HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KHEDEZLA safely and effectively. See full prescribing information for KHEDEZLA.

KHEDEZLA (desvenlafaxine) Extended-release Tablets, for oral use
Initial U.S. Approval: 2008

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)**.
- **KHEDEZLA is not approved for use in pediatric patients (8.4)**.

INDICATIONS AND USAGE

KHEDEZLA is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder (MDD) (1).

DOSAGE AND ADMINISTRATION

- Recommended dose: 50 mg once daily with or without food (2.1).
- There was no evidence that doses greater than 50 mg per day confer any additional benefit (2.1).
- Discontinuation: Reduce dose gradually whenever possible (2.1).
- Take tablets whole: Do not divide, crush, chew, or dissolve (2.1).
- Moderate renal impairment: Maximum dose 50 mg per day (2.2)
- Severe renal impairment and end-stage renal disease: Maximum dose 50 mg every other day (2.2).
- Moderate to severe hepatic impairment: Maximum dose 100 mg per day (2.2).

DOSAGE FORMS AND STRENGTHS

- Extended-release tablets: 50 mg and 100 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the KHEDEZLA Extended-release Tablets formulation (4).
- *Serotonin syndrome and MAOIs*: Do not use MAOIs intended to treat psychiatric disorders with KHEDEZLA or within 7 days of stopping treatment with KHEDEZLA. Do not use KHEDEZLA within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start KHEDEZLA in a patient who is being treated with linezolid or intravenous methylene blue (4).

WARNINGS AND PRECAUTIONS

- *Serotonin Syndrome:* Serotonin syndrome has been reported with SSRIs and SNRIs, including with KHEDEZLA, 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 KHEDEZLA and initiate supportive treatment. If concomitant use of KHEDEZLA 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).
- *Elevated Blood Pressure:* Control hypertension before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- *Abnormal Bleeding:* KHEDEZLA may increase risk of bleeding events. Caution patients about risk of bleeding associated with concomitant use of KHEDEZLA and NSAIDs, aspirin, or other drugs that affect coagulation (5.4).
- *Narrow-angle Glaucoma:* Mydriasis has occurred with desvenlafaxine. Monitor patients with raised intraocular pressure or those at risk of angle-closure glaucoma (5.5).
- *Activation of Mania/Hypomania:* Use cautiously in patients with Bipolar Disorder. Caution patients about risk of activation of mania/hypomania (5.6).
- *Discontinuation Syndrome:* Taper dose when possible and monitor for discontinuation symptoms (5.7).
- *Seizure:* Can occur. Use cautiously in patients with seizure disorder (5.8).
- *Hyponatremia:* Can occur in association with SIADH (5.9).
- *Interstitial Lung Disease and Eosinophilic Pneumonia:* Can occur (5.10).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5% and twice the rate of placebo in the 50 or 100 mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pernix Therapeutics, LLC at 1-877-745-3667 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3).
- Geriatric Use: There is an increased incidence of orthostatic hypotension in desvenlafaxine treated patients ≥ 65 years (6.1 and 8.5).

See 17 for Patient Counseling Information and Medication Guide

Revised: 02/2014

KHEDEZLA
(desvenlafaxine)
Extended-release Tablets
PC4623EP

4623EP

KHEDEZLA
(desvenlafaxine)
Extended-release Tablets
PC4623EP

FULL PRESCRIBING INFORMATION:
CONTENTS *

* 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 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)]*.**

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

1 INDICATIONS AND USAGE

KHEDEZLA, a serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) *[see Clinical Studies (14)* and *Dosage and Administration (2.1)]*. The efficacy of desvenlafaxine has been established in four short-term (8-week, placebo-controlled studies) in adult outpatients who met DSM-IV criteria for major depressive disorder.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended dose for KHEDEZLA is 50 mg once daily, with or without food.

In clinical studies, doses of 50 mg to 400 mg per day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg per day and adverse reactions and discontinuations were more frequent at higher doses.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms *[see Dosage and Administration (2.4)* and *Warnings and Precautions (5.7)]*.

