. Miranda Daleccio, Elsio Negrón, Dr. García Rinaldi, Dra. Maura Tapia, Ángel Enriquez y Mr. Teale.

Lcdo. Miranda Daleccio, Sr. Pedro Carral, Dr. Luis Rosa Toledo, Dr. Ignacio Acevedo, Dr. García Rinaldi, Dra. Maura Tapia, Mr. Teale y participantes del Torneo.

Participantes del Torneo con Dr. García Rinaldi, Dr. Navas de Hima, Mr. Teale, Lcdo. Miranda Daleccio y Dra. Maura Tapia.

eventos

Se celebró el 2º Congreso Internacional de Acupuntura Médica de Puerto Rico en el Embassy Suites Dorado delMar.

Dr. Jean Aubry, Dr. Wilfredo Ortiz Clas, Dr. Steven Aung y Dr. Silvio Siqueira.

Dra. Ferrer, presidenta electa de AAMPR, reconoce a los miembros fundadores de la Asociación. Dra. Belén Ferrer, Dr. Carlos Robles, Dr. Wilfredo Ortiz Clas, Dr. Marcos Valls, Dr. Carlos Náter y Dr. Milton Collazo

La junta directiva celebra el 25º Aniversario de AAMPR: Dr. Marcos Valls, Dr. Wilfredo Ortiz Clas, Dra. Belén Ferrer, Dra. Ginnette Sánchez, Dr. R. Iván Iriarte, Dr. Jaime Díaz y Dr. Marcelino Cintrón.

El Presidente de AAMPR, el Dr. Wilfredo Ortiz Clas reconociendo la labor realizada por la junta directiva: Dra. Belén Ferrer, Dra. Ginnette Sánchez, Dr. Marcelino Cintrón, Dr. Jaime Díaz, Dr. R. Iván Iriarte, Dr. Marcos Valls.

SIMPONI® is administered by 50 mg subcutaneous injection once a month[1]

- SIMPONI® is intended for use under the guidance and supervision of a physician. Patients may self-inject with SIMPONI® after physician approval and proper training

For adults with moderately to severely active rheumatoid arthritis, in combination with methotrexate

WHY MAKE STARTING A BIOLOGIC A BIGGER STEP THAN IT HAS TO BE?

SIMPONI® CAN HELP EASE THE TRANSITION WITH A COMPREHENSIVE RANGE OF SUPPORT SERVICES

SimponiOne® support services include cost support, nurse support, and the Safe Returns™ program.

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A BIO-LOGICAL START | Simponi® golimumab

Important Safety Information for SIMPONI® (golimumab)

SERIOUS INFECTIONS

Patients treated with SIMPONI® (golimumab) are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue SIMPONI® if a patient develops a serious infection.

Reported infections with TNF blockers, of which SIMPONI® is a member, include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before SIMPONI® use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI® use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with SIMPONI® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Do not start SIMPONI® in patients with clinically important active infections, including localized infections. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

Risk of infection may be higher in patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. Other serious infections observed in patients treated with SIMPONI® included sepsis, pneumonia, cellulitis, abscess and hepatitis B infection.

(continued on next page)

Important Safety Information for SIMPONI® (golimumab) (continued)

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers of which SIMPONI® is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies usually associated with immunosuppression and malignancies not usually observed in children or adolescents. Malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

In the controlled portions of clinical trials of all TNF-blocking agents including SIMPONI®, more cases of lymphoma have been observed among patients receiving TNF-blocking treatment compared with control patients. In clinical trials, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI® group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In clinical trials, the incidence of malignancies other than lymphoma was not increased with exposure to SIMPONI® and was similar to what would be expected in the general population. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. The risks and benefits of TNF-blocker therapy should be considered prior to initiating therapy in patients with a known malignancy or who develop a malignancy.

HEPATITIS B REACTIVATION

The use of TNF-blocking agents including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consult a physician with expertise in the treatment of hepatitis B before initiating TNF-blocker therapy. Exercise caution when prescribing SIMPONI® for patients identified as carriers of HBV and closely monitor for active HBV infection during and following termination of therapy with SIMPONI®. Discontinue SIMPONI® in patients who develop HBV reactivation, and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of SIMPONI®, and monitor patients closely.

