

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIIBRYD® safely and effectively. See full prescribing information for VIIBRYD.

VIIBRYD® (vilazodone HCl) Tablets for oral administration
Initial U.S. Approval: 2011

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).
- Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)
- VIIBRYD is not approved for use in pediatric patients (8.4).

RECENT MAJOR CHANGES

Boxed Warning	12/2013
Dosage and Administration (2.3)	12/2013
Warnings and Precautions (5.2)	04/2014

INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, placebo-controlled trials in adult patients with MDD (1, 14).

DOSAGE AND ADMINISTRATION

- The recommended dose for VIIBRYD is 40 mg once daily (2.1).
- VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily (2.1).
- VIIBRYD should be taken with food. Administration without food can result in inadequate drug concentrations and may diminish effectiveness (2.1, 12.3).
- When discontinuing treatment, reduce the dose gradually (2.4).

DOSAGE FORMS AND STRENGTHS

VIIBRYD is available as 10 mg, 20 mg and 40 mg tablets (3).

CONTRAINDICATIONS

- **Serotonin Syndrome and MAOIs:** Do not use MAOIs intended to treat psychiatric disorders with VIIBRYD or within 14 days of stopping treatment with VIIBRYD. Do not use VIIBRYD within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start VIIBRYD in a patient who is being treated with linezolid or intravenous methylene blue (4.1).

WARNINGS AND PRECAUTIONS

- **Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults:** Monitor patients for clinical worsening and suicidal thinking or behavior (5.1).
- **Serotonin Syndrome:** Serotonin syndrome has been reported with SSRIs and SNRIs, including VIIBRYD, both when taken alone, but

especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort). If such symptoms occur, discontinue VIIBRYD and initiate supportive treatment. If concomitant use of VIIBRYD with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).

- **Seizures:** Can occur with treatment. Use with caution in patients with a seizure disorder (5.3).
- **Abnormal Bleeding:** Treatment can increase the risk of bleeding. Use with caution in association with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.4).
- **Activation of Mania/Hypomania:** Can occur with treatment. Screen patients for bipolar disorder (5.5).
- **Discontinuation of Treatment with VIIBRYD:** A gradual reduction in dose is recommended rather than an abrupt cessation (5.6).
- **Hyponatremia:** Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).

ADVERSE REACTIONS

The most common adverse reactions (incidence \geq 5% and at least twice the rate of placebo) are: diarrhea, nausea, vomiting, and insomnia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Forest Laboratories, Inc. at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **MAOIs:** Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1, 7.2).
- **CYP3A4 inhibitors:** The VIIBRYD dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (2.3, 7.5).
- **CYP3A4 inducers:** Based on clinical response, consider increasing the dose of VIIBRYD up to 2-fold when used concomitantly with strong CYP3A4 inducers (e.g., carbamazepine) for greater than 14 days. The maximum daily dose should not exceed 80 mg. (2.3, 7.5).

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are no controlled human data regarding VIIBRYD use during pregnancy. Use only if the potential benefits outweigh the potential risks (8.1).
- **Nursing Mothers:** There are no human data regarding VIIBRYD concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks (8.3).
- **Pediatric Use:** The safety and efficacy of VIIBRYD in pediatric patients have not been studied (8.4).
- **Geriatric Use:** No dose adjustment is recommended on the basis of age (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Initial Treatment of Major Depressive Disorder
- 2.2 Maintenance/Continuation/Extended Treatment
- 2.3 Concomitant Use of CYP3A4 Inhibitors or CYP3A4 Inducers
- 2.4 Discontinuing Treatment
- 2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders
- 2.6 Use of VIIBRYD with Other MAOIs such as Linezolid or Methylene Blue

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Monoamine Oxidase Inhibitors (MAOIs)

5 WARNINGS AND PRECAUTIONS

- 5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
- 5.2 Serotonin Syndrome
- 5.3 Seizures
- 5.4 Abnormal Bleeding
- 5.5 Activation of Mania/Hypomania
- 5.6 Discontinuation of Treatment with VIIBRYD
- 5.7 Hyponatremia

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Post-marketing Experience

7 DRUG INTERACTIONS

- 7.1 Central Nervous System (CNS)-Active Agents
- 7.2 Monoamine Oxidase Inhibitors (MAOIs)
- 7.3 Serotonergic Drugs
- 7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
- 7.5 Potential for Other Drugs to Affect Vilazodone

7.6 Potential for Vilazodone to Affect Other Drugs

7.7 Drugs Highly Bound to Plasma Protein

7.8 Triptans

7.9 Alcohol

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

8.8 Gender Effect

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse and Dependence

10 OVERDOSAGE

10.1 Human Experience

10.2 Management of Overdose

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

17.2 Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see Warnings and Precautions (5.1)].