KHEDEZLA should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

2.2 Special Populations

Patients with renal impairment

The maximum recommended dose in patients with moderate renal impairment (24-hr creatinine clearance [CrCl] = 30 to 50 mL/min, Cockcroft-Gault [C-G]) is 50 mg per day. The maximum recommended dose in patients with severe renal impairment (24-hr CrCl less than 30 mL/min, C-G) or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis *[see Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

Patients with hepatic impairment

The recommended dose in patients with moderate to severe hepatic impairment is 50 mg per day. Dose escalation above 100 mg per day is not recommended *[see Clinical Pharmacology (12.3)]*.

2.3 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be periodically reassessed to determine the need for continued treatment.

2.4 Discontinuing KHEDEZLA

Symptoms associated with discontinuation of KHEDEZLA, other SNRIs and SSRIs have been reported *[see Warnings and Precautions (5.7)]*. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

2.5 Switching Patients From Other Antidepressants to KHEDEZLA

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

2.6 Switching Patients 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 KHEDEZLA. Conversely, at least 7 days should be allowed after stopping KHEDEZLA before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)]*.

Use of KHEDEZLA with other MAOIs such as Linezolid or Methylene Blue

Do not start KHEDEZLA in a patient who is being treated with linezolid or intravenous methylene blue because there is 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)]*.

In some cases, a patient already receiving KHEDEZLA 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, KHEDEZLA should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 7 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with KHEDEZLA 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 KHEDEZLA 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

KHEDEZLA (desvenlafaxine) Extended-release Tablets are available as 50 and 100 mg tablets.
- 50 mg, pink round tablet debossed with "OS" on one side and "231" on the other side.
- 100 mg, brown round tablet debossed with "OS" on one side and "232" on the other side.

4 CONTRAINDICATIONS

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the KHEDEZLA Extended-release Tablets formulation. Angioedema has been reported in patients treated with desvenlafaxine *[see Adverse Reactions (6.1)]*.
- The use of MAOIs intended to treat psychiatric disorders with KHEDEZLA or within 7 days of stopping treatment with KHEDEZLA is contraindicated because of an increased risk of serotonin syndrome. The use of KHEDEZLA within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.6)* and *Warnings and Precautions (5.2)]*.

Starting KHEDEZLA 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 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 (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 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 Dosage and Administration (2.4)* and *Warnings and Precautions (5.7)]*.

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 KHEDEZLA should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening patients for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that KHEDEZLA 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 desvenlafaxine, 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).

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 KHEDEZLA with MAOIs intended to treat psychiatric disorders is contraindicated. KHEDEZLA 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 a MAOI such as linezolid or intravenous methylene blue in a patient taking KHEDEZLA. KHEDEZLA should be discontinued before initiating treatment with the MAOI *[see Contraindications (4)* and *Dosage and Administration (2.6)]*.

If concomitant use of KHEDEZLA 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 KHEDEZLA and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Elevated Blood Pressure

Patients receiving KHEDEZLA should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies *[see Adverse Reactions (6.1)]*. Pre-existing hypertension should be controlled before initiating treatment with desvenlafaxine. Caution should be exercised in treating patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine.

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving KHEDEZLA, either dose reduction or discontinuation should be considered *[see Adverse Reactions (6.1)]*.

5.4 Abnormal Bleeding

SSRIs and SNRIs, including KHEDEZLA, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, 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 desvenlafaxine and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Narrow-angle Glaucoma

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

5.6 Activation of Mania/Hypomania

During all MDD phase 2 and phase 3 studies, mania was reported for approximately 0.02% of patients treated with desvenlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, KHEDEZLA should be used cautiously in patients with a history or family history of mania or hypomania.

5.7 Discontinuation Syndrome

Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with desvenlafaxine during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy.

During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (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.

Patients should be monitored for these symptoms when discontinuing treatment with KHEDEZLA. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate *[see Dosage and Administration (2.4)* and *Adverse Reactions (6.1)]*.

5.8 Seizure

Cases of seizure have been reported in pre-marketing clinical studies with desvenlafaxine. Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical studies. KHEDEZLA should be prescribed with caution in patients with a seizure disorder.

5.9 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including KHEDEZLA. In many cases, this 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 *[see Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.3)]*. Discontinuation of KHEDEZLA should be considered 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.