HEART FAILURE

Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported. Exercise caution and monitor patients with heart failure. Discontinue SIMPONI® if new or worsening symptoms of heart failure appear.

DEMYELINATING DISORDERS

TNF-blocking agents, of which SIMPONI® is a member, have been associated with cases of new-onset or exacerbation of demyelinating disorders, including multiple sclerosis (MS) and Guillain-Barré syndrome. In SIMPONI® clinical trials, cases of MS and peripheral demyelinating polyneuropathy were reported. Exercise caution in considering the use of SIMPONI® in patients with these disorders. Consider discontinuation if these disorders develop.

HEMATOLOGIC CYTOPENIAS

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving SIMPONI® in clinical trials. Additionally, aplastic anemia has been reported in patients receiving TNF-blocking agents, of which SIMPONI® is a member. Exercise caution when using SIMPONI® in patients who have or had significant cytopenias.

USE WITH OTHER DRUGS

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections, therefore the use of SIMPONI® in combination with these products is not recommended. Care should be taken when switching from one biologic to another since overlapping biological activity may further increase the risk of infection. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker.

VACCINATIONS

People receiving SIMPONI® can receive vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to SIMPONI® *in utero* is not recommended for 6 months following the mother's last SIMPONI® injection during pregnancy due to an increased risk of infection.

HYPERSENSITIVITY REACTIONS

Serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported with SIMPONI®, some occurring after the first dose. If an anaphylactic or other serious allergic reaction occurs, discontinue SIMPONI® immediately and institute appropriate therapy.

ADVERSE REACTIONS

The most serious adverse reactions were serious infections and malignancies.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI® as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI® compared with 2% of patients in the control group.

25SM11034

Please see Brief Summary of Prescribing Information on following pages.

Reference: 1. SIMPONI® (golimumab) Prescribing Information. Janssen Biotech, Inc.

www.simponi.com

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

SIMPONI® (golimumab) Injection, solution for subcutaneous use
See package insert for full Prescribing Information.

WARNINGS: SERIOUS INFECTIONS and MALIGNANCY
SERIOUS INFECTIONS

Patients treated with SIMPONI® are at increased risk for developing serious infections that may lead to hospitalization or death *(see Warnings and Precautions)*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. SIMPONI® should be discontinued if a patient develops a serious infection.

Reported infections with TNF-blockers, of which SIMPONI is a member, include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before SIMPONI® use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI® use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with SIMPONI® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *(see Warnings and Precautions)*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI® is a member *(see Warnings and Precautions)*.

INDICATIONS AND USAGE: Rheumatoid Arthritis SIMPONI®, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis. **Psoriatic Arthritis** SIMPONI®, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis. **Ankylosing Spondylitis** SIMPONI® is indicated for the treatment of adult patients with active ankylosing spondylitis. **CONTRAINDICATIONS:** None. **WARNINGS AND PRECAUTIONS (see Boxed WARNINGS): Serious Infections** Patients treated with SIMPONI are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended [*see Warnings and Precautions and Drug Interactions*]. Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating SIMPONI in patients: with chronic or recurrent infection; who have been exposed to tuberculosis; with a history of an opportunistic infection; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or with underlying conditions that may predispose them to infection. ***Monitoring*** Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI®. SIMPONI® should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI® should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. ***Serious Infection in Clinical Trials*** In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI®-treated patients and 1.3% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.7 (95% CI: 3.8, 8.2) for the SIMPONI® group and 4.2 (95% CI: 1.8, 8.2) for the placebo group. Serious infections observed in SIMPONI®-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection. ***Tuberculosis*** Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating SIMPONI® and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of

tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating SIMPONI®, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of SIMPONI® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI® treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI®-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. ***Invasive Fungal Infections*** For SIMPONI®-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. ***Hepatitis B Virus Reactivation*** The use of TNF-blockers including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI®, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely. ***Malignancies*** Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI® is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. The risks and benefits of TNF-blocker treatment including SIMPONI® should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy. In the controlled portions of clinical trials of TNF-blockers including SIMPONI®, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI® group compared with an incidence of 0 (95% CI: 0., 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI®-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of l eukemia. During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per

