

## EHR REPORT

## Poor Usability Keeps EHR Adoption Rates Low

BY JONATHAN BERTMAN, M.D., AND NEIL SKOLNIK, M.D.

Despite the federal government's pledges of financial incentives and eventual penalties, adoption rates of electronic health record (EHR) systems remain stubbornly low. When a product or service is still underutilized, even after being subsidized by public funds, we have to ask ourselves why.

Many vendors advise physicians that extensive training is needed to learn how to document a note using their system and that they should be prepared to reduce their patient volume throughout the EHR adoption period. This lost patient volume is the direct result of data collection gone awry.

Instead of focusing data collection on key elements required for interaction—checking and billing, for example—most EHR systems require users to codify all data. This means physicians and their staff will spend time navigating through multiple windows, drop-down menus, and check box lists to record something as simple as “3 days of productive cough.” Multiply that effort by all the data collected during a brief encounter and you have a note that takes more time to document than the visit itself. The very fact that vendors require extensive training is proof that these EHRs are neither intuitively designed nor easy to use.

The concept of “usability” is defined as the ease with which people can use a particular product to accomplish defined goals. The lack of usability has been a major cause of dissatisfaction with EHR systems. It has been esti-

mated that one in every three EHR adoptions fail, with poor usability likely a major contributing factor.

Unfortunately, the true experience of an EHR's usability only occurs well after an EHR contract is signed, training has completed, and the light patient load has ended. That is when the seriousness of poor EHR usability becomes apparent.

To compensate, many physicians end up using templates, macros, and preset lists. This may help alleviate the slowdown caused by an EHR's poor design, and the resulting patient notes may be full of data, but they often lack any real substance. The real story in each patient encounter is frequently lost. This is a common complaint reported by physicians attempting to use notes generated by an EHR.

To add insult to injury, there is an ever-growing list of horror stories reported by physicians who have given up on their EHRs. Unfortunately, many EHR vendors do not allow dissatisfied users out of their long-term contracts. Or if a vendor does allow a physician out of the contract at a reduced cost, there are often stipulations. One of the physicians we interviewed for this article said that he was negotiating an early termination of his contract, but to do so he had to sign a nondisclosure statement saying he would never comment on his poor experience with that EHR.

So how can a physician avoid ending up with an EHR that may be unusable? It is essential to review the experience of those who have already purchased

an EHR. The American Academy of Family Physicians' Center for Health IT provides a Web site through which members can rate their own EHR based on a five-point scale measuring quality, price, support, ease of use, and impact on productivity. Sorting the available list of 93 EHR systems by rating provides a clear look at overall user satisfaction ([www.centerforhit.org](http://www.centerforhit.org)).

User satisfaction studies are another indispensable resource. An October 2009 survey of over 3,700 EHR users published by Medscape.com found that over 30% of respondents would not recommend their EHR (<http://www.medscape.com/viewarticle/709856>).

Similarly, “The 2009 EHR User Satisfaction Survey,” published in the November/December 2009 issue of Family Practice Management, provides a troubling look at how physicians rate many of the best known EHRs. This survey's final question asked 2,012 family physicians if they agreed or disagreed with the following statement, “I am highly satisfied with this EHR system.” Astoundingly, nearly 50% of all respondents said that they would not agree.

With the current rate of physician dissatisfaction, EHR adoption rates will likely remain low despite the government incentives. Perhaps most ironic is that federal financial incentives to adopt EHR systems may contribute to delays in improvements in EHR usability. Rather than allowing competition to reward vendors who produce better software at lower prices, the stimulus mon-

ey encourages physicians to purchase mediocre software at inflated prices.

As physicians recognize the perils of signing EHR contracts before they truly know if an EHR is usable, they will begin to demand usable, intuitive EHRs. Increasingly, physicians will come to appreciate how financial incentives and initial system costs are dwarfed by the potential reduction in productivity and revenue when a system proves difficult to use. As they gain more exposure to the EHR market, physicians will start to ask the important questions and demand answers about the critical issue of usability, which ultimately makes or breaks their EHR experience.



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## Ten Rules for Developing a Health Information Exchange

BY JOYCE FRIEDEN

WASHINGTON — If you're trying to develop a health information exchange to share electronic health record data with other providers in your area, Dr. Larry Garber has some advice for you.

Dr. Garber, an internist who is medical director for informatics at Fallon Clinic, in Worcester, Mass., outlined his 10 rules for developing a health information exchange (HIE) at the eHealth Initiative Conference:

**10. Remember that patients are lousy historians.** “It's up to our information technology infrastructures that we build to deliver the vast majority of health information to providers at the point of care,” rather than relying on patients to deliver the data, said Dr. Garber, who is also vice-chair of the Massachusetts eHealth Collaborative.