In patients of all ages who are started on antidepressant therapy, monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.1)].

VIIBRYD is not approved for use in pediatric patients [see Use in Specific Populations (8.4)].

1 INDICATIONS AND USAGE

VIIBRYD[®] is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD [see *Clinical Studies (14)*].

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for VIIBRYD is 40 mg once daily. VIIBRYD should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. VIIBRYD should be taken with food. VIIBRYD blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients [see *Clinical Pharmacology (12.3)*].

2.2 Maintenance/Continuation/Extended Treatment

The efficacy of VIIBRYD has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

2.3 Concomitant Use of CYP3A4 Inhibitors or CYP3A4 Inducers

Patients receiving concomitant CYP3A4 inhibitors:

Reduce the VIIBRYD dose to 20 mg if co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole). During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. The VIIBRYD dose should be readjusted to the original level when CYP3A4 inhibitors are discontinued [see *Drug Interactions (7.5)*].

Patients receiving concomitant CYP3A4 inducers:

Based on clinical response, consider increasing the dose of VIIBRYD up to 2-fold when concomitantly used with strong CYP3A4 inducers (e.g., carbamazepine) for greater than 14 days. The maximum daily dose should not exceed 80 mg. If CYP3A4 inducers are discontinued, reduce the VIIBRYD dose to the original level in 14 days [see *Drug Interactions (7.5)*].

2.4 Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate [see *Warnings and Precautions (5.6)*].

2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with VIIBRYD. Conversely, at least 14 days should be allowed after stopping VIIBRYD before starting an MAOI intended to treat psychiatric disorders [see *Contraindications (4.1)*].

2.6 Use of VIIBRYD with Other MAOIs such as Linezolid or Methylene Blue

Do not start VIIBRYD in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered [see *Contraindications (4.1)*].

In some cases, a patient already receiving VIIBRYD therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, VIIBRYD should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with VIIBRYD may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [see *Warnings and Precautions (5.2)*].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with VIIBRYD is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

VIIBRYD Tablets are available as 10 mg, 20 mg and 40 mg immediate-release, film-coated tablets.

- 10 mg pink, oval tablet, debossed with 10 on one side
- 20 mg orange, oval tablet, debossed with 20 on one side
- 40 mg blue, oval tablet, debossed with 40 on one side

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with VIIBRYD or within 14 days of stopping treatment with VIIBRYD is contraindicated because of an increased risk of serotonin syndrome. The use of VIIBRYD within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated [see *Dosage and Administration (2.5)*, and *Warnings and Precautions (5.2)*].

Starting VIIBRYD in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome [see *Dosage and Administration (2.6)*, and *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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 (selective serotonin reuptake inhibitors [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 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**.

Table 1:

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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, i.e., 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 (5.6) and Dosage and Administration (2.4)*].

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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose [*see also Patient Counseling Information (17.1)*].

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 VIIBRYD is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including VIIBRYD, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Symptoms of serotonin syndrome were noted in 0.1% of MDD patients treated with VIIBRYD in premarketing clinical trials

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of VIIBRYD with MAOIs intended to treat psychiatric disorders is contraindicated. VIIBRYD should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking VIIBRYD. VIIBRYD should be discontinued before initiating treatment with the MAOI [*see Contraindications (4.1) and Dosage and Administration (2.5 and 2.6)*].

If concomitant use of VIIBRYD with other serotonergic drugs including, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with VIIBRYD and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Seizures

VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

5.4 Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs 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 VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.6 Discontinuation of Treatment with VIIBRYD

There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., 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.

Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate [see *Dosage and Administration* (2.4)].

