

LAW & MEDICINE

Informed Consent: Disclosure of Risks

Question: Regarding physician liability arising from medication injuries, which of the following is most accurate?

- A. Doctor is liable if drug was prescribed for unapproved off-label use.
 B. Doctor is liable for failing to warn of significant risks.
 C. Doctor is liable for failing to warn of all complications.
 D. Patient did not ask about side effects and therefore was contributorily negligent.
 E. Liability will attach to manufacturer for a "defective product."

Answer: B. The informed consent doctrine requires that physicians discuss all material risks, including rare but serious risks. Choice A is incorrect because prescribing a drug for an "off-label" use may be an acceptable practice. However, it is prudent for the doctor to document in the records the reason for using the drug. Choice C is overly broad. A warning is required for all material risks (i.e., those that significantly affect the patient's decision to accept or reject the recommended treatment), but a warning is not necessary for all risks.

Patients are assumed to have little or no

knowledge of medications, and they have no legal duty to inquire about side effects. The doctor, on the other hand, has an affirmative duty to warn of these side effects. In a malpractice case alleging lack of informed consent due to failure to warn, the defense cannot plead contributory negligence, so choice D is incorrect. Finally, E is also incorrect. The "learned intermediary" doctrine stipulates that the doctor, not the pharmaceutical company, is liable for medication-related injuries as he/she is a learned professional who directly communicates with the patient and who does the actual prescribing. This puts the doctor in the hot seat for an adverse drug reaction, unless the drug company has been negligent in identifying and/or communicating the risk.



BY S. Y. TAN,
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Disclosure of Material Risks

In order for patients to meaningfully give their consent to treatment, they should have sufficient information regarding the doctor's treatment plans. The consent must also be given voluntarily. The notion of patient autonomy is so entrenched that the law imposes upon

the practitioner the duty to disclose three fundamental aspects of treatment, easily remembered by the mnemonic PAR (P = procedure [or medication/device], A = alternatives, R = risks).

What constitutes a material risk is at the heart of the controversy surrounding the informed consent doctrine. Generally, the patient should be informed of all serious risks, even if unusual or rare. However, in one court case, a 1% risk of hearing loss required disclosure (*Scott v. Wilson*, 396 S.W.2d 532 [Tex. Civ. App. 1965]), whereas in another, the court appeared to say that a 1.5% chance of visual loss did not (*Yeats v. Harms*, 393 P.2d 982 [Kan. 1964]). The California Supreme Court has stated that "material information is that which the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended medical procedure," that "a (material) fact must also be one which is not commonly appreciated," and that the scope of disclosure may be expanded in patients with "unique concerns or lack of familiarity with medical procedures" (*Truman v. Thomas*, 27 Cal.3d 285 [1980]). There is, however, no legal requirement to deliver a "mini-course in medical science" (*Cobbs v. Grant*, 8 Cal.3d 229 [1972]).

Warren v. Schecter is one of the most dramatic cases to confront the material risk issue. The plaintiff won a \$9.6 million judgment against the doctor for his failure to disclose risk of osteoporosis (*Warren v. Schecter*, 67 Cal.Rptr.2d 573 [Cal. 1997]). Dr. Schecter had performed gastric surgery on Janet Warren for peptic ulcer disease, and had warned the patient of the risks of bowel obstruction, dumping syndrome, and anesthetic death. He did not believe osteoporosis, osteomalacia, and bone pain were risks of surgery, and so did not discuss those risks with her. The plaintiff testified at trial that had Dr. Schecter warned of the risk of metabolic bone disease, she would not have consented to surgery. A second operation was undertaken because she developed postoperative dumping syndrome and alkaline reflux gastritis, and the surgeon again failed to advise her of the risk of metabolic bone disease. She again asserted that she would not have consented to the second surgery had she been duly advised.

The plaintiff subsequently developed severe osteoporotic fractures, and filed a malpractice lawsuit alleging that Dr. Schecter was liable under an informed consent theory for performing surgery without advising her of the risk of bone

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Inaccurate Methods Often Used for Physician Cost Profiling

BY MARY ANN MOON

Current methods for profiling individual physicians as to whether they provide low-cost or high-cost care are often inaccurate and produce misleading results, according to a report.

Health plans use cost profiling to limit how many physicians get in-network contracts and to allot bonuses to the physicians whose "resource use" is lower than average. In each case, there must be a method for determining physicians' costs, yet the accuracy of these methods has never been proved, according to John L. Adams, Ph.D., of RAND Corp., and his associates.

"To our knowledge, the reliability of physician cost profiling has not been previously addressed," they noted.

Dr. Adams and his colleagues assessed the reliability of current methods of cost profiling using claims data from four Massachusetts insurance companies concerning 1.1 million adult patients treated during 2004-2005. A total of 12,789 physicians were included in the study. They were predominantly men who were board certified, had been trained in the United States, and had been in

practice for more than 10 years.

The physicians worked in 28 specialties, including cardiology, endocrinology, gastroenterology, and obstetrics and gynecology. Family physicians, general physicians, and internal medicine physicians comprised approximately one-third of the sample.

The investigators estimated the reliability of cost profiles on a scale of 0-1, with 0 representing completely unreliable profiles and 1 representing completely reliable profiles. They then estimated the proportion of physicians in each specialty whose cost performance would be calculated inaccurately.

Overall, only 41% of physicians across all specialties had cost profile scores of 0.70 or greater, a commonly used threshold of acceptable accuracy. Only 47% of internists, 30% of cardiologists, 41% of family or general physicians, 57% of ob.gyns., 59% of gastroenterologists, and 22% of endocrinologists received scores of 0.70.

Overall, only 9% of physicians in the study had scores of 0.90 or greater, indicating optimal accuracy.