SIMPONI® (golimumab)

100 patient-years of follow-up was not elevated in the combined SIMPONI® group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI®-treated patients was similar to that expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory 1-year clinical trial evaluating the use of 50, 100 and 200 mg of SIMPONI® in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI® groups compared to none in the control group. Three of the 6 patients were in the 200 mg SIMPONI® group. **Congestive Heart Failure** Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers, including SIMPONI®. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI® has not been studied in patients with a history of CHF and SIMPONI® should be used with caution in patients with CHF. If a decision is made to administer SIMPONI® to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI® should be discontinued if new or worsening symptoms of CHF appear. **Demyelinating Disorders** Use of TNF-blockers, of which SIMPONI® is a member, has been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. In clinical trials, cases of central demyelination, MS, and peripheral demyelinating polyneuropathy have been reported in patients treated with SIMPONI® *(see Adverse Reactions).* Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI®, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI® should be considered if these disorders develop. **Use with Abatacept** In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI® and abatacept is not recommended *(see Drug Interactions).* **Use with Anakinra** Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI®, is not recommended *(see Drug Interactions).* **Switching Between Biological Disease Modifying Antirheumatic Drugs (DMARDs)** Care should be taken when switching from one biologic to another since overlapping biological activity may further increase the risk of infection. **Hematologic Cytopenias** There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical studies, cases of pancytopenia, leukopenia, neutropenia, and thrombocytopenia have also occurred in SIMPONI®-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI®, in patients who have or have had significant cytopenias. **Vaccinations** Patients treated with SIMPONI® may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI®. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI®-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI®-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving methotrexate (MTX) compared with patients not receiving MTX. The data suggest that SIMPONI® does not suppress the humoral immune response to the pneumococcal vaccine. **Hypersensitivity Reactions** In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following SIMPONI administration. Some of these reactions occurred after the first administration of SIMPONI. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy instituted. **ADVERSE REACTIONS** 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. **Clinical Studies Experience** The safety data described below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA and AS) *(see Clinical Studies).* These 5 trials included 639 control-treated patients and 1659 SIMPONI®-treated patients including 1089 with RA, 292 with PsA, and 278 with AS. The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI®-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI® in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%). The most serious adverse reactions were: Serious Infections; Malignancies. Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI®-treated patients as compared with 6% and 5% of control-treated patients, respectively. ***Infections*** In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI®-treated patients compared to 25% of control-treated patients. ***Liver Enzyme Elevations*** There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI® in patients with RA, PsA, and AS through Week 16, ALT elevations ≥5 x ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI®-treated patients, and ALT elevations ≥3 x ULN occurred in 2% of control-treated patients and 2% of SIMPONI®-treated patients. Since many of the patients in the Phase 3 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between SIMPONI® and liver enzyme elevation is not clear. ***Autoimmune Disorders and Autoantibodies*** The use of TNF-blockers, including SIMPONI®, has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI® treatment and the development of newly positive anti-dsDNA antibodies. ***Injection Site Reactions*** In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI® treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with SIMPONI® developed anaphylactic reactions. ***Immunogenicity*** Antibodies to SIMPONI® were detected in 57 (4%) of SIMPONI®-treated patients across the Phase 3 RA, PsA, and AS trials through Week 24. Similar rates were observed in each of the 3 indications. Patients who received SIMPONI® with concomitant MTX had a lower proportion of antibodies to SIMPONI® than patients who received SIMPONI® without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI® in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay. The small number of patients positive for antibodies to SIMPONI® limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures. The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI® in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI® with the incidence of antibodies to other products may be misleading. ***Other Adverse Reactions*** The adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI® ± DMARD group and with a higher incidence than in the placebo ± DMARD group during the controlled period of the 5 pooled Phase 3 trials through Week 16 in patients with RA, PsA, and AS are summarized below. Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids (≤10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials). The numbers (percentages) of adverse drug reactions for SIMPONI® ± DMARDs-treated patients (n=1659) and Placebo ± DMARDs-treated patients (n=639), respectively, were: **Infections and Infestations:** Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis) 16%, 13%; Viral infections (such as influenza and herpes) 5%, 3%; Bronchitis 2%, 1%; Superficial fungal infections 2%, 1%; Sinusitis 2%, 1%; **General disorders and administration site conditions:** Injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paresthesia) 6%, 2%; **Investigations:** Alanine aminotransferase increased 4%, 3%; Aspartate aminotransferase increased 3%, 2%; **Vascular disorders:** Hypertension 3%, 2%; **Nervous system disorders:** Dizziness 2%, 1%; Paresthesia 2%, 1%; **Gastrointestinal Disorders:** Constipation 1%, <1%. ***Less common clinical trial adverse drug reactions*** Adverse drug reactions that occurred <1% in SIMPONI®-treated patients during the SIMPONI® clinical trials that do not appear in the Warnings and Precautions section included the following events listed by system organ class: *Infections and infestations:* Septic shock, atypical mycobacterial infection, pyelonephritis, arthritis bacterial, bursitis infective *Neoplasms benign, malignant and unspecified:* leukemia *Skin and subcutaneous tissue disorders:* psoriasis (new onset or worsening, palmar/plantar and pustular), vasculitis (cutaneous) *Vascular disorders:* Vasculitis (systemic) **Post-marketing Experience** The following adverse reactions have been identified during post-approval use of SIMPONI. 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 SIMPONI exposure. *Immune System Disorders:* Serious systemic hypersensitivity reactions (including anaphylactic reaction) *(see Warnings and Precautions).* **DRUG INTERACTIONS: Methotrexate**. For the treatment of RA, SIMPONI® should be used with MTX. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI® in the treatment of PsA or AS, SIMPONI® can be used with or without MTX in the treatment of PsA and AS. **Biologic Products for RA, PsA, and/or AS** An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI® with abatacept or anakinra is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information to provide recommendations regarding the concomitant use of SIMPONI® and other biologic products approved to treat RA, PsA, or AS. **Live Vaccines** Live vaccines should not be given concurrently with SIMPONI®. Infants born to women treated with SIMPONI during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI *in utero* is not