5.10 Interstitial Lung Disease and Eosinophilic Pneumonia

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of desvenlafaxine) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with KHEDEZLA who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of KHEDEZLA should be considered.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.
- Hypersensitivity *[see Contraindications (4)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Elevated Blood Pressure *[see Warnings and Precautions (5.3)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.4)]*
- Narrow-Angle Glaucoma *[see Warnings and Precautions (5.5)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[see Warnings and Precautions (5.7)]*
- Seizure *[see Warnings and Precautions (5.8)]*
- Hyponatremia *[see Warnings and Precautions (5.9)]*
- Interstitial Lung Disease and Eosinophilic Pneumonia *[see Warnings and Precautions (5.10)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, 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 the rates observed in clinical practice.

Patient exposure

Desvenlafaxine was evaluated for safety in 4,158 patients diagnosed with major depressive disorder who participated in multiple-dose pre-marketing studies, representing 1,677 patient-years of exposure. Among these 4,158 desvenlafaxine treated patients; 1,834 patients were exposed to desvenlafaxine in 8-week, placebo-controlled studies at doses ranging from 50 to 400 mg/day. Out of the 1,834 patients, 687 desvenlafaxine treated patients continued into a 10-month open-label study. Of the total 4,158 patients exposed to at least one dose of desvenlafaxine; 1,320 were exposed to desvenlafaxine for 6 months, representing 1058 patient-years of exposure, and 274 were exposed for one year, representing 241 patient-years of exposure.

Adverse reactions reported as reasons for discontinuation of treatment

In the pooled 8-week placebo-controlled studies in patients with MDD, 12% of the 1,834 patients who received desvenlafaxine (50 to 400 mg) discontinued treatment due to an adverse reaction, compared with 3% of the 1,116 placebo-treated patients. At the recommended dose of 50 mg, the discontinuation rate due to an adverse reaction for desvenlafaxine (4.1%) was similar to the rate for placebo (3.8%). For the 100 mg dose of desvenlafaxine the discontinuation rate due to an adverse reaction was 8.7%.

The most common adverse reactions leading to discontinuation in at least 2% and at a rate greater than placebo of the desvenlafaxine treated patients in the short-term studies, up to 8 weeks, were: nausea (4%); dizziness, headache and vomiting (2% each); in the longer-term studies, up to 11 months, the most common was vomiting (2%).

Common adverse reactions in placebo-controlled MDD studies

The most commonly observed adverse reactions in desvenlafaxine treated MDD patients in short-term fixed-dose studies (incidence ≥ 5% and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Table 2 shows the incidence of common adverse reactions that occurred in ≥ 2% of desvenlafaxine treated MDD patients and twice the rate of placebo at any dose in the pooled 8-week, placebo-controlled, fixed dose clinical studies.

Table 2: Common Adverse Reactions
(≥ 2% in any Fixed-Dose Group and Twice the Rate of Placebo)
in Pooled MDD 8-Week Placebo-Controlled Studies

		Percentage of Patients Reporting Reaction			
		Desvenlafaxine			
System Organ Class Preferred Term	Placebo (n=636)	50 mg (n=317)	100 mg (n=424)	200 mg (n=307)	400 mg (n=317)
Cardiac disorders					
Blood pressure increased	1	1	1	2	2
Gastrointestinal disorders					
Nausea	10	22	26	36	41
Dry mouth	9	11	17	21	25
Constipation	4	9	9	10	14
Vomiting	3	3	4	6	9
General disorders and administration site conditions					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
Metabolism and nutrition disorders					
Decreased appetite	2	5	8	10	10
Nervous system disorders					
Dizziness	5	13	10	15	16
Somnolence	4	4	9	12	12
Tremor	2	2	3	9	9
Disturbance in attention	<1	<1	1	2	1
Psychiatric disorders					
Insomnia	6	9	12	14	15
Anxiety	2	3	5	4	4
Nervousness	1	<1	1	2	2
Abnormal dreams	1	2	3	2	4
Renal and urinary disorders					
Urinary hesitation	0	<1	1	2	2
Respiratory, thoracic and mediastinal disorders					
Yawning	<1	1	1	4	3
Skin and subcutaneous tissue disorders					
Hyperhidrosis	4	10	11	18	21
Special Senses					
Vision blurred	1	3	4	4	4
Mydriasis	<1	2	2	6	6
Vertigo	1	2	1	5	3
Tinnitus	1	2	1	1	2
Dysgeusia	1	1	1	1	2
Vascular disorders					
Hot flush	<1	1	1	2	2

Sexual function adverse reactions

Table 3 shows the incidence of sexual function adverse reactions that occurred in ≥ 2% of desvenlafaxine treated MDD patients in any fixed-dose group (pooled 8-week, placebo-controlled, fixed and flexible-dose, clinical studies).

