PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVIIBRYD®

vilazodone hydrochloride

10 mg, 20 mg, 40 mg Oral tablets

Antidepressant

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Date of Initial Authorization:
January 23, 2019

Date of Revision:
March 03, 2021

Submission Control No: 237588

RECENT MAJOR LABEL CHANGES

INDICATIONS, Pediatrics (1.1)	March 2021
WARNINGS AND PRECAUTIONS, Pediatric (7.1.3)	March 2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VIIBRYD (vilazodone hydrochloride tablets) is indicated for the symptomatic relief of Major Depressive Disorder (MDD).

The short-term efficacy of VIIBRYD was demonstrated in randomized, double-blind, placebo-controlled studies of 8 to 10-weeks. See 14 CLINICAL TRIALS. Long-term maintenance efficacy has not been established. Physicians should periodically re-evaluate the usefulness of the drug for individual patients.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of VIIBRYD in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7 WARNINGS AND PRECAUTIONS and 8.2.1 Clinical Trial Adverse Reactions - Pediatrics.

1.2 Geriatrics

Geriatrics (> 65 years of age): No dose adjustment is recommended on the basis of age. See 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION and 10.3 Special Populations and Conditions.

2 CONTRAINDICATIONS

VIIBRYD is contraindicated in:

- patients with known hypersensitivity to vilazodone or any of the excipients of the drug product. For a complete listing of excipients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- patients with concomitant use of Monoamine Oxidase Inhibitors (MAOIs). See 9.4 Drug-Drug Interactions and 7 WARNINGS AND PRECAUTIONS.

Monoamine Oxidase Inhibitors (MAOIs)

VIIBRYD increases serotonergic neurotransmission and must not be used in patients concomitantly taking, or having stopped taking for less than 14 days, MAOIs, including linezolid, an antibiotic, methylene blue, a dye used in certain surgeries due to the risk of serious, sometimes fatal, drug interactions. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome or serotonin toxicity, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Therefore, at least 14 days should be allowed after discontinuing treatment with a MAOI before starting treatment with VIIBRYD. See 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

At the time of authorization, no serious warnings or precautions have been identified.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **VIIBRYD is not indicated for use in children under 18 years of age. See 7 WARNINGS AND PRECAUTIONS.**

- 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 10.3 Pharmacokinetics.

- **Switching a Patient to or from Monoamine Oxidase Inhibitors (MAOIs)**
  At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with VIIBRYD. Conversely, at least 14 days must be allowed after stopping VIIBRYD before starting an MAOI. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS.

- **Concomitant Use of CYP3A4 Inhibitors**
  The VIIBRYD dose should not exceed 20 mg if co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole). The VIIBRYD dose should be readjusted to the original level when CYP3A4 inhibitors are discontinued. See 9.4 Drug-Drug Interactions.

- **Concomitant Use of CYP3A4 Inducers**
  Concomitant use of VIIBRYD with a strong inducer of CYP3A4 (carbamazepine 400 mg/day) decreased vilazodone systemic exposure by approximately 45%. As knowledge of safety with doses > 40 mg is limited, no dosage adjustment is recommended. See 9.4 Drug-Drug Interactions.

4.2 Recommended Dose and Dosage Adjustment

4.2.1 Initiating Treatment

Adults
The recommended dose for VIIBRYD is 20 mg to 40 mg once daily with food. VIIBRYD should be initiated at a dose of 10 mg once daily for 7 days, followed by 20 mg once daily. Based on individual patient efficacy and tolerability, the dose may be increased from 20 mg to 40 mg once daily after 7 days. Therapeutic response is usually seen after 1 - 2 weeks of treatment.

Pediatrics (<18 years of age)
Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics.

Geriatrics (> 65 years of age)
No dose adjustment is recommended on the basis of age. Greater sensitivity of some older individuals cannot be ruled out. In the context of a greater potential for other concomitant medical conditions and drug therapies in elderly patients, caution should be exercised when treating the elderly. See 7.1.4 Geriatrics and 10.3 Pharmacokinetics.

4.2.2 Dosing in Special Populations and Conditions

Hepatic Impairment
No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Data in patients with severe hepatic impairment is limited; therefore caution should be exercised if patients with severe hepatic impairment are treated. See 10.3 Pharmacokinetics.

Renal Impairment
No dose adjustment is recommended in patients with mild, moderate or severe renal impairment. Patients with severe renal were not studied therefore, VIIBRYD should be used with caution in these patients. See 10.3 Pharmacokinetics.

4.2.3 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 7 WARNINGS AND PRECAUTIONS.

4.5 Missed Dose

In the event that a dose is missed, the patient should take the missed dose as soon as they remember. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the regular time. The patient should not take two doses of VIIBRYD at the same time.

5 OVERDOSAGE

There is limited clinical trial experience regarding human overdosage with VIIBRYD. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin toxicity, lethargy, restlessness, hallucinations, and disorientation.

Management of Overdose
No specific antidotes for vilazodone are known. Management of overdose should consider the possibility of multiple drug involvement and should consist of treatment of clinical symptoms and relevant monitoring. Medical follow-up in a specialized environment is recommended. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 10 mg, 20 mg and 40 mg	colloidal silicon dioxide, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

VIIBRYD immediate-release tablets are available as 10 mg, 20 mg and 40 mg strengths.

- 10 mg tablets: each film-coated, pink, oval tablet is debossed with “10” on one side. Available in bottles of 30 tablets.

- 20 mg tablets: each film-coated, orange, oval tablet is debossed with “20” on one side. Available in bottles of 30 tablets.

- 40 mg tablets: each film-coated, blue, oval tablet is debossed with “40” on one side. Available in bottles of 30 tablets.

VIIBRYD is also available in Patient Starter Kit format consisting of:
- Seven 10 mg tablets and twenty-three 20 mg tablets in a single blister card

7 WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

<u>Pediatrics: Placebo-Controlled Clinical Trial Data</u>
- **Recent analyses of placebo-controlled clinical trial safety databases from Selective Serotonin Reuptake Inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

<u>Adults and Pediatrics: Additional data</u>
- **There are clinical trials and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse**

events coupled with self-harm and harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients aged 18 to 24 years with psychiatric disorder showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Discontinuation Symptoms

Patients currently taking VIIBRYD should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended. See 4 DOSAGE AND ADMINISTRATION.

Discontinuation of Treatment

At the time that a medical decision is made to discontinue VIIBRYD, a gradual reduction in the dose, rather than an abrupt cessation, is recommended.

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 4.2.3 Discontinuing Treatment.

General

Bone Fracture Risk

Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs (serotonin and norepinephrine-reuptake inhibitors). The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with VIIBRYD. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs/SNRIs, including VIIBRYD, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Carcinogenesis and Mutagenesis
For animal data see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Blood Pressure
Patients with severe cardiac function impairment or with an identified risk of a serious cardiac arrhythmia, uncontrolled hypertension, or severe or unstable coronary heart disease were excluded from clinical trials with VIIBRYD. Caution should be exercised in treating patients with uncontrolled hypertension or with other cardiovascular or cerebrovascular conditions that might be compromised by increases in blood pressure. See 10.2 Pharmacodynamics and 8.2 Clinical Trial Adverse Reactions.

Dependence/Tolerance

Abuse Liability
While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behaviour 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 behaviour, increases in dose).

Dependence Liability
VIIBRYD has been systematically studied in animals and did not demonstrate dependence potential.

Driving and Operating Machinery
Any psychoactive drug may impair judgment, thinking, or motor skills. VIIBRYD may be associated with undesirable effects such as sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not affect their ability to engage in such activities.

Hematologic

Abnormal Bleeding
SSRIs and SNRIs, including VIIBRYD, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), 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 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 VIIBRYD and NSAIDs, ASA, or other drugs that affect coagulation. See 9.4 Drug-Drug Interactions. Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g., thrombocytopenia).

Hepatic/Biliary/Pancreatic

Hepatic Impairment
Based on a study conducted with VIIBRYD in patients with mild to moderate hepatic impairment, no impact was observed on the pharmacokinetics of vilazodone. Subsequently no dose adjustment is recommended for patients with mild or moderate hepatic impairment.

