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

QUDEXY® XR (topiramate) extended-release capsules, for oral use
Initial U.S. Approval: 1996

---- RECENT MAJOR CHANGES ----
Indications and Usage, Adjunctive Therapy in Pediatric Patients 10 Years of Age and Older (12/2019)
Contraindications (12/2019)
Warnings and Precautions (5.4, 5.7, 5.8, 5.10) (02/2019)

---- INDICATIONS AND USAGE ----
QUDEXY XR is indicated for:
- Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older (1.1), adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age and older (1.2)
- Prophylaxis of migraine in patients 12 years of age and older (1.3)

---- DOSAGE AND ADMINISTRATION ----
- Qudexy XR initial dose, titration, and recommended maintenance dose varies by indication and age (2 through 16). See Full Prescribing Information for recommended dosage, and dosing considerations in patients with renal impairment, patients taking concomitant medications, or patients undergoing hemodialysis (2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7)
- Capsules may be swallowed whole or opened and sprinkled on a small amount of soft food (2.6).

---- DOSAGE FORMS AND STRENGTHS ----
Extended-release capsules: 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg (3)

---- CONTRAINDICATIONS ----
None (4)

---- WARNINGS AND PRECAUTIONS ----
- Acute myopia and secondary angle closure glaucoma: Monitor for visual loss. Discontinue QUDEXY XR as soon as possible (5.1)
- Visual field defects: consider discontinuation of QUDEXY XR (5.2)
- Oligohydrosis and hyperthermia: decrease monitoring and increased body temperature, especially in pediatric patients (5.3)
- Metabolic acidosis: baseline and periodic measurement of serum bicarbonate is recommended; consider dose reduction or discontinuation of QUDEXY XR if clinically appropriate (5.4)
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.5)
- Cognitive/neuropsychiatric adverse reactions: use caution when operating machinery including cars; depression and mood problems may result (5.6)
- Fetal toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age (5.7)
- Withdrawal of AEDs: withdraw QUDEXY XR gradually (5.8)
- Hyperammonemia/encephalopathy: measure ammonia if encephalopathic symptoms occur (5.9)
- Kidney stones: avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, or in patients on ketogenic diet (5.10)
- Hypothermia: has been reported with and without hyperammonemia; topiramate treatment with concomitant valproic acid (5.11)

---- ADVERSE REACTIONS ----
Epilepsy: The most common (≥10% more frequent than placebo or low-dose topiramate) adverse reactions in adult and pediatric patients were paresthesia, anorexia, weight loss, speech disorders/ related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision, and upper respiratory tract infection (6.1).

Migraine: Most common (≥5% more frequent than placebo) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, difficulty with attention, language perversion, diarrhea, hypoesthesia, hypoesthesia oral, pain, and upper respiratory tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Upsher-Smith Laboratories, LLC at 1-866-849-3758 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---- DRUG INTERACTIONS ----
- Oral contraceptives: decreased contraceptive efficacy and breakthrough bleeding, especially at doses greater than 200 mg per day (7.1)
- Monitor lithium levels if lithium is used with QUDEXY XR (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 2/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

QUDEXY XR is indicated as initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older *[See Clinical Studies (14.2)]*.

1.2 Adjunctive Therapy Epilepsy

QUDEXY XR is indicated as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age and older *[See Clinical Studies (14.2)]*.

1.3 Migraine

QUDEXY XR is indicated for the prophylaxis of migraine headache in patients 12 years of age and older *[See Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years of Age and Older

The recommended dose fully dose of QUDEXY XR as adjunctive therapy in adults with partial-onset or primary generalized tonic-clonic seizures is 200 mg per day, administered in the morning or evening. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 25 mg per day every week may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of QUDEXY XR as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 mg/kg/day or 250 mg/day, whichever is less. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 1 mg/kg/day to 3 mg/kg/day given nightly for the first two weeks may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of QUDEXY XR as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 mg/kg/day or 250 mg/day, whichever is less. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 1 mg/kg/day to 3 mg/kg/day given nightly for the first two weeks may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults 17 Years of Age and Older

The recommended total daily dose of QUDEXY XR as adjunctive therapy in adults with partial-onset or primary generalized tonic-clonic seizures is 200 mg per day, administered in the morning or evening. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 25 mg per day every week may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of QUDEXY XR as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 mg/kg/day or 250 mg/day, whichever is less. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 1 mg/kg/day to 3 mg/kg/day given nightly for the first two weeks may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of QUDEXY XR as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 mg/kg/day or 250 mg/day, whichever is less. Titrate to the effective dose in 25 mg per day increments. Titrating in increments of 1 mg/kg/day to 3 mg/kg/day given nightly for the first two weeks may allow the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset.

