

## THE OFFICE

## To Discount or Not to Discount

As the “Great Recession” continues, there is much discussion on medical forums about how to increase cash flow, decrease administrative expenses, and deal with ever-increasing numbers of unemployed and uninsured patients.

Extending discounts to patients who pay at the time of service or pay out of pocket is one effective way of addressing all three of these issues. Exercise caution, because discounts can run afoul of federal and state laws. These include state antikickback statutes, the anti-inducement provision of the Health Insurance Portability and Accountability Act, the Medicare exclusion provision, and state insurance antidiscrimination provisions.

From a legal standpoint, any discount is a kickback of sorts—you are returning part of your fee to the patient—and many laws designed to thwart real kickbacks can apply in such situations.

Take the straightforward case of time-of-service discounts for cosmetic procedures and other services not covered by insurance. You would think such transactions are just between you and your patients, but you need to avoid the appearance of using these discounts as marketing incentives (inducements to attract patients).

Also, a shrewd third-party payer could try to pull a fast one on you. Many provider agreements contain what are often called “most favored nation” clauses, which require you to automatically give that provider the lowest price you offer to anyone else, regardless of what they would otherwise pay. In other words, they could demand that you give them the same discount.

My response in that situation would be that a time-of-service discount is exactly that: It is offered only when payment is made immediately. Third parties never pay at the time of service and are not entitled to it.

Things get complicated if you also want to extend discounts for covered services. Be sure that the discounted fee you charge the patient is also reflected on the claim submitted to the insurer. Billing the insurer more than you charged the patient invites a charge of fraud. Avoid discounting so regularly that the discounted fee becomes your new usual and customary rate.

Waiving coinsurance and deductibles can be trouble, too, particularly with Medicare and Medicaid. You might intend it as a good deed, but the Centers for Medicare and Medicaid Services may see it as an inducement or kickback, especially if you do it routinely. The CMS has no problem with an occasional waiver, especially “after determining in good faith that the individual is in financial need” (according to the Office of Inspector General), but thorough documentation is in order in such cases.

Waiving copays for privately insured patients can be equally problematic. Nearly all insurers impose a contractual duty on providers to make a reasonable effort to collect applicable copays and/or deductibles. They view the routine waiver of patient payments as a breach of contract, and there has been litigation against providers who flout this requirement. As with the CMS, accommodating patients with individually documented financial limitations is acceptable, but when

there is a pattern of routine waivers and no documentation, you will have difficulty defending it.

In addition to antikickback laws, some states have antidiscrimination laws that forbid either lower charges to any subset of insurance payers or any noninsurance payer than to any insurance payer. Some states make specific exceptions for legitimate discounts—as in cases of financial hardship, or when you are just trying to pass along your lower billing and collections costs—but others do not. Check your state’s laws and run everything past your attorney.

As for how much of a discount you can give, I cannot suggest an amount, but if it is completely out of proportion to the administrative costs of submitting paperwork and the hassles associated with waiting for your money, you could, once again, be accused of offering a discount that is a de facto increase to insurance carriers, and that could result in charges of fraud.

In cases of legitimate financial hardship, the most effective and least problematic strategy may be to offer a sliding scale. Many large clinics and community agencies and all hospitals have a written policy for this, often based on federal poverty guidelines. Do a little homework: Contact local social service agencies and welfare clinics, learn the community standard in your area, and formulate a written policy with guidelines for determining a patient’s indigence. Once again, consistency of administration, objectivity in policies, and documentation of individual eligibility are essential. ■

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BY JOSEPH S. EASTERN, M.D.



BY S. Y. TAN, M.D., J.D.

**Question:** A witness may be qualified as an expert based on:

- A. Knowledge or education, but not experience alone.
- B. Skill, but not training alone.
- C. Knowledge, skill, experience, training, or education.
- D. Whether a witness qualifies as an expert is determined by the judge and jury.
- E. A nurse may equally offer expert testimony in a medical malpractice case.