Data in patients with severe hepatic impairment is limited; these patients were excluded from phase 3 clinical trials. Therefore, caution should be exercised if patients with severe hepatic impairment are treated. See 4.2.2 Dosing in Special Populations and Conditions and 10.3 Pharmacokinetics.

Neurologic

Seizures
VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Seizures are a potential risk with antidepressant drugs. VIIBRYD should be prescribed with caution in patients with a seizure disorder.

Serotonin toxicity / Serotonin syndrome
Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with SNRIs and SSRIs, including VIIBRYD.

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with VIIBRYD and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. See 2 CONTRAINDICATIONS,4 DOSAGE AND ADMINISTRATION, and 9 DRUG INTERACTIONS. If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Cognitive and Motor Disturbances
The effects of vilazodone on the ability to drive or to operate machinery were not systematically evaluated in the vilazodone development program.

Ophthalmologic

Glaucoma
As with other SSRIs/SNRIs, VIIBRYD can cause mydriasis and should be used with caution in patients with raised intraocular pressure or those with narrow-angle glaucoma.

Psychiatric

Suicide
The possibility of a suicide attempt is inherent to Major Depressive Disorder (MDD) and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high risk patients.

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania and other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or regimen.

Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions should be written for the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug. See 7 WARNINGS AND PRECAUTIONS.

Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in short-term clinical studies of patients with MDD and in which patients with bipolar disorder were excluded. 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 and VIIBRYD should be discontinued in any patient entering a manic phase.

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should be made only after patients have been adequately assessed to determine if they are at risk for bipolar disorder. It should be noted that VIIBRYD is not approved for use in treating bipolar depression.

Electroconvulsive Therapy (ECT)
The safety and efficacy of the concurrent use of VIIBRYD and ECT have not been studied, and therefore, caution is advisable.

Renal

Hyponatremia
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 and SNRIs. 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.

Renal impairment
The safety profile of vilazodone after a single oral dose of 20 mg did not differ in subjects with mild or moderate renal impairment when compared with subjects with normal renal function. Patients with severe renal impairment were not studied; VIIBRYD should be used with caution in these patients. No dose adjustment is recommended in patients with mild, moderate or severe renal impairment.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of VIIBRYD in human pregnancy has not been established. 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 to the fetus. See 10.3 Pharmacokinetics and 16 NON-CLINICAL TOXICOLOGY.

Animal studies did not demonstrate a teratogenic effect of vilazodone, but lower fetal weight and delayed ossification were seen in rats at systemic exposures corresponding to approximately 48 times the C_{max} at the maximum recommended human dose (40 mg/day) and in rabbits at approximately 17 times the C_{max} at the maximum recommended human dose. See 16 NON-CLINICAL TOXICOLOGY.

Nonteratogenic Effects: Post-marketing reports indicate that some neonates exposed to serotonergic antidepressants 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 serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin toxicity. See 7 WARNINGS AND PRECAUTIONS.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistant 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.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. If VIIBRYD is used until or shortly before birth, discontinuation symptoms in the newborn should be considered.

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

7.1.2 Breast-feeding

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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VIIBRYD treatment, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): VIIBRYD is not approved for use in pediatric patients. See 7 WARNINGS AND PRECAUTIONS.

The effectiveness of VIIBRYD in pediatric patients with MDD has not been established. Efficacy was not demonstrated in two adequate and well controlled, 8-week studies including a total of 1002 pediatric patients aged 7 years to 17 years of age with MDD. The following adverse reactions were reported in at least 5% of pediatric patients treated with VIIBRYD and occurred at a rate at least twice that for pediatric patients receiving placebo: nausea, vomiting, diarrhea, abdominal pain/discomfort, and dizziness. For further details see 8.2.1 Clinical Trial Adverse Reactions - Pediatrics.

7.1.4 Geriatrics (> 65 years of age):

Of the 3,007 patients in clinical studies with VIIBRYD, 65 (2.2%) were 65 to 70 years of age, and 378 (12.6%) were 55 to 64 years of age. An insufficient number of older patients 65-70 were included in the randomized, double-blind, placebo-controlled studies to conclude whether the safety and efficacy in these patients differs from younger patients.

Results from a single-dose (20 mg) pharmacokinetic study in elderly (65-80 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups. As with any medicine, in the context of a greater potential for other concomitant medical conditions and drug therapies in elderly patients, caution should be exercised when treating the elderly.

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 7 WARNINGS AND PRECAUTIONS, 4.2.2 Dosing in Special Populations and Conditions and 10.3 Pharmacokinetics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VIIBRYD was evaluated in 3,007 patients (18-70 years of age) diagnosed with MDD, representing 676 patient-years of exposure. Of the 3,007 VIIBRYD-treated patients, 2,408 were exposed to VIIBRYD in short-term, placebo-controlled studies. In the phase 3 placebo-controlled studies, the mean age of patients was 41 years (18-70 years) and of these patients, approximately 57% were women and 43% were men. In an open-label 52-week study at 40 mg once daily, 599 patients were exposed to VIIBRYD with 314 patients exposed for at least 6 months and 118 patients exposed for at least 12 months.

The most commonly observed adverse reactions in VIIBRYD-treated MDD patients (n=1266) in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting and insomnia.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment
Overall, 7.3% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.5% of placebo-treated patients in these studies. The most common adverse reaction leading to discontinuation in at least 1% of the VIIBRYD-treated patients in the placebo-controlled studies was nausea (1.4%) and diarrhea (1.1%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The information presented in these sections was derived from studies of VIIBRYD in major depressive disorder including: 1) 4 placebo-controlled 8 to 10-week studies in 2233 patients, including 1266 receiving VIIBRYD; and 2) an open-label 52-week study of 599 patients. Patients in these studies were either titrated over one week to a dose of 20 mg daily or over two weeks to a dose of 40 mg daily of VIIBRYD. In these clinical trials, VIIBRYD was administered with food.

Common Adverse Reactions in Placebo-Controlled MDD Studies
Table 1 shows the incidence of common adverse reactions that occurred in ≥ 2% of VIIBRYD-treated MDD patients and at a greater rate than placebo-treated patients in the four placebo-controlled studies. Table 1 presents the adverse reactions of placebo and VIIBRYD as pooled data.

Table 1: Adverse Reactions Occurring in ≥ 2% of VIIBRYD-treated Patients and at a greater rate than Placebo-treated Patients in MDD Placebo-Controlled Studies

System Organ Class Preferred Term	Placebo N=967 (%)	VIIBRYD 20 mg/day N=288 (%)	VIIBRYD 40 mg/day N=978 (%)
Gastrointestinal disorders			
Diarrhea	10	26	29
Nausea	7	22	24
Dry mouth	5	8	7
Vomiting	2	4	5
Abdominal pain[1]	3	7	4
Dyspepsia	2	2	3
Flatulence	1	3	3
Gastroenteritis	1	1	2
Abdominal distension	1	2	1
Nervous system disorders			
Headache[2]	14	15	14
Dizziness	5	6	8
Somnolence	2	4	5
Paresthesia	1	1	2

System Organ Class Preferred Term	Placebo N=967 (%)	VIIBRYD 20 mg/day N=288 (%)	VIIBRYD 40 mg/day N=978 (%)
Psychiatric disorders			
Insomnia	2	7	6
Abnormal dreams	2	2	3
Restlessness[3]	1	2	3
General disorders			
Fatigue	3	4	3
Cardiac disorders			
Palpitations	<1	1	2
Metabolism and nutrition disorders			
Increased appetite	1	1	3
Musculoskeletal and connective tissue disorders			
Arthralgia	1	2	1
Investigations			
Increased weight	1	1	2

[1] Includes abdominal discomfort, abdominal pain upper, and abdominal pain.