Table 3: Sexual Function Adverse Reactions
(≥ 2% in Men or Women in any Desvenlafaxine Group) During the On-Therapy Period

		Desvenlafaxine			
	Placebo (n=239)	50 mg (n=108)	100 mg (n=157)	200 mg (n=131)	400 mg (n=154)
Men only					
Anorgasmia	0	0	3	5	8
Libido decreased	1	4	5	6	3
Orgasm abnormal	0	0	1	2	3
Ejaculation delayed	<1	1	5	7	6
Erectile dysfunction	1	3	6	8	11
Ejaculation disorder	0	0	1	2	5
Ejaculation failure	0	1	0	2	2
Sexual dysfunction	0	1	0	0	2
		Desvenlafaxine			
	Placebo (n=397)	50 mg (n=209)	100 mg (n=267)	200 mg (n=176)	400 mg (n=163)
Women only					
Anorgasmia	0	1	1	0	3

Other adverse reactions observed in clinical studies

Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of < 2% in MDD patients treated with desvenlafaxine were:

Cardiac disorders – tachycardia.
General disorders and administration site conditions – Asthenia.
Investigations **–** Weight increased, liver function test abnormal, blood prolactin increased.
Musculoskeletal and connective tissue disorders **–** Musculoskeletal stiffness.
Nervous system disorders **–** Syncope, convulsion, dystonia.
Psychiatric disorders **–** Depersonalization, bruxism.
Renal and urinary disorders – Urinary retention.
Skin and subcutaneous tissue disorders **–** Rash, alopecia, photosensitivity reaction, angioedema.

In clinical studies, there were uncommon reports of ischemic cardiac adverse reactions, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo.

Laboratory, ECG and vital sign changes observed in MDD clinical studies

The following changes were observed in placebo-controlled, short-term MDD studies with desvenlafaxine.

Lipids

Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant.

The percentage of patients who exceeded a predetermined threshold value is shown in Table 4.

Table 4: Incidence (%) of Patients With Lipid Abnormalities of Potential Clinical Significance*

		Desvenlafaxine			
	Placebo	50 mg	100 mg	200 mg	400 mg
Total Cholesterol *(Increase of ≥ 50 mg/dl and an absolute value of ≥ 261 mg/dl)	2	3	4	4	10
LDL Cholesterol *(Increase ≥ 50 mg/dl and an absolute value of ≥ 190 mg/dl)	0	1	0	1	2
Triglycerides, fasting *(Fasting: ≥ 327 mg/dl)	3	2	1	4	6

Proteinuria

Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 5). This proteinuria was not associated with increases in BUN or creatinine and was generally transient.

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Table 5: Incidence (%) of Patients with Proteinuria in the Fixed-dose Clinical Studies

		Desvenlafaxine			
	Placebo	50 mg	100 mg	200 mg	400 mg
Proteinuria	4	6	8	5	7

Vital sign changes
Table 6 summarizes the changes that were observed in placebo-controlled, short-term, pre-marketing studies with desvenlafaxine in patients with MDD (doses 50 to 400 mg).

Table 6: Mean Changes in Vital Signs at Final on Therapy for All Short-term, Fixed-dose Controlled Studies

		Desvenlafaxine			
	Placebo	50 mg	100 mg	200 mg	400 mg
Blood pressure					
Supine systolic bp (mm Hg)	-1.4	1.2	2.0	2.5	2.1
Supine diastolic bp (mm Hg)	-0.6	0.7	0.8	1.8	2.3
Pulse rate					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
Weight (kg)	0.0	-0.4	-0.6	-0.9	-1.1

Treatment with desvenlafaxine at all doses from 50 mg/day to 400 mg/day in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits (see Table 7). Analyses of patients in desvenlafaxine short-term controlled studies who met criteria for sustained hypertension revealed a consistent increase in the proportion of patients who developed sustained hypertension. This was seen at all doses with a suggestion of a higher rate at 400 mg/day.