**Answer:** C. In a malpractice trial, the plaintiff has to show via expert medical testimony that the defendant doctor has breached the standard of care. Court rules of evidence dictate that the expert must possess “the knowledge, skill, experience, training, or education” necessary for establishing that standard. These qualification criteria are not overly restrictive, and evidence is admissible so long as it is relevant and reliable. However, lay testimony usually is insufficient to define the standard of care, unless it falls under the “common knowledge” exception (*res ipsa loquitur*). The judge, not the jury, makes these determinations.

The expert’s proffered standard must take into account the circumstances of the case and the qualifications of the de-

fendant-doctor. For example, in litigated cases involving diabetic complications, the courts have disallowed using an internist’s standard for a general practitioner, or an endocrinologist’s standard for an internist.

A qualified doctor rather than a nurse or an allied health professional usually will serve as the expert, although doctors have been allowed to testify outside their specialty, for example, an internist with subspecialty training in infectious diseases was qualified as a plaintiff expert in a stroke case. However, Arizona has a recent statute, ARS §12-2604 (A), which requires a medical expert to be a specialist who is actively practicing or teaching in that area of medicine. The state Court of Appeals held that this violated the separation of powers doctrine (conflicting with Arizona Rule of Evidence 702), but the Supreme Court of Arizona subsequently reversed and reinstated the law, which makes it more difficult to qualify as a medical expert in an Arizona courtroom.

Most malpractice lawyers have a listing of available experts, derived from past experiences, contacts, or word-of-mouth recommendations. Some plaintiff organizations have access to willing medical

experts, and ads in the media and legal journals identify doctors wishing to act as experts. Attorneys generally seek experts who communicate well. How the jury perceives the expert is crucial. Qualifications might be what are initially assessed, but communication skills, credibility, and demeanor can matter more.

Can a physician be forced to testify as an expert?

The Wisconsin Supreme Court has held that whereas a treating physician might be required to provide expert testimony regarding the care of his/her own patient, he/she cannot be forced to give expert testimony regarding the standard of care of another physician’s patient unless the judge has determined that there are compelling circumstances. Additionally, there must be reasonable compensation and no requirement to do additional preparation in order to provide expert testimony.

The reimbursement rate for an expert varies widely, usually in the range of \$200-\$500/hour for review work. These figures are of course higher for depositions and live testimony in open court. A Colorado court has held that a deposition fee of \$2,000/hour was grossly excessive, and a New Jersey federal magistrate judge characterized a neurosurgeon’s charge of \$7,000 for two hours of deposition as “near to being extortionate.” In

Europe, expert witnesses are appointed by the courts, and are compensated according to a standard fee schedule.

*Continued on page 75*

## INDEX OF ADVERTISERS

<b>Amgen Inc.</b> Prolia	22-24
<b>Bayer HealthCare LLC</b> Aspirin	31
<b>Boehringer Ingelheim Pharmaceuticals, Inc.</b> Pradaxa	20a-20b
<b>Endo Pharmaceuticals</b> Lidoderm	26-28
<b>Forest Laboratories, Inc.</b> Bystolic Namenda Lexapro Savella	17-20 28a-28b 33-37 65-68
<b>Kowa Pharmaceuticals America, Inc. and Lilly USA, LLC</b> Livalo	48a-48b
<b>Lilly USA, LLC</b> EVISTA	42-45
<b>Ortho-McNeil-Janssen Pharmaceuticals, Inc.</b> Nucynta	38a-38d, 39
<b>Pfizer Inc.</b> Corporate Lyrica Pristiq	3 13-15 75-76
<b>Purdue Pharma L.P.</b> OxyContin	50-53
<b>sanofi-aventis U.S. LLC</b> Lantus SoloSTAR	6-10, 57-62
<b>Sanofi Pasteur Inc.</b> Fluzone	30-32

## LAW &amp; MEDICINE

## Expert Medical Testimony

Continued from page 70

In 1995, the American College of Cardiology put forth seven criteria for expert witnesses. Of particular import is criterion seven, which states: "Expert witness testimony should be fair, thorough, and objective. It should not exclude any relevant information that has a bearing on the case." Various other medical associations and malpractice insurers have published similar guidelines for those asked to testify as experts.