[2] Includes headache and tension headache

[3] Includes restlessness, akathisia, and restless legs syndrome

Sexual adverse reactions are presented in Table 2

Gastrointestinal

The most frequent gastrointestinal events reported in vilazodone treated patients were diarrhea (28.1% vs 9.5% in placebo), nausea (23.4% vs. 6.8% in placebo) and vomiting (4.7% vs 1.7% in placebo). No serious adverse reactions occurred in the four placebo-controlled studies. The onset of diarrhea and nausea occurred mostly during the initial 2-week titration period and median duration was 5 days for nausea (mean duration of 15 days) and 8 days for diarrhea (mean duration of 19 days). Approximately half of the vomiting occurred in the initial 2 weeks of treatment and the median duration was 1 day (mean duration of 3.4 days). Adverse reactions related to gastrointestinal disorders led to discontinuation in 3.2% of all vilazodone-treated patients versus 0.6% of placebo patients.

In the 52-week open label study, the most frequently occurring adverse events were diarrhea (35.7%), nausea (31.6%), dry mouth (11.0%) and vomiting (7.3%). The majority of events were either mild or moderate in intensity. Only one patient experienced serious gastrointestinal adverse event of duodenal stenosis. Adverse Events related to Gastrointestinal Disorders led to discontinuation in 4.0% of vilazodone treated patients in this 52-week study.

Discontinuation symptoms

Discontinuation symptoms were evaluated in 4 placebo-controlled trials (8 or 10 weeks in duration) following both abrupt discontinuation (2 studies) and gradual discontinuation over a 2-week period (2 studies). Discontinuation of vilazodone was associated with a somewhat greater incidence of adverse events vs. placebo in general. No specific adverse event occurred at a rate of 1% or greater and there was no discernible pattern seen with respect to specific system, organ, or class. When discontinuing VIIBRYD, a gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible. See 4.2.3 Discontinuing Treatment.

Cardiovascular parameters

Blood Pressure
VIIBRYD and placebo groups in MDD patients participating in the 4 placebo-controlled studies were compared with respect to mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in blood pressure or heart rate associated with VIIBRYD treatment.

In a randomized, placebo- and positive-controlled, parallel group, ECG assessment study in 157 healthy subjects, serial blood pressure assessments were conducted. VIIBRYD treatment was associated with statistically significant, dose-dependent increases in systolic blood pressure at doses of 20 mg/day and higher and statistically significant, dose-dependent increases in diastolic blood pressure at doses of 40 mg/day and higher. The maximum mean difference from placebo in systolic blood pressure of 4.4 mmHg (90% CI 1.7, 7.2) for VIIBRYD 20 mg/day and 5.3 mmHg (90% CI 2.5, 8.1) for VIIBRYD 40 mg/day were observed. The maximum mean difference from placebo in diastolic blood pressure of 0.8 mmHg (90% CI -1.4, 3.0) for VIIBRYD 20 mg/day and 3.9 mmHg (90% CI 1.4, 6.3) for VIIBRYD 40 mg/day were observed. See 10 CLINICAL PHARMACOLOGY.

In the pooled short-term studies in MDD, the mean change in systolic blood pressure from baseline to last assessment was 0.3 mmHg for all vilazodone doses combined and -0.2 mmHg for placebo. For vilazodone 20 mg alone the mean change was 0.2 mmHg. In the long term open-label 52 week study in MDD, the mean change in systolic blood pressure from baseline to last assessment was 0.4 mmHg for vilazodone 40 mg.

Electrocardiograms
At the end of the double-blind treatment period, mean changes in all ECG parameters (ventricular heart rate, QRS, PR, and QT intervals) were similar among vilazodone- and placebo-treated patients.

The effects of vilazodone on ECG interval and haemodynamic parameters were studied in a randomized, placebo- and positive-controlled, parallel group ECG assessment study performed in 157 healthy subjects. See 10.2 Pharmacodynamics.

Weight
In the four placebo-controlled 8 to 10-week studies, slight mean changes in body weight were observed in the vilazodone 20-mg (+ 0.59 kg) and 40-mg (+ 0.32 kg) groups compared with placebo (+ 0.22 kg). The proportion of patients with a weight increase of ≥ 7% were 1.7% in 20 mg group, 1.3 % in 40 mg group and 1.0% in the placebo group. The proportion of patients with a weight decrease of ≥ 7% were 1.7% in 20 mg group, 0.7 % in 40 mg group and 0.7% in the placebo group.

In the 52 week open-label study, mean weight increased mildly over time. The mean increase in weight from baseline at the last visit (mean duration: 31 weeks) for all patients who entered the study was 1.0 kg. However, the mean increase in weight from baseline at Week 52 was 1.7 kg. Weight change was generally consistent with the results from the four 8 or 10-week, placebo-controlled clinical studies.

Sexual Function
While changes in sexual function often occur as a manifestation of depression, they may also be a consequence of pharmacologic treatment. The incidence of self-reported adverse sexual reactions was low and similar to placebo in clinical studies, as measured by the total score on either the ASEX (Arizona Sexual Experiences Scale) or the CSFQ (Changes in Sexual Function Questionnaire). Reported effects were generally mild and transient in nature. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies. Table 2 shows the incidence of adverse reactions associated with sexual dysfunction in the placebo-controlled studies.

Table 2: Common Sexual Adverse Reactions Occurring in ≥ 2% of VIIBRYD-treated Patients and Greater than the Rate of Placebo-Treated Patients

Preferred Term	Males			Females		
	Placebo N=416	VIIBRYD 20 mg/day N=122	VIIBRYD 40 mg/day N=417	Placebo N=551	VIIBRYD 20 mg/day N=166	VIIBRYD 40 mg/day N=561
Abnormal Orgasm*	<1%	2%	2%	0%	1%	1%
Erectile dysfunction	1%	0%	3%	-	-	-
Libido decreased	<1%	3%	4%	<1%	2%	2%
Ejaculation disorder	0%	1%	2%	-	-	-

- Not applicable*Includes abnormal orgasm and anorgasmia

Because adverse reactions related to sexual function are believed to be voluntarily underreported, validated measures (the Arizona Sexual Experiences Scale and the Changes in Sexual Function Questionnaire) designed to identify sexual side effects of antidepressants were used prospectively in the placebo-controlled trials. Physicians should routinely inquire about possible sexual side effects. See 14 CLINICAL TRIALS.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Two 8-week, randomized, placebo-controlled, double-blind safety and efficacy studies and one 26-week, open-label safety study of VIIBRYD in pediatric patients (aged 7 – 17) with MDD found few differences in the safety profile of adults in comparison to pediatrics. Notable differences occurring in ≥ 2% of pediatric subjects, at a greater rate than placebo, and not reported in Table 1 include nightmare, suicidal ideation, irritability, sedation, heart rate increased, and initial insomnia.

8.3 Less Common Clinical Trial Adverse Reactions (<2%)

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*: tachycardia, ventricular extrasystoles

Eye disorders: *infrequent:* dry eye, vision blurred; *rare:* cataract

General disorders: *frequent*: feeling jittery, *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *infrequent:* decreased appetite

Musculoskeletal and connective tissue disorders: *frequent*: muscle spasm

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

Psychiatric disorders: *infrequent*: panic attack

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval 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:

Gastrointestinal system - acute pancreatitis

General disorders - irritability

Nervous System disorders - sleep paralysis

Psychiatric disorders - aggression, agitation, anxiety, hallucinations, suicide attempt, suicidal ideation

Skin and subcutaneous tissue disorders - drug eruption, generalized rash, rash, urticaria

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
Monoamine Oxidase Inhibitors: **See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions**

9.2 Drug Interactions Overview

Vilazodone is primarily metabolized by CYP3A4, with minor contributions from CYP2C19 and CYP2D6. See 10.3, Pharmacokinetics; 9.4 Drug-Drug Interactions. Vilazodone is not a general inducer of CYP enzymes. In vitro studies indicate that vilazodone is a moderate inhibitor of CYP2C19 and CYP2D6. See 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

Alcohol: As with other psychotropic drugs, the use of alcohol by patients taking VIIBRYD is not recommended. See 9.4 Drug-Drug Interactions.