Table 7: Proportion of Patients with Sustained Elevation of Supine Diastolic Blood Pressure

Treatment Group	Proportion of Patients with Sustained Hypertension
Placebo	0.5%
Desvenlafaxine 50 mg/day	1.3%
Desvenlafaxine 100 mg/day	0.7%
Desvenlafaxine 200 mg/day	1.1%
Desvenlafaxine 400 mg/day	2.3%

Orthostatic hypotension
In the short-term, placebo-controlled clinical studies with doses of 50 to 400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving desvenlafaxine (8%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving desvenlafaxine (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218).

6.2 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of desvenlafaxine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Skin and subcutaneous tissue disorders – Stevens-Johnson syndrome.

7 DRUG INTERACTIONS
7.1 Monoamine Oxidase Inhibitors (MAOIs)
Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to desvenlafaxine (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI *[see Dosage and Administration (2.6), Contraindications (4)* and *Warnings and Precautions (5.2)]*.

7.2 Serotonergic Drugs
Based on the mechanism of action of KHEDEZLA and the potential for serotonin syndrome, caution is advised when KHEDEZLA is co-administered with other drugs that may affect the serotonergic neurotransmitter systems *[see Dosage and Administration (2.6), Contraindications (4)* and *Warnings and Precautions (5.2)]*.

7.3 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 that 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 co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when KHEDEZLA is initiated or discontinued *[see Warnings and Precautions (5.4)]*.

7.4 Potential for Desvenlafaxine to Affect Other Drugs
Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Substrates primarily metabolized by CYP2D6 (e.g., desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine) should be dosed at the original level when co-administered with KHEDEZLA 100 mg or lower. Reduce the dose of these substrates by one-half if co-administered with 400 mg of KHEDEZLA. The substrate dose should be increased to the original level when 400 mg of KHEDEZLA is discontinued.

7.5 Other Drugs Containing Desvenlafaxine or Venlafaxine
Avoid use of KHEDEZLA with other desvenlafaxine-containing products or venlafaxine products. The concomitant use of KHEDEZLA with other desvenlafaxine-containing products or venlafaxine will increase desvenlafaxine blood levels and increase dose-related adverse reactions *[see Adverse Reactions (6)]*.

7.6 Ethanol
A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking KHEDEZLA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C

Risk summary
There are no adequate and well-controlled studies of KHEDEZLA in pregnant women. In reproductive developmental studies in rats and rabbits with desvenlafaxine succinate, evidence of teratogenicity was not observed at doses up to 30 times a human dose of 100 mg/day (on a mg/m^2 basis) in rats, and up to 15 times a human dose of 100 mg/day (on a mg/m^2 basis) in rabbits. An increase in rat pup deaths was seen during the first 4 days of lactation when dosing occurred during gestation and lactation, at doses greater than 10 times a human dose of 100 mg/day (on a mg/m^2 basis). KHEDEZLA should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Clinical considerations
A prospective longitudinal study of 201 women with history of major depression who were euthymic at the beginning of pregnancy, showed women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Human data
Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Animal data
When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 300 mg/kg/day and 75 mg/kg/day, respectively, no teratogenic effects were observed. These doses are 30 times a human dose of 100 mg/day (on a mg/m^2 basis) in rats and 15 times a human dose of 100 mg/day (on a mg/m^2 basis) in rabbits. However, fetal weights were decreased and skeletal ossification was delayed in rats in association with maternal toxicity at the highest dose, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m^2 basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation at the highest dose of 300 mg/kg/day. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 10 times a human dose of 100 mg/day (on a mg/m^2 basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine succinate at a dose 30 times a human dose of 100 mg/day (on a mg/m^2 basis).

8.3 Nursing Mothers
Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from desvenlafaxine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established *[see Boxed Warning and Warnings and Precautions (5.1)]*. Anyone considering the use of KHEDEZLA in a child or adolescent must balance the potential risks with the clinical need.

8.5 Geriatric Use
Of the 4,158 patients in clinical studies with desvenlafaxine, 6% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with desvenlafaxine *[see Adverse Reactions (6)]*. For elderly patients, possible reduced renal clearance of KHEDEZLA should be considered when determining dose *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

SSRIs and SNRIs, including desvenlafaxine, 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 (5.9)]*.