recommended for 6 months following the mother's last SIMPONI injection during pregnancy *(see Use in Specific Populations)*. **Cytochrome P450 Substrates** The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI® in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **USE IN SPECIFIC POPULATIONS: Pregnancy** Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI® in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI® should be used during pregnancy only if clearly needed. An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus. A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since SIMPONI is an IgG antibody, infants born to women treated with SIMPONI during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI *in utero* is not recommended for 6 months following the mother's last SIMPONI injection during pregnancy (see Warnings and Precautions). **Nursing Mothers** It is not known whether SIMPONI® is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations. **Pediatric Use** Safety and effectiveness of SIMPONI® in patients less than 18 years of age have not been established. **Geriatric Use** In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI®-treated patients ages 65 or older (N=155) compared with younger SIMPONI®-treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI®. **OVERDOSAGE** In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI® without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMPONI®. There were no SIMPONI® overdoses in the clinical studies. **PATIENT COUNSELING INFORMATION Patient Counseling** Patients should be advised of the potential benefits and risks of SIMPONI®. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI® therapy and to read it each time the prescription is renewed. ***Infections*** Inform patients that SIMPONI® may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation. ***Malignancies*** Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI®. ***Allergic Reactions*** Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect® autoinjector contains dry natural rubber (a derivative of latex). ***Other Medical Conditions*** Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

REFERENCES: 1. SEER [database online]. U.S. Population Data—1969-2004. Bethesda, MD; National Cancer Institute. Release date: January 3, 2007. Available at: http://www.seer.cancer.gov/popdata.

eventos

La Sociedad Radiológica de Puerto Rico participó del Simposio Educativo *MRI Safe Cardiac Implantable Devices: New Pacemaker Systems.*

Dr Dennis Pérez, Presidente Sociedad Radiológica de Puerto Rico junto a radiólogo.

Dr Carlos Méndez, pasado presidente de SRPR, junto a Pedro Monserrate y Gabriel Lazarus de Medtronic.

Dr. Nelson Matos junto a un grupo de radiólogos.

Dr Fernando Zualdondo junto a Dr Pedro Díaz.

Gabriel Lazarus, Dr. Daniel Arzola, Dr. Dennis Pérez, Dr. Pedro Díaz y Pedro Monserrate.