5.7 Hyponatremia

Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness,

which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Clinical Worsening and Suicide Risk [see *Warnings and Precautions* (5.1)]
- Serotonin Syndrome [see *Warnings and Precautions* (5.2)]
- Seizure [see *Warnings and Precautions* (5.3)]
- Abnormal Bleeding [see *Warnings and Precautions* (5.4)]
- Activation of Mania/Hypomania [see *Warnings and Precautions* (5.5)]
- Discontinuation of Treatment with VIIBRYD [see *Warnings and Precautions* (5.5)]
- Hyponatremia [see *Warnings and Precautions* (5.7)]

6.1 Clinical Studies Experience

The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence $\geq 5\%$ and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

Patient Exposure

The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years.

The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food.

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

Adverse reactions reported as reasons for discontinuation of treatment

In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in $> 1\%$ of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in placebo-controlled MDD studies

Table 2 shows the incidence of common adverse reactions that occurred in $\geq 2\%$ of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies.

Table 2: Common Adverse Reactions Occurring in $\geq 2\%$ of VIIBRYD-treated Patients and $>$ Placebo-treated Patients

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Metabolism and nutrition disorders		
Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Table 3: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

Preferred Term	Males		Females	
	VIIBRYD N= 170	Placebo N= 182	VIIBRYD N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–
Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

– Not applicable

*Includes anorgasmia

Laboratory Tests

VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG

VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies [see *Clinical Pharmacology (12.2)*].

Vital Signs

VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight

VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain $\geq 7\%$ were 0.9% in the VIIBRYD group and 1.2% in the placebo group. The proportions of patients with a weight decrease $\geq 7\%$ were 1.4% in the VIIBRYD group and 1.4% in the placebo group.

Other adverse reactions observed in clinical studies

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: *infrequent*: ventricular extrasystoles

Eye disorders: *frequent*: vision blurred, dry eye; *infrequent*: cataracts

General disorders: *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *frequent*: decreased appetite

Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia

Psychiatric disorders: *infrequent*: panic attack, mania

Renal and Urinary disorder: *infrequent*: pollakiuria

Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

6.2 Post-marketing Experience

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

General Disorders and administrative site conditions - irritability

Psychiatric Disorders - hallucinations, suicide attempt, suicidal ideation

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents

The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated.

Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs.

7.2 Monoamine Oxidase Inhibitors (MAOIs)

[see Dosage and Administration (2.5, 2.6), Contraindications (4.1), and Warnings and Precautions (5.2)].

7.3 Serotonergic Drugs

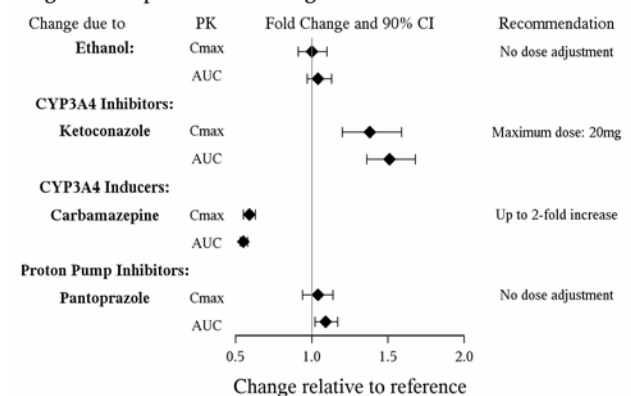
[see Dosage and Administration (2.5, 2.6), Contraindications (4.1), and Warnings and Precautions (5.2)].

7.4 Drugs that Interfere with Hemostasis (e.g., 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 VIIBRYD is initiated or discontinued [see Warnings and Precautions (5.4)].

7.5 Potential for Other Drugs to Affect Vilazodone

Figure 1. Impact of other drugs on Vilazodone PK



Inhibitors of CYP3A4

Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine) [see *Dosage and Administration* (2.3)].

Inducers of CYP3A4

Based on clinical response, consider increasing the dose of VIIBRYD up to 2-fold when concomitantly used with strong CYP3A4 inducers (e.g., carbamazepine) for greater than 14 days. The maximum daily dose should not exceed 80 mg. Concomitant use of VIIBRYD with strong inducers of CYP3A4 (e.g., carbamazepine) can decrease vilazodone systemic exposure by approximately 45% (see Figure 1). If CYP3A4 inducers are discontinued, reduce the VIIBRYD dose to the original level in 14 days [see *Dosage and Administration* (2.3)].