The proportion of physicians who were classified as "lower

cost" but who were not in fact lower cost ranged from 29% to 67%, depending on the specialty. Fully 50% of internists, 40% of cardiologists, 39% of family or general physicians, 36% of ob.gyns., 32% of gastroenterologists, and 50% of endocrinologists were misclassified as "lower-cost" providers when they were not.

Also, 22% of internists were misclassified as "higher cost" when they were not in fact higher cost. This same misclassifica-

tion occurred for 14% of cardiologists, 16% of family or general physicians, 10% of ob.gyns., 11% of gastroenterologists, and 19% of endocrinologists.

These findings indicate that standard methods of cost profiling are highly unreliable, and that many individuals and groups are basing important decisions on inaccuracies. "Consumers, physicians, and purchasers are all at risk of being misled by the results produced by these tools," the investigators

concluded (*N. Engl. J. Med.* 2010;362:1014-21).

The study findings also suggest that using cost profiles that are based on these unreliable methods will not reduce health care spending, they added. ■

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Abandon Flawed Evaluation Programs

The RAND Corp. study verifies the American Medical Association's long-standing contention that there are serious flaws in health insurer programs that attempt to rate physicians based on cost of care.

The RAND study shows that physician ratings conducted by insurers can be wrong up to two-thirds of the time for some groups of physicians. Inaccurate information can erode patient confidence and trust in caring physicians, and disrupt patients' relationships with physicians who have cared for them for years.

Patients should always be able to trust that the information they receive on physicians is

valid and reliable, especially when the data are used by insurers to influence or restrict patients' choice of physicians.

Given the potential for irreparable damage to the patient-physician relationship, the AMA calls on the health insurance industry to abandon flawed physician evaluation and ranking programs, and join with the AMA to create constructive programs that produce meaningful data for increasing the quality and efficiency of health care.



J. JAMES ROHACK, M.D., is president of the American Medical Association. He reported having no conflicts of interest.

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complications. The jury found that Dr. Schecter did not disclose to Ms. Warren all relevant information that would have enabled her to make an informed decision regarding surgery and that a reasonably prudent person in her position would not have consented to surgery if adequately informed of all the significant perils.

Other Aspects of Disclosure

Besides risks associated with surgery or a medication, courts have also looked at other aspects of disclosure in the doctor-

patient relationship. Some litigated examples include disclosing the limited experience of a neurosurgeon (*Johnson v. Kokemoor*, 545 N.W.2d 495 [Wis. 1996]), financial incentives amounting to a breach of fiduciary responsibility (*Moore v. The Regents of the University of California*, 793 P.2d 479 [Cal. 1990]), and a surgeon's disclosure of his positive HIV status (*Estate of Behringer v. The Medical Center at Princeton*, 192 A.2d 1251 [N.J. Super. 1991]) or alcoholism (*Hidding v. Williams*, 578 So.2d 1192 [La.App. 1991]). However, in *Arato v. Avedon*, the California Supreme Court held that the law did not require physi-

cians to inform their terminally ill patients of their prognosis and life expectancy (*Arato v. Avedon*, 858 P.2d 598 [Cal. 1993]).

An example of statutory law regarding informed consent is found in Hawaii Revised Statutes §671-3. Amended by the 2003 legislature, the statute mandates disclosure of "recognized material risks of serious complications or mortality" but does not define the word "material." This amended language replaced the earlier version's "recognized, serious, possible risks, complications and anticipated benefits," arguably lightening the doctor's duty regarding risk disclosure. In reality,

the new language is unlikely to have a significant practical effect. An earlier 1976 version of the law merely required the disclosure of "probable risks and effects." ■

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Pristiq[®] 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 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. Monoamine 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 1,000 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 antiparkinsonian 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) ≥ 90 mm Hg and ≥ 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—SSRIs 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 SSRIs 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 Elevations—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)]. 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]. Dosage 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]. Seizures—Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. Hyponatremia—Hyponatremia can occur as a result of treatment with SSRIs 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 SSRIs 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 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 $< 2\%$ 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 ≥ 30 mm Hg from supine to standing position) occurred more frequently in patients ≥ 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)]. Monoamine 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 SSRIs 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 does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. Potential for Other Drugs to Affect Desvenlafaxine—Inhibitors of CYP3A4 (ketoconazole)—CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes—Based on *in vitro* data, drugs that inhibit CYP isozymes 1A2, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. Potential for Desvenlafaxine to Affect Other Drugs—Drugs Metabolized by CYP2D6 (desipramine)—*In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in higher concentrations of that drug. Drugs Metabolized by CYP3A4 (midazolam)—*In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19—*In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. P-glycoprotein Transporter—*In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. Electroconvulsive Therapy—There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. USE IN SPECIFIC POPULATIONS: Pregnancy—Pristiq should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects—Pregnancy Category C—There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects—Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see Warnings and Precautions (5.2)]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [see Dosage and Administration (2.2)]. Labor and Delivery—The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. Nursing Mothers—Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether to nurse or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. Pediatric Use—Safety and effectiveness in the pediatric population have not been established [see Box Warning and Warnings and Precautions (5.1)]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. Geriatric Use—Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥ 65 years of age compared to patients < 65 years of age treated with Pristiq [see Adverse Reactions (6)]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see Warnings and Precautions (5.12)]. Greater sensitivity of some older individuals cannot be ruled out. Renal Impairment—In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information]. Hepatic Impairment—The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see Clinical Pharmacology (12.6)].

OVERDOSAGE: Human Experience with Overdose. There is limited clinical experience with desvenlafaxine succinate overdose in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the Overdose section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, increase in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdose, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. 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. Management of Overdose—Treatment should consist of those general measures employed in the management of overdose with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR).

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