9.4 Drug-Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs)
VIIBRYD is contraindicated in patients taking MAOIs (including the antibiotic linezolid and the dye methylene blue), or within at least 14 days of discontinuation of MAOIs. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, and 4.1 Dosing Considerations.

Serotonergic Drugs
Based on the mechanism of action of vilazodone and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, tryptophan, triptans, lithium, St-John's Wort, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine. See 7 WARNINGS AND PRECAUTIONS.

Triptans ($5HT_1$ agonists)
Cases of life-threatening serotonin toxicity have been reported during combined use of SSRIs/SNRIs and triptans. 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 7 WARNINGS AND PRECAUTIONS.

Lithium and tryptophan
There have been reports of enhanced effects when antidepressants with serotonergic effect have been given together with lithium or tryptophan, therefore concomitant use of vilazodone with these medicinal products should be undertaken with caution.

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.

Drugs Affecting Platelet Function (e.g., NSAIDs, ASA and other anticoagulants)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued. See 7 WARNINGS AND PRECAUTIONS.

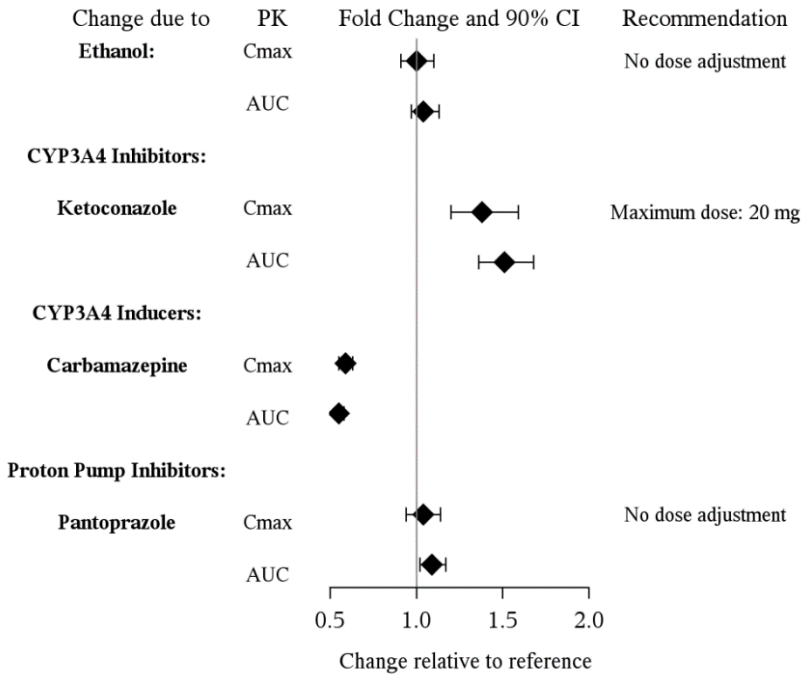
Potential for Other Drugs to Affect Vilazodone

Table 3: Summary of Effect of Co-administered Drugs on Exposure to Vilazodone

Co-administered Drug	Ref	Dose Schedule Clinical comment		Effect on VIIBRYD Pharmacokinetics		Recommendation
		Co-administered Drug	VIIBRYD	C_{max}	AUC	
Ethanol (alcohol)	CT	single 30 mL oral dose	single 40 mg dose	No change	No change	No VIIBRYD dose adjustment required
Pantoprazole (proton pump inhibitor)	CT	40 mg qd for 7 days	single 40 mg dose	No change	No change	No VIIBRYD dose adjustment required
Ketoconazole (strong CYP3A4 Inhibitor)	CT	200 mg qd for 13 days	single 5 or 10 mg dose	Increased by ~50%	Increased by ~50%	Maximum VIIBRYD dose is 20 mg. Readjust to original dose when strong CYP3A4 inhibitors are discontinued.
Carbamazepine (strong CYP3A4 Inducer)	CT	400 mg qd for 9 days	20 mg qd for 2 days followed by 40 mg qd for 7 days	Decreased by 41%	Decreased by 45%	No VIIBRYD dose adjustment required
Inhibitors of other CYP enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2E1)	*In vitro*	N/A	N/A	N/A	N/A	In vitro studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone. No VIIBRYD dose adjustment required
Inhibitors of P-gp transporter	*In vitro*	N/A	N/A	N/A	N/A	In vitro studies demonstrated that vilazodone is not a substrate of P-glycoprotein. No VIIBRYD dose adjustment required

Legend: CT = Clinical Trial

Figure 1: Impact of Other Drugs on Vilazodone Pharmacokinetics



Potential for Vilazodone to Affect Other Drugs

Table 4: Summary of Effect of VIIBRYD on Exposure to Co-administered Drugs

Co-administered Drug	Ref	Dose Schedule Clinical comment		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	VIIBRYD	C_{max}	AUC	
Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19	CT	Caffeine 100 mg single dose, flurbiprofen 50 mg single dose, nifedipine, 20 mg single dose debrisoquine 10 mg single dose	VIIBRYD 20 mg for 8-10 days	No change	No change	No VIIBRYD dose adjustment required

Co-administered Drug	Ref	Dose Schedule Clinical comment		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	VIIBRYD	C_{max}	AUC	
Drugs metabolized by CYP2C19	CT	Mephenytoin 100 mg single dose	VIIBRYD 20 mg for 8-10 days	Mephenytoin bioconversion increased by 11%, suggestive of a minor induction of CYP2C19.		No VIIBRYD dose adjustment required
Drugs metabolized by CYP2C8	In vitro	N/A	N/A	In vitro studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8.		Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug.
Induction of CYP isoforms	In vitro	N/A	Hepatocytes were exposed to 60 µM vilazodone (approximately 200-times the plasma C_{max} with 40 mg qd dosing in humans) for 24, 48, and 60 hours.	Vilazodone did not induce CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, or CYP3A5 isoforms.		No VIIBRYD dose adjustment required
Digoxin (Substrate of P-glycoprotein)	CT	Digoxin single 0.5 mg dose	VIIBRYD 40 mg qd for 10 days	Increased by 18%	Increased by 8%	Since digoxin has a narrow therapeutic range, monitoring is recommended

Legend: CT = Clinical Trial

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

9.5 Drug-Food Interactions

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. See10.3 Pharmacokinetics.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

St. John's Wort
Concomitant use of antidepressants with serotonergic effect and herbal remedies containing St. John´s Wort (Hypericum perforatum) may result in an increased incidence of adverse reactions including serotonin toxicity. See 7 WARNINGS AND PRECAUTIONS. St. John's Wort is also known as an inducer of CYP3A4. See 9.4 Drug-Drug Interactions.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VIIBRYD is both a selective serotonin reuptake inhibitor and a partial agonist of the 5-hydroxytryptamine1A (5HT1A) receptors. The precise mechanism of the antidepressant effect of VIIBRYD is not fully understood but presumed to be related to enhancement of serotonergic activity in the central nervous system.

10.2 Pharmacodynamics

VIIBRYD selectively binds with high affinity to, and inhibits, serotonin reuptake sites (Ki=0.1 nM; IC50=1.6 nM). Viladozone also exhibits partial agonist activity at 5HT1A receptors (IC50=2.1 nM). Vilazodone is more selective for inhibition of serotonin reuptake than dopamine (Ki=37 nM) or norepinephrine (Ki=56 nM) reuptake.

Cardiac Electrophysiology and Haemodynamics
The effects of vilazodone on ECG interval and haemodynamic parameters were studied in a randomized, placebo- and positive-controlled (moxifloxacin 400 mg), parallel group ECG assessment study performed in 157 healthy subjects to evaluate QT prolongation. Subjects randomized to vilazodone treatment (N=66) received sequential ascending doses of 10 mg/day, 20 mg/day, 40 mg/day, 60 mg/day, and 80 mg/day over a 15 day period, with each dose being administered for three days. ECG assessments were performed at 13 timepoints at baseline and on the third day of administration of the vilazodone at therapeutic doses of 20 mg and 40 mg and at supratherapeutic doses of 60 mg and 80 mg and at corresponding days in the control groups.