The American Medical Association considers providing expert medical testi-

mony to be analogous to the practice of medicine. It has this to say about the ethical responsibilities of medical experts: "... they should have recent and substantive experience or knowledge in the area in which they testify, and be committed to evaluating cases objectively and to providing an independent opinion. ... Physician testimony must not be influenced by financial compensation; for example, it is unethical for a physician to accept compensation that is contingent upon the outcome of litigation."

Finally, in *Austin vs. American Association of Neurological Surgeons*, the seventh U.S.

Circuit Court of Appeals reaffirmed an association's right to discipline a physician for improper medical testimony. The case involved a Detroit neurosurgeon who testified for the plaintiff against a fellow association member who allegedly caused permanent recurrent laryngeal nerve damage following an anterior cervical fusion. The court wrote, "There is a great deal of skepticism about expert evidence. It is well known that expert witnesses are often paid very handsome fees, and common sense suggests that a financial stake can influence an expert's testimony, especially when the testimony

is technical and esoteric and hence difficult to refute in terms intelligible to judges and jurors. More policing of expert witnessing is required, not less." ■

DR. TAN is professor of medicine and former adjunct professor of law at the University of Hawaii. This article is meant to be educational and does not constitute medical, ethical, or legal advice. It is adapted from the author's book, "Medical Malpractice: Understanding the Law, Managing the Risk" (2006). For additional information, contact the author at [siang@hawaii.edu](mailto:siang@hawaii.edu).

## **Pristiq**<sup>®</sup> desvenlafaxine Extended-Release Tablets

**BRIEF SUMMARY.** See package insert for full Prescribing Information. For further product information and current package insert, please visit [www.wyeth.com](http://www.wyeth.com) or call our medical communications department toll-free at 1-800-934-5556.

### **WARNING: Suicidality and Antidepressant Drugs**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients [see *Warnings and Precautions (5.1)*]. Use in Specific Populations (8.4), and Patient Counseling Information (17.1 in the full prescribing information).

**INDICATIONS AND USAGE:** Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).

**CONTRAINDICATIONS:** Hypersensitivity—Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. **Monamine Oxidase Inhibitors—**Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [see *Dosage and Administration (2.5)* in the full prescribing information].

**WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk—**Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Warnings and Precautions (5.9)* and *Dosage and Administration (2.3)* in the full prescribing information for a description of the risks of discontinuation of Pristiq]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening patients for bipolar disorder—**A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Pristiq is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions—**The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Pristiq treatment, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Serotonin syndrome in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Pristiq with MAOIs intended to treat depression is contraindicated [see *Contraindications (4.2)*]. If concomitant treatment of Pristiq with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Pristiq with serotonin precursors (such as tryptophan) is not recommended. Treatment with Pristiq and any concomitant serotonergic or antipsychotic agents, including antipsychotics, should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated. **Elevated Blood Pressure—**Patients receiving Pristiq should have regular monitoring of blood pressure since dose-dependent increases were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq. **Sustained hypertension—**Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [see *Adverse Reactions (6.1)*]. Treatment with Pristiq in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP)  $\geq 90$  mm Hg and  $\geq 10$  mm Hg above baseline for