Inhibitors of other CYP enzymes

Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

7.6 Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19

Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6.

Drugs metabolized by CYP2C8

Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*.

Induction of CYP isoforms

VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

7.7 Drugs Highly Bound to Plasma Protein

The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

7.8 Triptans

There are postmarketing reports of serotonin syndrome with concomitant use of a serotonergic antidepressant and a triptan. If concomitant treatment with VIIBRYD and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Warnings and Precautions* (5.2)].

7.9 Alcohol

As with other psychotropic medications, the use of alcohol by patients taking VIIBRYD is not recommended, because of the potential for pharmacodynamic interactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m² basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.

When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects

Neonates exposed to VIIBRYD and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), 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)].

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including VIIBRYD) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with VIIBRYD, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

8.2 Labor and Delivery

The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk.

8.3 Nursing Mothers

Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child.

8.4 Pediatric Use

Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients [see *Box Warning and Warnings and Precautions* (5.1)].

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age.

Greater sensitivity of some older individuals cannot be ruled out.

Serotonergic antidepressants 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* (5.7)].

8.6 Hepatic Impairment

Vilazodone is eliminated primarily by hepatic metabolism. In mild, moderate, and severe hepatic impairment, no dose adjustment is necessary (see Figure 2).

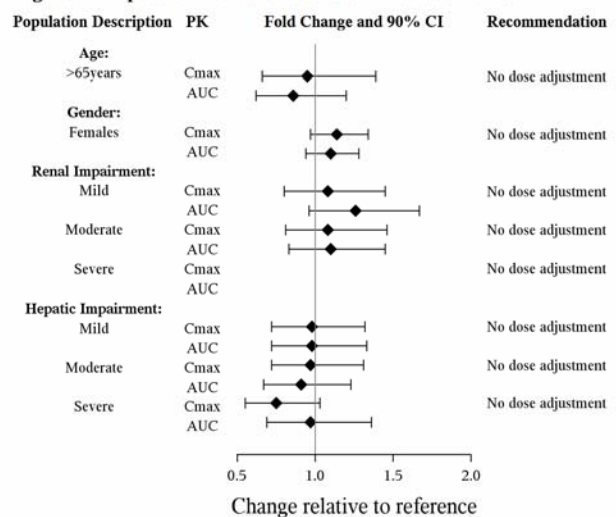
8.7 Renal Impairment

In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2).

8.8 Gender Effect

After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2).

Figure 2. Impact of intrinsic factors on Vilazodone PK



The data shown for elderly subjects (>65 years) is relative to subjects (24-55 years).

The data shown for female subjects is relative to male subjects.

The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic functions, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VIIBRYD is not a controlled substance.

9.2 Abuse and Dependence

VIIBRYD has been systematically studied in animals and did not demonstrate abuse or dependence potential. While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of VIIBRYD (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

10.1 Human Experience

There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

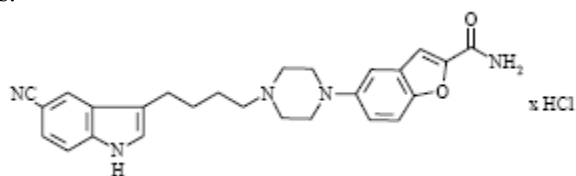
10.2 Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. 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 considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

11 DESCRIPTION

VIIBRYD Tablets for oral administration contain polymorph Form IV vilazodone hydrochloride (HCl), a selective serotonin reuptake inhibitor and a 5HT_{1A} receptor partial agonist.

Vilazodone HCl is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99. The structural formula is:



In addition to the active ingredient, VIIBRYD Tablets contain lactose monohydrate, microcrystalline cellulose, magnesium

stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT_{1A} receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

12.2 Pharmacodynamics

Vilazodone binds with high affinity to the serotonin reuptake site ($K_i = 0.1$ nM), but not to the norepinephrine ($K_i = 56$ nM) or dopamine ($K_i = 37$ nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin ($IC_{50} = 1.6$ nM). Vilazodone also binds selectively with high affinity to 5-HT_{1A} receptors ($IC_{50} = 2.1$ nM) and is a 5-HT_{1A} receptor partial agonist.