Vilazodone was associated with a concentration-dependent increase in heart rate, with statistically significant differences from placebo at supratherapeutic doses of 60 mg/day and higher. On day 15, during treatment with vilazodone at supratherapeutic doses of 80 mg, statistically significant increases in ventricular heart rate were observed from 3-6 h post-dosing, with a maximum mean difference from placebo of 7.6 bpm (90% CI 5.9, 9.3) at 6 h.

Vilazodone was associated with shortening of the PR interval at doses of 20 mg/day and higher. On day 9, during treatment with vilazodone 40 mg, statistically significant negative mean differences from placebo were observed at 10 of 13 timepoints, with a maximum mean difference from placebo of -5.9 ms (90% CI -7.8, -3.9) at 8 h. On day 15, during treatment with vilazodone 80 mg, statistically significant negative mean differences from placebo were observed at 10 of 13 timepoints, with a maximum mean difference from placebo of -8.2 ms (90% CI -10.3, -6.1) at 6 h.

No consistent or dose-dependent effects on the QTc interval or QRS duration were observed.

Vilazodone was associated with transient increases in systolic blood pressure at doses of 20 mg/day and higher. At 30 min post-dosing on the third day of each sequential ascending dose treatment, statistically significant mean differences from placebo in systolic blood pressure were observed with vilazodone. Statistically significant and dose-dependent increases in diastolic blood pressure were observed at vilazodone doses of 40 mg/day and higher (see Table 5).

Table 5: Change from Baseline in Blood Pressure[a]

	Systolic BP (mmHg) Mean Change from Baseline (90% CI)			Diastolic BP (mmHg) Mean Change from Baseline (90% CI)		
Dose	Placebo	Vilazodone	Difference	Placebo	Vilazodone	Difference
20 mg	-1.1 (-3.2, 1.0)	3.3 (1.5, 5.1)	4.4[b] (1.7, 7.2)	-2.0 (-3.9, -0.1)	-1.5 (-3.1, 0.1)	0.5 (-2.0, 3.0)
40 mg	-3.1 (-5.3, -0.9)	2.0 (0.1, 3.8)	5.0[b] (2.2, 7.9)	-3.3 (-5.3, -1.4)	-1.6 (-3.2, 0.1)	1.7 (-0.8, 4.3)
60 mg	-1.1 (-3.3, 1.1)	6.0 (4.1, 7.9)	7.1[b] (4.2, 10.0)	-2.2 (-4.0, -0.4)	0.8 (-0.7, 2.3)	3.0[c] (0.7, 5.4)
80 mg	-4.3 (-6.6, -1.9)	2.5 (0.5, 4.6)	6.8[b] (3.7, 9.9)	-4.7 (-6.6, -2.9)	-0.1 (-1.7, 1.5)	4.6[b] (2.2, 7.1)

a: Based on the measurement at 30 minutes post dosing on the third day of the corresponding dose.
b: $p < 0.01$
c: $p < 0.05$

In pooled short-term studies in 2,233 MDD patients, the mean changes between baseline and end of treatment in heart rate, PR-Interval, QRS duration, QTc interval, systolic blood pressure, and diastolic blood pressure were similar in patients who received vilazodone or placebo. The mean change in systolic blood pressure from baseline to last assessment was 0.3 mmHg for all Vilazodone doses combined and -0.2 mmHg for placebo. The mean change in diastolic blood pressure from baseline to last assessment was 0.9 mmHg for all vilazodone doses combined and 0.2 mmHg for placebo.

10.3 Pharmacokinetics

Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone, after administration of once daily VIIBRYD doses, 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 (Tmax) 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%).

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: VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase) 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, inducers of CYP3A4 can decrease vilazodone exposure. See 9.4 Drug-Drug Interactions.

Elimination

VIIBRYD is eliminated primarily by hepatic metabolism, with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone.

Special Populations and Conditions

Pediatrics (< 18 years of age): The safety and efficacy of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients. See 7.1.3 Pediatrics.

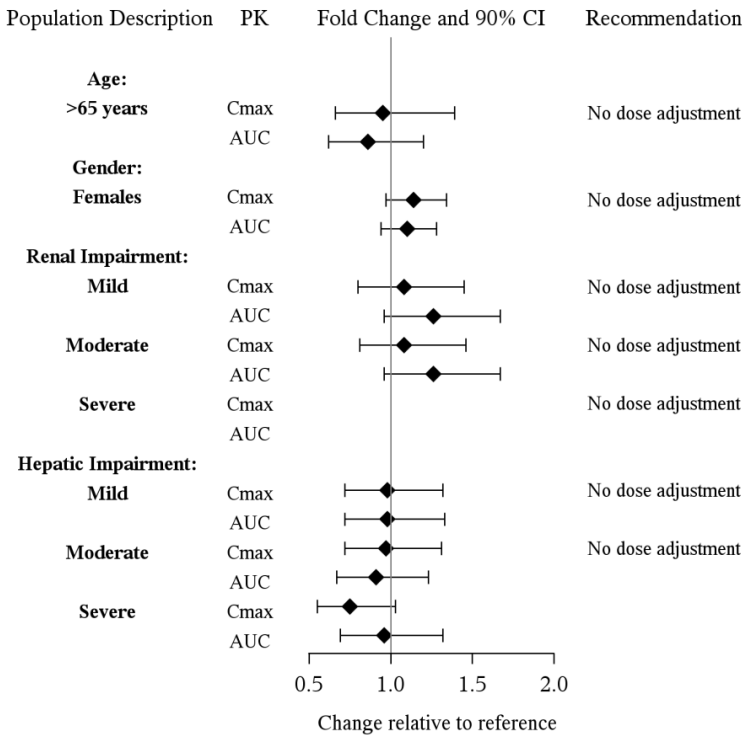
Geriatrics (> 65 years of age): No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (65 to 80 years old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

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

Hepatic Insufficiency: After administration of a 20 mg dose to subjects with mild (Child-Pugh A: score = 5 – 6; n=8) hepatic impairment or moderate (Child Pugh B: score = 7 – 9; n=8) hepatic impairment, ratios of vilazodone C_{max} and AUC relative to healthy matches were 0.977 to 0.980 for mild/healthy and 0.895 to 0.972 for moderate/healthy comparisons. After administration of a 20 mg dose to subjects with severe (Child-Pugh C: score = 10 – 15; n= 8) hepatic impairment, half (n=4) of the impaired subjects vomited within 2 to 4 hours of dosing, preventing assessment of PK in these patients. The geometric mean ratios of vilazodone C_{max} and AUC were 0.750 and 0.960, respectively, for subjects with severe hepatic impairment (who did not vomit; n=4) versus subjects with normal hepatic function. In mild or moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). Caution should be exercised if patients with severe hepatic impairment are treated.

Renal Insufficiency: After administration of a 20 mg dose, the presence of mild (50 mL/min < GFR ≤ 80 mL/min) to moderate (30 mL/min< GFR ≤ 50 mL/min) renal impairment did not affect the apparent clearance of vilazodone. Ratios of vilazodone C_{max} and AUC were 1.076 to 1.286 for mildly impaired subjects relative to their matches, and 1.083 to 1.098 for moderate impairment relative to their matches. In mild, moderate or severe renal impairment, no dose adjustment is necessary (see Figure 2).

Figure 2: Impact of Intrinsic factors on Vilazodone Pharmacokinetics



The data shown for elderly subjects (>65 years) are relative to younger subjects (24 - 55 years).
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

Animal Pharmacology

The pharmacology of vilazodone was studied to characterize its serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibition, receptor binding, regulation of 5-HT neurotransmission and effects in animal models of depression and anxiety. Vilazodone combines serotonin reuptake inhibition with partial agonism of 5-HT1A receptors.