3 consecutive on-therapy visits. In clinical studies, regarding the proportion of patients with sustained hypertension, the following rates were observed: placebo (0.5%), Pristiq 50 mg (1.3%), Pristiq 100 mg (0.7%), Pristiq 200 mg (1.1%), and Pristiq 400 mg (2.3%). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding—**SNRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SNRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma—**Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania—**During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease—**Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [see *Adverse Reactions (6.1)*]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation—**Dose-related elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [see *Adverse Reactions (6.1)*]. **Discontinuation of Treatment with Pristiq—**Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in major depressive disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [see *Dosage and Administration (2.4)* and *Adverse Reactions (6.1)* in the full prescribing information]. **Renal Impairment—**In patients with moderate or severe renal impairment or end-stage renal disease (ESRD), the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [see *Clinical Pharmacology (12.6)* in the full prescribing information]. Dose adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [see *Dosage and Administration (2.2)* in the full prescribing information]. **Seizure—**Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hypонатremia—**Hypонатremia can occur as a result of treatment with SNRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SNRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [see *Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.6)* in the full prescribing information]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine—**Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia—**Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

**ADVERSE REACTIONS: Clinical Studies Experience:** The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence  $\geq 5\%$  and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. **Adverse reactions reported as reasons for discontinuation of treatment:** The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). **Common adverse reactions in placebo-controlled MDD studies—**Table 3 in the full PI shows the incidence of common adverse reactions that occurred in  $\geq 2\%$  of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. **Cardiac disorders:** Palpitations, Tachycardia, Blood pressure increased; **Gastrointestinal disorders:** Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; **General disorders and administration site conditions:** Fatigue, Chills, Feeling jittery, Asthenia, Metabolism and nutrition disorders; **Decreased appetite, weight decreased; Nervous system disorders:** Dizziness, Somnolence, Headache, Tremor, Paresthesia, Disturbance in attention; **Psychiatric disorders:** Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; **Renal and urinary disorders:** Urinary hesitation; **Respiratory, thoracic, and mediastinal disorders:** Yawning; **Skin and subcutaneous tissue disorders:** Hyperhidrosis, Rash; **Special Senses:** Vision blurred; **Mydriasis, Tinnitus, Dysgeusia; Vascular disorders:** Hot flush. **Sexual function adverse reactions—**Table 4 shows the incidence of sexual function adverse reactions that occurred in  $\geq 2\%$  of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). **Men Only:** Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; **Women Only:** Anorgasmia; **Other adverse reactions observed in premarketing clinical studies:** Other infrequent adverse reactions occurring at an incidence of  $\geq 2\%$  in MDD patients treated with Pristiq were: **Immune system disorders—**Hypersensitivity. **Investigations—**Weight increased, liver function test abnormal, blood prolactin increased. **Nervous system disorders—**Convulsion, syncope, extrapyramidal disorder. **Musculoskeletal and connective tissue disorders—**Musculoskeletal stiffness. **Psychiatric disorders—**Depersonalization, hypomania. **Respiratory, thoracic and mediastinal disorders—**Epistaxis. **Vascular disorders—**Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [see *Warnings and Precautions (5.7)*]. **Discontinuation events—**Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of  $\geq 5\%$  include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.9)* in the full prescribing information]. **Laboratory, ECG and vital sign changes observed in MDD clinical studies—**The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. **Lipids—**Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [see *Warnings and Precautions (5.8)*]. **Proteinuria—**Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. **ECG changes—**Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. **Vital sign changes—**Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. **Orthostatic hypotension—**In the short-term, placebo-

controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease  $\geq 30$  mm Hg from supine to standing position) occurred more frequently in patients  $\geq 65$  years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients  $< 65$  years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **Adverse Reactions Identified During Post-Approval Use—**The following adverse reaction has been identified during post-approval use of Pristiq. Because post-approval 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: *Skin and subcutaneous tissue disorders—*Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents—**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [see *Warnings and Precautions (5.13)*]. **Monamine Oxidase Inhibitors (MAOIs)—**Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [see *Contraindications (4.2)*]. **Serotonergic Drugs—**Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [see *Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)—**Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol—**A clinical study has shown that desvenlafaxine of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. 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