**9. Don't let physicians and patients become a bottleneck to HIE.** “It's hard enough to get emergency room physicians to look at something right under their noses, let alone to start thinking about a consent process,” he said. “And patients cannot be expected to use their

personal health record as a way of controlling the flow of data.”

**8. Create a statewide enterprise master person index (EMPI).** Each state should have statewide universal consent forms that a patient can sign once and that apply throughout the system, Dr. Garber said. But to ensure that the consent form that John Smith signed applies to him whether he is in his primary care physician's office, a specialist's office, or the hospital, an EMPI is needed to make sure all the John Smiths are the same person.

The EMPI helps reconcile continuity of care documents. “What do I do when I get 20 medication lists and 20 allergy lists?” he said. “You can only [solve that problem] if you have an EMPI recognizing that these are all the same person.”

**7. Don't promise to segregate specially protected information such as HIV status or mental health issues.** “In order to make that work ... the systems will have to err on the side of not sending information, and as a result we will have a true Swiss cheese of data being exchanged,” he said. In Massachusetts, health care organizations tried an HIE in which emergency departments filtered

out potentially protected data. “It turned out that the resulting medication lists were useless and the project had to be stopped. ... You're either all in or all out. It's dangerous [to withhold information], and patients don't understand the implications of not letting certain data flow.”

**6. Keep the overhead low.** The local HIE that Dr. Garber helped start had its software written internally in order to avoid paying licensing fees. The HIE also hosts its servers in its own data center, and the exchange members did not create a legal entity—such as a regional health information organization—in order to avoid paying attorneys' fees. As a result, the exchange's operating expenses are \$7,000 annually, he said. “This may take a little more [money] in other communities, but the bottom line is that you have to lower operating fees if you want the HIE to be sustainable.”

**5. Store the data based on the content, not on the source.** “When the data is stored, you need to file it properly,” Dr. Garber said. “If you have outside electronic documents coming in, don't put them in an ‘Outside Records’ folder; they need to be integrated with the rest

of the data. If I want to find the last MRI of the brain, I want to look in the imaging section and find the last MRI regardless of where it was done. File labs with labs and radiology with radiology.”

**4. Make the electronic health record (EHR) “one-stop shopping.”** “I only want to go look in one place for information; I don't want to have to go outside the EHR to a different portal to look for things,” he said. “I want one place with one common user interface.”

**3. Re-use data.** The beauty of an EHR is that you can take the data and repurpose it, according to Dr. Garber. For example, the clinic uses claims data to populate medication lists, past medical history, and past surgical history.

**2. Don't require people to think.** “If you want some process done consistently correctly, you have to kind of take the brain out of [it],” he said. For example, if a hospital needs to have patients sign consent forms for HIV testing, “when patients are checking in and being registered, don't ask the registration clerk to check if they have consented or need to consent; let that

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process happen automatically—the consent form appears when it's appropriate; it doesn't appear when it's not appropriate." The same should be true for ordering health maintenance and disease management tests.

**1. Remember that this is the real world.** "Don't forget that we're dealing with the real world and real people," Dr. Garber said. "Everything we do affects real people and their health and their happiness. That also includes the physicians and nurses and staff that work in

these organizations; everything we do affects [them] as well."

No one should expect physicians and staff to fill out forms just for the sake of collecting data so someone can do some analysis on the back end. Data collection should be a byproduct of the care that we give. "Everything we build is affecting real workloads of real people."

The conference was sponsored by Ingenix, the American Medical Association, and several other industry groups and trade associations. Dr. Garber did not disclose any conflicts of interest related to his presentation.

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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](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 antidepressant 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—**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 effects 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 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 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 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. **Hypotension—**Hypotension can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hypotension appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hypotension 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 full prescribing information]. Discontinuation of Pristiq should be considered in patients with symptomatic hypotension 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, Paraesthesia, 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 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 (6.0%, 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 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 (ketocozazole): 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 1A1, 1A2, 2A6, 2B6, 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 CYP2D6 substrate by CYP2D6 can 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—**Patients 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 SNRIs and SSRIs 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 (0-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 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  $\geq 65$  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 Overdosage—**There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdosage of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdosage  $> 600$  mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paraesthesia, 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 *Overdosage* 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, changes 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 overdosage 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 Overdosage—**Treatment should consist of those general measures employed in the management of overdosage 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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