Vilazodone inhibited 5-HT reuptake in rat brain synaptosomes with an IC50 of 0.2 nM and was relatively weaker in the inhibition of the reuptake of norepinephrine (IC50 = 60 nM) and dopamine (IC50 = 90 nM). Following oral administration, vilazodone blocked 5-HT reuptake with an ED50 = 1.4 mg/kg in mice. In an ex vivo study in rats, 3 mg/kg and 10 mg/kg of orally-administered vilazodone produced approximately 50% and 90% occupancy of cortical 5-HT1A receptors, respectively. In rat brain slices, vilazodone produced different levels of agonist activity that were region-dependent. Along with other ex vivo and in vivo studies, the findings suggest that vilazodone is a partial agonist at 5-HT1A receptors with both similarities to, and differences from, known 5-HT1A receptor agonists.

Antidepressant effects of vilazodone have been demonstrated in behavioral despair tests in both mice and rats and in the tail suspension test in mice. Vilazodone demonstrated activity in some, but not all tests, in anti-anxiety models, including footshock induced vocalizations, mouse four plate test, and light-dark box.

Safety pharmacology studies were conducted to assess central nervous system (CNS), cardiovascular, and gastrointestinal effects as well as the effects of vilazodone on isolated tissues and on drug dependence. After oral administration at 36-360 mg/kg, vilazodone hydrochloride showed CNS stimulation (increased locomotion) in rats and mice and had no effect on gastric transit, gastric emptying, or gastric acid secretion in rats. Vilazodone hydrochloride had no sedative or cholinergic effects in mice or effects on blood pressure or heart rate in spontaneously hypertensive rats at doses up to 100 mg/kg administered orally. In isolated tissue preparations, vilazodone had no anticholinergic or antiserotoninergic effects and showed weak antihistaminic, spasmolytic, and negative inotropic activities. There was no indication of abuse liability for vilazodone in three rodent models assessing potential for drug dependence. Plasma vilazodone hydrochloride concentrations were not determined in these studies, but oral dosing at 25 mg/kg in the rat would approximate therapeutic exposures at the MHRD.

The pharmacokinetics of vilazodone were studied in mice, rats, pregnant rats, pregnant rabbits, dogs, monkeys, and humans. Vilazodone was absorbed after oral administration with plasma exposure in all species sufficient for assessing pharmacological effects and establishing toxicological safety margins, although bioavailabilty in all toxicology species was low (5 to 28% compared to 72-81% in humans). Serum protein binding was determined in vitro using rat, dog, mouse, monkey, and human serum and was high (>96%) in all species tested. Tissue distribution of vilazodone and/or total radioactivity following a single oral or intravenous dose of 14C vilazodone was evaluated in mice and rats, with levels of vilazodone measured in select tissues as part of repeat-dose toxicology studies in mice, rats, and dogs. The volumes of distribution were greater than total body water in all species, including humans, and ranged from 4-8 L/kg indicating that vilazodone is widely distributed into tissues. Plasma clearance ranged from 0.2-3L/h/kg. In pregnant rats administered 14C labelled vilozadone as a single oral or IV dose, 0.14-0.76% of was recovered in fetuses up to 24 hours post dose indicating limited placental transfer. Suckling pups contained up to 0.42% of the dose administered to lactating rats suggesting limited secretion via milk.

The biotransformation of vilazodone was studied in vitro and in vivo in mice, rats, rabbits, dogs, monkeys, and humans. In all species, including humans, vilazodone was extensively metabolized. The primary route of excretion of vilazodone-related material in the non-human species was fecal, which is the primary route in humans. Vilazodone was not a significant inducer of hepatic microsomal enzymes in mice.

11 STORAGE, STABILITY AND DISPOSAL

VIIBRYD tablets should be stored at controlled room temperature (15-30°C).

Keep out of reach and sight of children.

Disposal of VIIBRYD tablets should be in keeping with recommendations governing the disposal of pharmaceutical biohazardous waste.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

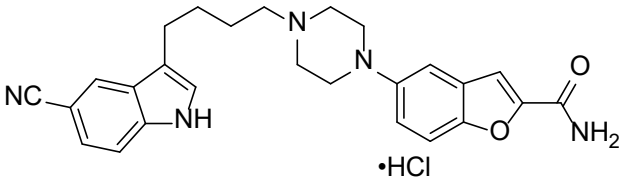
Drug Substance

Proper name: Vilazodone hydrochloride

Chemical name: 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)

Molecular formula and molecular weight: $C_{26}H_{27}N_5O_2 \times HCl$; 477.99 (vilazodone hydrochloride)

Structural formula:



Physicochemical properties:

Description: White to cream-coloured solid.

Solubility: Water (32 mg/100 mL)
Physiological NaCl solution (0.2 mg/100 mL)
Simulated gastric fluid (0.2 mg/100 mL)
Simulated intestinal fluid (0.04 mg/100 mL)
Ethanol (31 mg/100 mL)

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of VIIBRYD (vilazodone hydrochloride) as a treatment for major depressive disorder (MDD) was demonstrated in four 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.

Three 8-week studies evaluated the efficacy of VIIBRYD 40 mg (Studies 1-3) and one 10-week study (Study 4) evaluated the efficacy of VIIBRYD 20 mg and 40 mg. In these studies, patients were randomized to either VIIBRYD 20 mg, 40 mg, or placebo once daily with food. Patients were either titrated over 1 week to a dose of 20 mg daily or over 2 weeks to a dose of 40 mg daily of VIIBRYD with food. The designs of the four studies are summarized in Table 6.

The main inclusion criteria were a HAM-D-17 score of ≥ 22 and a HAM-D item 1 (depressed mood) score of ≥ 2 at the screening and baseline visits in Studies 1 and 2 and a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 26 in Studies 3 and 4.

Table 6: Summary of Clinical Studies Supporting Efficacy of VIIBRYD in the Treatment of MDD (Intent-to-Treat Population)

Study #	Trial Design/Duration	Oral Dosage (once daily)	Number of Study Subjects (N) [Female/Male (F/M)]	Mean Age (Range)	Mean Baseline MADRS Score
1	8-week, multicenter, parallel, double-blind, randomized, placebo-controlled	VIIBRYD titrated to 40 mg, or placebo	N= 397 40 mg: n=198 Placebo: n=199 [251 F/ 146 M]	40.1 (18-65)	31
2	8-week, multicenter, parallel, double-blind, randomized, placebo-controlled	VIIBRYD titrated to 40 mg, or placebo	N= 463 40 mg: n=231 Placebo: n=232 [261 F/ 202 kM]	41.7 (18-70)	32
3	8-week, multicenter, parallel, double-blind, randomized, placebo-controlled	VIIBRYD titrated to 40 mg, or placebo	N=505 40 mg: n=253 Placebo: n=252 [272 F/233 M]	40.1 (18-69)	31
4	10-week, multicenter, parallel, double-blind, randomized, placebo- and active-controlled	VIIBRYD titrated to 20 mg or 40 mg, or Citalopram 40 mg, or placebo	N=1133 20 mg: n=288 40 mg: n=284 Citalopram: n=280 Placebo: n=281 [651 F/482 M]	41.8 (18-70)	31

The primary efficacy parameter in all studies was the change in total score from baseline to week 8 (Studies 1-3) or week 10 (Study 4) in the Montgomery-Asberg Depression Rating Scale (MADRS). The secondary efficacy parameter in Studies 3 and 4 was the change from baseline in the Clinical Global Impression-Severity (CGI-S) score.

14.2 Study Results

In the four studies, VIIBRYD demonstrated superiority over placebo in the improvement of depressive symptoms as measured by the change from baseline to endpoint visit in the MADRS total score (see Table 7).