8.6 Renal Impairment
In subjects with renal impairment the clearance of desvenlafaxine was decreased. In subjects with severe renal impairment (24-hr CrCl <30 mL/min, Cockcroft-Gault) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to desvenlafaxine; therefore, dosage adjustment is recommended in these patients *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
The mean terminal half life ($t_{1/2}$) changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with moderate to severe hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
KHEDEZLA is not a controlled substance.

10 OVERDOSAGE
10.1 Human Experience with Overdosage
There is limited clinical trial experience with desvenlafaxine succinate overdosage in humans. However, desvenlafaxine is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of desvenlafaxine) is presented below; the identical information can be found in the Overdosage section of the venlafaxine package insert.

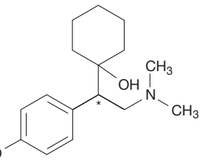
In postmarketing experience, overdose with venlafaxine (the parent drug of desvenlafaxine) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear.

10.2 Management of Overdosage
No specific antidotes for KHEDEZLA are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION
KHEDEZLA Extended-release Tablets for oral administration contains desvenlafaxine, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a medication used to treat major depressive disorder.

Desvenlafaxine is designated *RS*-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of $C_{16}H_{25}NO_2$. Desvenlafaxine has a molecular weight of 263.38. The structural formula is shown below.



* Chiral Centre

Desvenlafaxine is a white to off-white crystalline powder that is sparingly soluble in dimethyl sulfoxide. The solubility of desvenlafaxine is pH dependent.

KHEDEZLA is formulated as an extended-release tablet for once-a-day oral administration.

Each 50 mg or 100 mg extended-release tablet contains 50 or 100 mg of desvenlafaxine, respectively.

Inactive ingredients for the 50 mg tablet consist of citric acid monohydrate, hypromellose, microcrystalline cellulose, talc, magnesium stearate and colloidal silicon dioxide, and film coating, which consist of titanium dioxide, polyethylene glycol, talc, polyvinyl alcohol and iron oxides.

Inactive ingredients for the 100 mg tablet consist of citric acid monohydrate, hypromellose, microcrystalline cellulose, talc, magnesium stearate and colloidal silicon dioxide, and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, talc, polyvinyl alcohol, iron oxides, and FD&C yellow #6.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The exact mechanism of the antidepressant action of KHEDEZLA is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake. Non-clinical studies have shown that desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI).

12.2 Pharmacodynamics
Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro*. Desvenlafaxine also lacked monoamine oxidase (MAO) inhibitory activity.

ECG changes
Electrocardiograms were obtained from 1,492 desvenlafaxine treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between desvenlafaxine treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval.

12.3 Pharmacokinetics
The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

The mean ± SD terminal half-life, $t_{1/2}$, after administration of KHEDEZLA is about 9.5 ± 1.5 hours. The median (range) time to peak concentration (T_{max}) is 6 (3 – 14) hours after administration of 50 mg KHEDEZLA.

Absorption and Distribution
KHEDEZLA 50 mg and 100 mg demonstrated similar exposures (C_{max}, AUC) to a 50 mg and 100 mg extended-release desvenlafaxine succinate product, respectively.

The absolute oral bioavailability after the administration of desvenlafaxine succinate is about 80%. There was no clinically significant food effect seen when KHEDEZLA was administered with a high fat meal. Therefore, KHEDEZLA can be taken without regard to meals *[see Dosage and Administration (2.1)]*.

The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. The desvenlafaxine volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

Metabolism and Elimination
Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

Drug Interaction Studies
Inhibitors of CYP3A4 (ketoconazole)
CYP3A4 is a minor pathway for the metabolism of desvenlafaxine. In a clinical study, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine (400 mg single dose) by about 43% and C_{max} by about 8%. Concomitant use of KHEDEZLA with potent inhibitors of CYP3A4 may result in higher concentrations of desvenlafaxine.

Inhibitors of other CYP enzymes
Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of KHEDEZLA.