Thorough QT Study: Treatment with VIIBRYD did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

12.3 Pharmacokinetics

Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of VIIBRYD 40 mg under fed conditions, the mean C_{max} value is 156 ng/mL, and the mean AUC (0-24 hours) value is 1645 ng·h/mL.

Absorption

Vilazodone concentrations peak at a median of 4-5 hours (T_{max}) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Coadministration of VIIBRYD with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent

of vilazodone absorption [see *Drug Interactions (7.5, Figure 1)*]. In addition, neither the T_{max} nor terminal elimination rate of vilazodone was altered by coadministration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution

Vilazodone is widely distributed and approximately 96-99% protein-bound

Metabolism and Elimination

VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. *In vitro* studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an *in vivo* study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates. However, an *in vivo* study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, strong inducers of CYP3A4 (e.g., carbamazepine) can decrease vilazodone exposure [see *Drug Interactions (7.5)*].

The presence of mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment did not affect the apparent clearance of vilazodone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which B6C3F1 mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m² basis.

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the MRHD, with statistical significance at 16.5 the MRHD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.

In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis

Vilazodone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test). Vilazodone was negative in the *in vitro* V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two *in vitro* mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an *in vivo* rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an *in vivo/in vitro* unscheduled DNA synthesis assay in rats.

Impairment of Fertility

Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the maximum recommended human dose (MRHD) of 40 mg on a mg/m² basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

14 CLINICAL STUDIES

The efficacy of VIIBRYD as a treatment for major depressive disorder was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of VIIBRYD with food (n=436) or placebo (n = 433) once daily. VIIBRYD was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Examination of population subgroups based on age (there were few patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness.

Table 4: Summary of Results for the Primary Efficacy Endpoint

Study Number	Primary Endpoint	LS Mean (95% CI) ^a difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

^a Least Squares Mean (95% Confidence Interval)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VIIBRYD (vilazodone HCl) Tablets are supplied in the following configurations:

10 mg, pink, oval tablet, debossed with 10 on one side

0456-1110-30: 30-count bottles

20 mg, orange, oval tablet, debossed with 20 on one side

0456-1120-30: 30-count bottles

40 mg, blue, oval tablet, debossed with 40 on one side

0456-1140-30: 30-count bottles

Patient Starter Kit

0456-1100-31: blister card containing 30 tablets:

10 mg, pink, oval, debossed with 10 on one side: 7 tablets
20 mg, orange, oval, debossed with 20 on one side: 7 tablets
40 mg, blue, oval, debossed with 40 on one side: 16 tablets

16.2 Storage

VIIBRYD (vilazodone HCl) Tablets should be stored at 25°C (77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Information for Patients

Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicidal Thoughts and Behaviors

Advise patients and caregivers to monitor for the emergence of suicidal thoughts or behaviors, especially early during treatment and when the dose is adjusted up or down. Advise them to notify their healthcare provider if these occur [see Boxed Warning and Warnings and Precautions (5.1)].

Dosing and Administration

Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication

Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [see Contraindications (4.1)].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of VIIBRYD with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid) [see Warnings and Precautions (5.2) and Drug Interactions (7.2, 7.3)].

Seizures

Caution patients about using VIIBRYD if they have a history of a seizure disorder [see Warnings and Precautions (5.3)]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding

Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [see Warnings and Precautions (5.4)].

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania [see Warnings and Precautions (5.5)].

Discontinuation of Treatment

Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [see Warnings and Precautions (5.6)].

Hyponatremia

Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [see Warnings and Precautions (5.7)].

Alcohol

Advise patients to avoid alcohol while taking VIIBRYD [see Drug Interactions (7.5, 7.9)].

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [see Use in Specific Populations (8.1)].

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [see Use in Specific Populations (8.3)].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

Distributed by

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Licensed from Merck KGaA,
Darmstadt, Germany

VIIBRYD® is a registered trademark of Forest Laboratories, Inc.

© 2011, 2012, 2013, 20XX Forest Laboratories, Inc.