Table 7: Efficacy of VIIBRYD in the Treatment of MDD (Intent-to-Treat Population)

Endpoints	Study 1	Study 2	Study 3	Study 4	
	VIIBRYD 40 mg	VIIBRYD 40 mg	VIIBRYD 40 mg	VIIBRYD 20 mg	VIIBRYD 40 mg
MADRS Total Score[a] (Change from baseline)					
LSMD	-3.2	-2.5	-5.1	-2.6	-2.8
95% CI	(-5.2, -1.3)	(-4.4, -0.6)	(-6.9, -3.3)	(-4.3, -0.8)	(-4.6, -1.1)
p-value	0.0010	0.0093	<0.00001	0.0073[b]	0.0034[b]

a: Analyses for Studies 1 and 2 were based on Last Observation Carried Forward at the end of double-blind treatment. Studies 3 and 4 were based on Observed Cases at the end of double-blind treatment.
b: Adjusted p-value to control multiplicity
LSMD = Least Square Mean Difference; CI = Confidence Interval

Results of the secondary efficacy parameter CGI-S Score (studies 3 and 4) was supportive of the primary efficacy results.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

GENERAL TOXICOLOGY

Single-Dose Toxicity
Vilazodone has a low level of acute toxicity in mice and rats with no mortality after oral dosing of 1500 mg/kg in mice and 5000 mg/kg in rats. The dog appears more susceptible to the effects of vilazodone and intravenous administration of ≥0.25 mg/kg resulted in vocalization, full body tremors, fully dilated pupils, and agitation.

Repeat-Dose Toxicity
Vilazodone hydrochloride was well tolerated after repeated oral dosing in mice and rats with no vilazodone-related clinical signs at 580 mg/kg/day in mice and no mortality at 1000 mg/kg/day in rats. In rats, reddening of hairless skin areas at ≥3 mg/kg/day was noted post-dose daily throughout dosing periods (up to 26 weeks). In the dog, salivation, fearfulness, hypokinesia, and/or mydriasis were observed at ≥10 mg/kg/day. The signs were transient and not present with continued dosing from Week 4 onwards. In the 52 week study, there were 4 deaths at 40 mg/kg/day occurring during Weeks 9 through 50. Convulsions preceding death were observed in 3 of these animals and vilazodone exposure at this dose was 7 to 24 times higher than that at MRHD (maximum recommended human dose). Corneal opacities were noted in some dogs at 10 and 40 mg/kg/day. The corneal opacities were sometimes noted in one eye only and did not progress or persist with repeated dosing. No other treatment-related ocular effects were observed during ophthalmologic examinations in the dogs and there were no treatment-related ocular findings in rats.

There were no effects of vilazodone on heart rate, blood pressure, or ECG morphology and intervals collected in dogs at the approximate C_{max} (2 h post dose) after repeated dosing at

levels up to 40 mg/kg/day for 52 weeks.

Clinical pathology changes were generally slight, not always consistent between studies and/or seen in one sex only.

There were no test article related histopathological findings in the dog at dose levels up to 40 mg/kg/day. After 13 weeks of dosing, slight to severe histiocytosis in the intestine and abdominal lymphatic system were noted at ≥270 mg/kg/day in the mouse and ≥300 mg/kg/day in the rat. The histiocytes had a generally vacuolated cytoplasm and the vacuoles had an appearance of crystal clefts consistent with intracytoplasmic storage of vilazodone or its metabolites. In the mouse, but not the rat, erythropoiesis in the spleen and myeloid hyperplasia in the bone marrow were noted, probably a systemic reaction to the inflammatory condition. In the mouse, after 13 weeks of dosing, slight hypertrophy of the ovaries and/or increased number of corpora lutea, slight to moderate atrophy of the uterine endometrium, and mammary gland hyperplasia and ductal dilation with increased secretory material were noted at ≥135 mg/kg/day and mild hyperplasia of the mammary gland and increased number of corpora lutea were noted at 45 and 135 mg/kg/day. In the 26-week rat study, at ≥15 mg/kg/day, there was low incidence of mammary secretion in males and mammary atrophy in a single male at 75 mg/kg/day.

All adverse findings in the repeat dose toxicity studies occurred at vilazodone systemic exposures exceeding exposure after clinical use. The margin of safety for vilazodone based on exposure at the NOAEL (no-observed adverse-effect level) in the nonclinical species was ≥2 compared to vilazodone exposures at MHRD.

Carcinogenicity

Carcinogenicity studies were conducted in which oral doses of vilazodone of 15, 45, and 135 mg/kg/day were administered to B6C3F1 mice and doses of 7.5, 25, 65, and 150 mg/kg/day were given to Wistar rats for 2 years. The high doses are approximately 16.5 and 36 times MRHD on a mg/m2 basis, in mice and rats, respectively.

In mice, the incidence of malignant mammary gland tumors was increased in females at 45 and 135 mg/kg/day with systemic exposure to vilazodone at the 15 mg/kg/day NOEL about twice that at the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone at comparable vilazodone doses/systemic exposure. Increases in prolactin levels are known to cause mammary tumors in rodents.

The incidence of hepatocellular adenomas and/or carcinomas was increased in males and/or females at all dose levels. Increased incidences of thyroid gland follicular cell hyperplasia in males and/or females at all dose levels and adenomas in males and females given 45 and 145 mg/kg/day were observed. The low dose of 15 mg/kg/day was a NOEL for increased incidences of thyroid follicular adenomas at which systemic exposure to vilazodone was about double that at the MRHD. The mechanism for the increased hepatic and thyroid tumors in mice is not known. Thyroid tumors can result from higher plasma TSH levels in rodents, which is a mechanism that is generally considered not relevant for humans; however the evidence for increased TSH after vilazodone administration to mice was minimal and inconsistent. Vilazodone was not a significant inducer of hepatic microsomal drug metabolizing enzymes.

In the rat study, vilazodone was not carcinogenic in either sex.

Genotoxicity

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.

Reproductive and Developmental Toxicology

Fertility was evaluated separately in male and female rats at vilazodone hydrochloide dose levels of 5, 25, and 125 mg/kg/day. Fertility was not affected in female rats at dosages as high as 125 mg/kg/day at which systemic exposure to vilazodone was estimated to be about 10 times that at the MRHD. At this same 125 mg/kg/day dose, the fertility of male rats was impaired, with systemic exposure to vilazodone at the no effect dose level of 25 mg/kg/day predicted to be about 4 times that at the MRHD.

When vilazodone was administered during the period of organogenesis to pregnant rats at dose levels of 8, 40, and 200 mg/kg/day and rabbits at 1.6, 7.8, and 35.8 mg/kg/day no teratogenic effects were observed. However, embryofetal toxicity evident from lower fetal body weight gain and delayed skeletal ossification occurred at the high dose in rats and at the mid and high dose levels in rabbits. Systemic exposure to vilazodone hydrochloride at the no-effect dose of 40 mg/kg/day in rats was about 6 times that at the MRHD and at the no-effect dose of 1.6 mg/kg/day in rabbits less than that at the MRHD.

When vilazodone was administered to pregnant rats at 5, 25, and 125 mg/kg/day during the period of organogenesis and throughout pregnancy and lactation, maternal and developmental toxicity, including reduced pup survival and delayed maturation, was observed at all dose levels and therefore a no-effect dose level was not identified. Impairment of reproductive performance in the F1 generation was confined to the high dose of 125 mg/kg/day, with systemic exposure to vilazodone hydrochloride at the no-effect dose of 25 mg/kg/day estimated to be about 4 times that at the MRHD.

In a juvenile toxicology study conducted in rats, oral vilazodone hydrochloride doses of 10, 50, and 200 mg/kg/day were administered from postnatal day 21 to 90. The 50 mg/kg/day dose was a no-effect level for physical development at which the systemic exposures to vilazodone were 10 and 15 times that at the MRHD in male and female rats, respectively. The 10 mg/kg/day dose was a no-effect level for F1 neurobehavioral development (impaired auditory startle response at higher doses) at which the systemic exposures were slightly below and above that at the MRHD in male and female rats, respectively. The 200 mg/kg/day dose was a no-effect level for reproductive toxicity at which the systemic exposures were 18 and 28 times that at the MRHD in male and female rats, respectively.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVIIBRYD®
vilazodone hydrochloride tablets

Read this carefully before you start taking **VIIBRYD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VIIBRYD**.

What is VIIBRYD used for?