Drugs metabolized by CYP2D6 (e.g. desipramine, dextromethorphan, metoprolol, atomoxetine)
In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the C_{max} and AUC of desipramine increased approximately 25% and 17%, respectively. When 400 mg (8 times the recommended 50 mg dose) was administered, the C_{max} and AUC of desipramine increased approximately 50% and 90%, respectively. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug *[see Drug Interactions (7.4)]*.

Drugs metabolized by CYP3A4 (midazolam)
In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. In a clinical study, desvenlafaxine 400 mg daily (8 times the recommended 50 mg dose) was co-administered with a single 4 mg dose of midazolam (a CYP3A4 substrate). The AUC and C_{max} of midazolam decreased by approximately 31% and 16%, respectively. Concomitant use of KHEDEZLA with a drug metabolized by CYP3A4 can result in lower exposures to that drug.

Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19
In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes.

In vitro, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of KHEDEZLA are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and KHEDEZLA is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter.

Special Populations
Age
In a study of healthy subjects administered doses of up to 300 mg, there was an approximate 32% increase in C_{max} and a 55% increase in AUC in subjects older than 75 years of age (n = 17), compared with subjects 18 to 45 years of age (n = 16). Subjects 65 to 75 years of age (n = 15) had no change in C_{max}, but an approximately 32% increase in AUC, compared to subjects 18 to 45 years of age *[see Dosage and Administration (2.2)]*.

Gender
In a study of healthy subjects administered doses of up to 300 mg, women had an approximately 25% higher C_{max} and an approximately 10% higher AUC than age-matched men. No adjustment of dosage on the basis of gender is needed.

Race
Pharmacokinetic analysis showed that race (White, n = 466; Black, n = 97; Hispanic, n = 39; Other, n = 33) had no apparent effect on the pharmacokinetics of desvenlafaxine. No adjustment of dosage on the basis of race is needed.

Hepatic insufficiency
The disposition of desvenlafaxine succinate after administration of 100 mg was studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and to healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were similar in subjects with mild hepatic impairment and healthy subjects (< 5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5% difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended *[see Use in Specific Populations (8.7)]*.

Renal insufficiency
The disposition of desvenlafaxine after administration of 100 mg was studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) (n = 9) requiring dialysis and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Increases in AUCs of about 42% in mild renal impairment (24-hr CrCl = 50 to 80 mL/min, Cockcroft-Gault [C-G]), about 56% in moderate renal impairment (24-hr CrCl = 30 to 50 mL/min, C-G), about 108% in severe renal impairment (24-hr CrCl ≤30 mL/min, C-G), and about 116% in ESRD subjects were observed, compared with healthy, age-matched control subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the control subjects to approximately 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively. Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure.

The maximum recommended dose in patients with moderate renal impairment is 50 mg per day. Dosage adjustment of 50 mg every other day is recommended in patients with severe renal impairment or ESRD. *[see Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Desvenlafaxine succinate administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumors in either study.

Mice received desvenlafaxine succinate at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose is 15 times a human dose of 100 mg/day on a mg/m^2 basis.

Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose is 29 (males) or 48 (females) times a human dose of 100 mg/day on a mg/m^2 basis.

Mutagenesis
Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

Impairment of fertility
When desvenlafaxine succinate was administered orally to male and female rats, fertility was reduced at the high dose of 300 mg/kg/day, which is 30 times a human dose of 100 mg/day (on a mg/m^2 basis). There was no effect on fertility at 100 mg/kg/day, approximately 10 times a human dose of 100 mg/day (on a mg/m^2 basis).

14 CLINICAL STUDIES
The efficacy of desvenlafaxine as a treatment for depression was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies (at doses of 50 mg/day to 400 mg/day) in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder. In the first study, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of desvenlafaxine once daily, or placebo (n = 118). In a second study, patients received either 200 mg (n = 121) or 400 mg (n = 124) of desvenlafaxine once daily, or placebo (n = 124). In two additional studies, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of desvenlafaxine once daily, or placebo (n = 150 and n = 161).

Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) total score in four studies and overall improvement, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg/day and 100 mg/day there was no suggestion of a greater effect with the higher dose and adverse reactions and discontinuations were more frequent at higher doses *[see Dosage and Administration (2.1)]*.