MEDICATION GUIDE

VIIBRYD® *[vi-brid]* (vilazodone hydrochloride) Tablets

Read this Medication Guide carefully before you start taking VIIBRYD and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIIBRYD?

VIIBRYD and other antidepressant medicines may cause serious side effects.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if there is an emergency:

1. Suicidal thoughts or actions:

- **VIIBRYD and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
- New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
- Pay particular attention to such changes when VIIBRYD is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses

- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you (mania)
- other unusual changes in behavior or mood

2. Serotonin Syndrome:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- fast heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle stiffness or tightness

3. Abnormal bleeding: VIIBRYD and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

4. Seizures or convulsions.

5. Manic episodes:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas

- excessive happiness or irritability
- talking more or faster than usual

6. Low salt (sodium) levels in the blood.

Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop VIIBRYD without first talking to your healthcare provider.

Stopping VIIBRYD suddenly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or sleepy
- headache, sweating, nausea, dizziness
- electric shock-like sensations, tremor, confusion

What is VIIBRYD?

VIIBRYD is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD). It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

Talk to your healthcare provider if you do not think that your condition is getting better with VIIBRYD treatment.

It is not known if VIIBRYD is safe and effective in children.

Who should not take VIIBRYD?

Do not take VIIBRYD if you:

- Take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 2 weeks of stopping VIIBRYD unless directed to do so by your physician.
- Do not start VIIBRYD if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

People who take VIIBRYD close in time to taking an MAOI may have

serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)

What should I tell my healthcare provider before taking VIIBRYD?

Before starting VIIBRYD, tell your healthcare provider if you:

- have liver problems
- have kidney problems
- have or had seizures or convulsions
- have bipolar disorder (manic depression) or mania
- have low sodium levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions
- Are pregnant or plan to become pregnant. It is not known if VIIBRYD will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
- Are breastfeeding or plan to breastfeed. It is not known if VIIBRYD passes into breast milk. You and your healthcare provider should decide if you should take VIIBRYD while breastfeeding.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. VIIBRYD and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics,

lithium, SSRIs, SNRIs, buspirone, or antipsychotics

- tramadol
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- aspirin
- warfarin (Coumadin, Jantoven)
- mephenytoin (Mesantoin)
- diuretics

Your healthcare provider or pharmacist can tell you if it is safe to take VIIBRYD with your other medicines. Do not start or stop any medicine while taking VIIBRYD without talking to your healthcare provider first.

How should I take VIIBRYD?

- Take VIIBRYD exactly as prescribed. Your healthcare provider may need to change the dose of VIIBRYD until it is the right dose for you.
- **Take VIIBRYD with food.** VIIBRYD may not work as well if you take it on an empty stomach.
- If you miss a dose of VIIBRYD, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of VIIBRYD at the same time.
- If you take too much VIIBRYD, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking VIIBRYD?

- VIIBRYD can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how VIIBRYD affects you.
- You should avoid drinking alcohol while taking VIIBRYD. See "What should I tell my healthcare provider before taking VIIBRYD?"

What are the possible side effects of VIIBRYD?

VIIBRYD may cause serious side effects, including:

- See "What is the most important information I should know about VIIBRYD?"

Common side effects in people who take VIIBRYD include:

- diarrhea
- nausea or vomiting
- trouble sleeping

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of VIIBRYD. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIIBRYD?

Store VIIBRYD at room temperature (59°F to 86°F or 15°C to 30°C).

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

General information about VIIBRYD.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIIBRYD for a condition for which it was not prescribed. Do not give VIIBRYD to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about VIIBRYD. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about VIIBRYD that is written for healthcare professionals.

For more information about VIIBRYD call 1-800-678-1605.

What are the ingredients in VIIBRYD?

Active ingredient: vilazodone hydrochloride
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene

glycol, talc, and FD&C Blue #1 (40 mg only),
FD&C Yellow #6 (20 mg only) and FD&C Red
#40 (10 mg only).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Licensed from Merck KGaA, Darmstadt, Germany

VIIBRYD[®] is a registered trademark of Forest Laboratories, Inc.

© 2012 Forest Laboratories, Inc.

Revised: December 2012