VIIBRYD has been prescribed for you by your healthcare professional to relieve your symptoms of depression which may include:
- feeling sad
- loss of interest in usual activities
- significant change in weight or appetite
- change in sleeping habits
- having a hard time concentrating
- feeling tired
- having suicidal thoughts

How does VIIBRYD work?
VIIBRYD is an antidepressant medication. It is thought to work by increasing the activity of serotonin in your brain. Serotonin is a brain chemical that helps to improve mood. It works at two different receptors in the brain.

What are the ingredients in VIIBRYD?
Medicinal ingredients: vilazodone hydrochloride
Non-medicinal ingredients: colloidal silicon dioxide, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only), FD&C Red #40 (10 mg only), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

VIIBRYD comes in the following dosage forms:
- 10 mg tablets (pink), 20 mg tablets (orange), 40 mg tablets (blue)

Do not use VIIBRYD if:
- you are allergic to any of the ingredients in VIIBRYD.
- you take a Monoamine Oxidase Inhibitor (MAOI).
    - Ask your healthcare professional or pharmacist if you are not sure if you take a MAOI.
    - Examples of MAOIs include linezolid which is an antibiotic, methylene blue which is a dye used in certain surgeries.
    - If you stopped taking a MAOI within the last 14 days, only start VIIBRYD if your healthcare professional tells you to.
    - Do not take a MAOI within 14 days of stopping VIIBRYD unless directed to do so by your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VIIBRYD. Talk about any health conditions or problems you may have, including if you:

- are taking or have recently taken a monoamine oxidase inhibitor (MAOI)
- have high blood pressure that is not controlled by your medication or any heart problems
- have a history of drug abuse
- have a bleeding disorder
- take certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin, dabigatran), acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (e.g., ibuprofen)
- have or had seizures or convulsions
- have glaucoma or increased pressure in your eyes
- have suicidal thoughts
- have a family history of mania or bipolar disorder
- are pregnant or plan to become pregnant. It is not known if VIIBRYD will harm your unborn baby. Talk to your healthcare professional 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 professional should decide if you should take VIIBRYD while breastfeeding.
- have any other medical conditions

VIIBRYD is not for use in children under 18 years of age.

Other warnings you should know about:
It is important to talk to your healthcare professional about the risks of treating depression and also the risk of not treating it. You should discuss all treatment options with your healthcare professional.

New or Worsened Emotional or Behaviour Problems:
Treatment with these types of medications is most safe and effective when you and your healthcare professional have good communication about how you are feeling. You may find it helpful to tell a relative or close friend that you are depressed. You might ask them to tell you if they think you are getting worse or if they are worried about changes in your behavior.

Some patients may feel worse instead of better when they first start taking drugs like VIIBRYD or when changing the dose. You may have:

- new or worsened feelings of nervousness, tension, anger, agitation, or aggression
- thoughts about suicide, hurting yourself or other people. Thoughts and actions about suicide can occur especially if you have had thoughts of hurting yourself in the past. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. **If this happens, seek immediate medical help**. Do NOT stop taking VIIBRYD on your own.

Effects on pregnancy and newborns:
If you are pregnant or are planning to become pregnant while taking VIIBRYD, talk to your healthcare professional about the risks and benefits of various treatment options. It is very important that you keep taking VIIBRYD until your healthcare professional tells you to stop.

When pregnant women took drugs in the same group of medications as VIIBRYD, some newborn babies had complications at birth. This happened especially when the medication was taken in the last three months of pregnancy. Some newborns:

- required breathing support, tube feeding and a longer stay in the hospital
- had difficulty feeding or breathing, seizures, tense or overly relaxed muscles and were jittery and cried constantly
- had a serious condition called persistent pulmonary hypertension. This made the babies breathe faster and appear blue in color.

These symptoms normally go away over time. However, if your baby experiences any of these symptoms, consult your healthcare professional as soon as possible.

Risk of breaking a bone
You should tell your doctor if you:

- are elderly and had a recent bone fracture or
- were told you have osteoporosis or risk factors for osteoporosis.

Taking VIIBRYD may increase your risk of breaking a bone if you are elderly or have osteoporosis or have other major risk factors for breaking a bone. This is especially true when you first start taking VIIBRYD and soon after you stop taking it. Take extra care to avoid falling, especially if you get dizzy or have low blood pressure.

Discontinuation Symptoms:
If your healthcare professional recommends that you stop taking VIIBRYD, they will gradually lower the dose of VIIBRYD you are taking. This may help manage any symptoms of discontinuation, such as:

- dizziness, headache, ringing in the ears, seizures
- nausea, diarrhea, vomiting
- tingling, burning, or prickling sensation of your skin, excessive sweating
- feeling nervous, confused, irritated, restless, or having an unstable mood
- fatigue, insomnia (inability to sleep), nightmares

These symptoms will usually disappear without needing treatment. Tell your healthcare professional immediately if you have these or any other symptoms. Your healthcare professional may adjust the dosage of VIIBRYD to alleviate the symptoms.

Serotonin toxicity (also known as Serotonin syndrome): VIIBRYD can cause Serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin toxicity if you take VIIBRYD with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;

- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Driving and Using Machines:
VIIBRYD can make you feel sleepy or may affect your ability to think clearly, make decisions or react quickly. Wait until you know how you feel after you have taken VIIBRYD before you drive or use heavy machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
- other antidepressants
- other drugs that affect serotonin such as lithium, linezolid, sibutramine, tryptophan, triptans, St. John's Wort
- certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin, dabigatran), acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (e.g., ibuprofen)
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine
- certain medicines used to treat cough, such as dextromethorphan
- when taking certain medicines such as antifungals (e.g. ketoconazole); antibiotics (e.g. erythromycin) or medicines used to treat seizures (carbamazepine). Your healthcare professional may adjust your dose of VIIBRYD when taking these medicines.
- mephenytoin
- diuretics

You should avoid drinking alcohol while taking VIIBRYD.

How to take VIIBRYD:
It is important to take VIIBRYD exactly as your healthcare professional has told you. Your healthcare professional may need to change the dose until it is right for you.
- Always take VIIBRYD with food. VIIBRYD may not work as well if you take it on an empty stomach.
- Even if you feel better, do not stop taking VIIBRYD without talking to your healthcare professional.
- It is important to keep taking VIIBRYD as recommended by your healthcare professional.

Usual dose:
The usual adult dose is 20 mg to 40 mg once a day:
- For the first 7 days, the dose is one 10 mg tablet once a day.
- After 7 days, you will take a 20 mg tablet once a day.
- If you are still not feeling better, your healthcare professional may increase your dose to a 40 mg tablet taken once a day.

Overdose:

If you think you have taken too much VIIBRYD, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
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.

What are possible side effects from using VIIBRYD?

These are not all the possible side effects you may feel when taking VIIBRYD. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects in people who take VIIBRYD include:

- diarrhea
- nausea or vomiting
- trouble sleeping

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Mania/Hypomania**: elevated or irritated mood, decreased need for sleep, racing thoughts		✓	
Seizures: loss of consciousness with uncontrollable shaking			✓
RARE **Serotonin toxicity:** a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (> 38°C), or rigid muscles			✓
Glaucoma: increased pressure in the eyes, eye pain and blurred vision		✓	
Low sodium level in blood: symptoms of tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles		✓	
UNKNOWN **Allergic reaction:** red skin, hives, itching, swelling of the lips, face, tongue or throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Low platelets: bruising or unusual bleeding from the skin or other areas		✓	
New or worsened Emotional or Behavioural Problems: feeling angry, aggressive, worried, agitated, hostile or impulsive. Feeling violent or suicidal. Thoughts of hurting yourself or other people. Feeling like you are not yourself or that you are less inhibited			✓
Swelling of the pancreas: symptoms include pain in your upper abdomen that may extend to your back, nausea and vomiting, fever, increased heart rate and loss of appetite			✓
Sleep paralysis: temporary inability to move or talk for up to several minutes while you are going to sleep or waking up		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store VIIBRYD at room temperature (15-30°C).

Keep out of reach and sight of children.

If you want more information about VIIBRYD:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.allergan.ca, or by calling 1-800-668-6424.

This leaflet was prepared by Allergan Inc.

Last Revised March 03, 2021