Table 8: Primary Efficacy (HAM-D_{17}) Results for Short-term Studies

			Desvenlafaxine			
Study No.	**Primary Endpoint: HAM-D_{17}**	**Placebo**	**50 mg/day**	**100 mg/day**	**200 mg/day**	**400 mg/day**
1	Baseline Score (SD[a])	23.1 (2.5)		23.2 (2.5)	22.9 (2.4)	23.0 (2.2)
	Difference from Placebo (95% CI[c])			-2.9[b] (-5.1, -0.8)	-2.0	-3.1[b] (-5.2, -0.9)
2	Baseline Score (SD[a])	25.3 (2.3)			24.8 (2.9)	25.2 (3.2)
	Difference from Placebo (95% CI[c])				-3.3[b] (-5.3, -1.2)	-2.8[b] (-4.8, -0.7)
3	Baseline Score (SD[a])	23.0 (2.6)	23.4 (2.6)	23.4 (2.6)		
	Difference from Placebo (95% CI[c])		-1.9[b] (-3.5, -0.3)	-1.5		
4	Baseline Score (SD[a])	24.3 (2.6)	24.3 (2.4)	24.4 (2.7)		
	Difference from Placebo (95% CI[c])		-2.5[b] (-4.1, -0.9)	-3.0[b] (-4.7, -1.4)		

[a] Standard deviation;
[b] Adjusted p-value < 0.05;
[c] Difference between least squares means at final evaluation, calculated as drug response minus placebo response; unadjusted 95% confidence intervals

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these studies.

16 HOW SUPPLIED/STORAGE AND HANDLING
KHEDEZLA (desvenlafaxine) Extended-release Tablets are available as follows:

50 mg, pink, round tablet debossed with "OS" on one side and "231" on the other
NDC 65224-880-31, bottle of 30 tablets in unit-of-use package
NDC 65224-880-90, bottle of 90 tablets in unit-of-use package

100 mg, brown, round tablet debossed with "OS" on one side and "232" on the other
NDC 65224-890-31, bottle of 30 tablets in unit-of-use package
NDC 65224-890-90, bottle of 90 tablets in unit-of-use package

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

Each 50 mg or 100 mg KHEDEZLA Extended-release Tablet contains 50 or 100 mg of desvenlafaxine, respectively.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).
Advise patients, their families, and their caregivers about the benefits and risks associated with treatment with KHEDEZLA and counsel them in its appropriate use.

Advise patients, their families, 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.

Suicide Risk
Advise patients, their families and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Concomitant Medication
Advise patients taking KHEDEZLA Extended-release Tablets not to use concomitantly other products containing desvenlafaxine or venlafaxine. Healthcare professionals should instruct patients not to take KHEDEZLA with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping KHEDEZLA before starting an MAOI *[see Contraindications (4)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of KHEDEZLA with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John"s Wort supplements) *[see Warnings and Precautions (5.2)]*.

Elevated Blood Pressure
Advise patients that they should have regular monitoring of blood pressure when taking KHEDEZLA *[see Warnings and Precautions (5.3)]*.

Abnormal Bleeding
Patients should be cautioned about the concomitant use of KHEDEZLA 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 bleeding *[see Warnings and Precautions (5.4)]*.

Narrow-angle Glaucoma
Advise patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) that mydriasis has been reported and they should be monitored *[see Warnings and Precautions (5.5)]*.

Activation of Mania/Hypomania
Advise patients, their families and caregivers to observe for signs of activation of mania/hypomania *[see Warnings and Precautions (5.6)]*.

Discontinuation
Advise patients not to stop taking KHEDEZLA without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping desvenlafaxine *[see Warnings and Precautions (5.7)* and *Adverse Reactions (6.1)]*.

Switching Patients from Other Antidepressants to KHEDEZLA
Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

Interference with Cognitive and Motor Performance
Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that KHEDEZLA therapy does not adversely affect their ability to engage in such activities.

Alcohol
Advise patients to avoid alcohol while taking KHEDEZLA *[see Drug Interactions (7.6)]*.

Allergic Reactions
Advise patients to notify their physician if they develop allergic phenomena such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

Nursing
Advise patients to notify their physician if they are breastfeeding an infant *[see Use in Specific Populations (8.3)]*.

Residual Inert Matrix Tablet
Patients receiving KHEDEZLA may notice an inert matrix tablet passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

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