2.3 Dosing in Migraine Prophylaxis

The recommended total daily dose of QUDEXY XR as treatment for prophylaxis of migraine headache in adults and adolescents 12 years of age and older is 100 mg once daily. The recommended titration rate for QUDEXY XR for migraine prophylaxis is as follows:

Table 2: Migraine Prophylaxis Titration Schedule for Adults 18 Years of Age and Older

QUDEXY XR Once Daily Dose	
Week 1	25 mg
Week 2	50 mg
Week 3	75 mg
Week 4	100 mg

Dose and titration rate should be guided by clinical outcome. If required, increase between dose adjustment can be used.

2.4 Dose Modifications in Patients With Renal Impairment

In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m²), one-half of the usual adult dose of Qudexy XR is recommended *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

2.5 Dosage in Patients Undergoing Hemodialysis

To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of Qudexy XR may be required. The actual adjustment should take into account 1) the clearance rate of the hemodialysis system in the patient being dialyzed, 2) the effective renal clearance of topiramate in the patient being dialyzed *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.6 Administration Instructions

QUDEXY XR capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount of soft food. The drug/food mixture should be swallowed immediately and not chewed or crushed. It should not be stored for future use. QUDEXY XR can be taken without regard to meals *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

QUDEXY XR (topiramate) extended-release capsules are available in the following strengths and colors:
- 25 mg: light pink and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "25 mg" on the body in black ink
- 50 mg: golden yellow and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "50 mg" on the body in black ink
- 100 mg: reddish brown and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "100 mg" on the body in black ink
- 150 mg: pale yellow and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "150 mg" on the body in black ink
- 200 mg: brown and gray capsules, printed with "UPSHER-SMITH" on the cap in white ink and "200 mg" on the body in black ink

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 hour of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of QUDEXY XR as rapidly as possible, according to the treating physician's judgment. Other measures, in conjunction with discontinuation of QUDEXY XR, may be helpful.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

5.2 Visual Field Defects

Visual field defects independent of elevated intraocular pressure have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, visual field defects were reversible after topiramate discontinuation. If visual field problems occur at any time during treatment with topiramate, consideration should be given to discontinuation of QUDEXY XR.

5.3 Oligohydrosis and Hyperthermia

Oligohydrosis (decreased sweating), resulting in hospitalization in some cases, has been reported in association with topiramate. Decreased sweating and elevated body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in pediatric patients. Patients, especially pediatric patients, treated with QUDEXY XR should be monitored closely for evidence of decreased sweating and increased body temperature, especiallyin hot weather. Monitoring for such effects when QUDEXY XR is prescribed with other drugs that predispose patients to heat-related disorders; these include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

5.4 Metabolic Acidosis

QUDEXY XR can cause hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is characterized by decreased serum bicarbonate, anion gap hypokalemia, and hyperchloremia. Metabolic acidosis may occur with QUDEXY XR, QUDEXY XR-induced metabolic acidosis can occur at any time during treatment. In adult epilepsy monotherapy trials, metabolic acidosis was observed at 4 mEq/L at daily doses of 400 mg in adults and approximately 6 mg/kg/day in pediatric patients, which is the lowest dose studied in pediatric patients. Decreases of 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disease, status epilepticus, diarrhea, surgery, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of QUDEXY XR.

Metabolic acidosis was commonly observed in adult and pediatric patients treated with immediate-release topiramate in clinical trials. In adjunctive therapy in adult epilepsy trials, in pediatric trials, for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial seizures was as high as 67% for immediate-release topiramate doses of 6 mg/kg/day2, and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (defined as serum ≤ 17 mEq/L and ≥5 mEq/L decrease from pretreatment) in these trials was up to 11%, compared to ≤ 2% for placebo.

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or impair Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic treatment of pediatric patients may also reduce growth rates, which may decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been adequately investigated in long-term, placebo-controlled trials. Long-term, open-label treatment of pediatric patients 1 to 24 months with intractable partial epilepsy, for up to 1 year, showed no effect from baseline in length, weight, and head circumference compared to age and sex-matched controlled data, although these patients with epilepsy are likely to have different growth rates than normal 1 to 24 month old patients. Reductions in length and weight were correlated to the degree of acidosis *[see Use in Specific Populations (8.4)]*. QUDEXY XR-induced metabolic acidosis, acidosis during pregnancy could potentially cause adverse effects on the fetus and also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.

Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients

Measurement of baseline and periodic serum bicarbonate during QUDEXY XR treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing QUDEXY XR (using dose tapering). If the patient is to continue patients on QUDEXY XR in the face of persistent metabolic acidosis, alkali treatment should be considered.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including QUDEXY XR increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients taking any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thoughts or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation was 0.37 per 383 patient-years, or 0.43%, compared to 0.24%, among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal behavior or ideation for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of various mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 4: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug-Treated Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.8
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing QUDEXY XR or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.6 Cognitive/Neuropsychiatric Adverse Reactions

Immediate-release topiramate can cause, and therefore expected to be caused by QUDEXY XR, cognitive/neuropsychiatric adverse reactions. The frequency of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with attention, difficulty with concentration, difficulty speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive Related Dysfunction

Impact Rates are higher with initial dose were associated with the occurrence of cognitive-related dysfunction.

In adult epilepsy add-on controlled trials, which used rapid titration (100 to 200 mg/day titration), cognitive-related dysfunction was observed in approximately 3% of the 100 mg/day, 56% of patients in the 800 mg/day and 1000 mg/day dose groups experienced cognitive-related dysfunction, compared to approximately 1% of the placebo, 6% of the 400 mg/day groups and 14% for placebo. In this rapid titration regimen, these dose-related effects appeared to begin in the titration or in the maintenance phase, and in some patients these events began during titration and persisted into the maintenance phase.

In the monotherapy epilepsy controlled trial conducted with immediate-release topiramate, the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg per day and 26% for 400 mg per day.

In the 6-month migraine prophylaxis controlled trials of immediate-release topiramate using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 4% for topiramate 50 mg/day, 22% for 100 mg/day (the recommended dose), 28% for 200 mg/day, and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (e.g., depression or mood) were dose-related for both the adjunctive epilepsy and migraine populations treated with topiramate *[see Warnings and Precautions (5.6)]*.

Somnolence/Fatigue

Somnolence and fatigue were the adverse reactions most frequently reported during clinical trials of topiramate for adjunctive epilepsy. For the adjunctive epilepsy trials, the incidence of fatigue appeared dose-related. For the monotherapy epilepsy population, the incidence of somnolence was dose-related. For the migraine population, the incidences of both somnolence and fatigue were dose-related and more common in the titration phase.

Pediatric Patients

In pediatric epilepsy trials (adjunctive and monotherapy), the incidence of cognitive/ neuropsychiatric adverse reactions was generally lower than that observed in adults. These adverse reactions included language or speech disorders/related speech problems, speech disorders/related speech problems, and language problems. The most frequently reported cognitive/neuropsychiatric adverse reactions in pediatric patients treated with topiramate therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/ neuropsychiatric adverse reactions in pediatric patients treated with QUDEXY XR add-on groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

In pediatric migraine patients, the incidence of cognitive/neuropsychiatric adverse reactions was increased in topiramate-treated patients compared to placebo.

Table 5 represents the incidence of adverse reactions that were dose-dependent and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was not observed in pediatric patients 2 to 16 years of age with epilepsy (2 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in pediatric patients treated with topiramate was difficulty with attention. Other adverse reactions in pediatric patients were dose-dependent and sometimes persisted for various durations after completing therapy.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years of age) to assess the effects of topiramate on cognitive function at baseline and at the end of the double-blind, 6-month, add-on, fixed-dose, placebo-controlled trial. Adolescents who were taking topiramate showed tasks that suggested that topiramate may result in psychomotor slowing and decreased verbal fluency.

5.7 Fetal Toxicity

QUDEXY XR can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants born to mothers who took oral clefts have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring *[see Use in Specific Populations (8.1)]*.

Consider the benefits and risks of QUDEXY XR when administering the drug in women of childbearing potential. Patients who are pregnant or planning to become pregnant should be prescribed QUDEXY XR only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

5.8 Withdrawal of Antiepileptic Drugs

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including QUDEXY XR, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In epilepsy clinical trials, QUDEXY XR was withdrawn rapid withdrawal of QUDEXY XR is medically required, appropriate monitoring is recommended.

5.9 Hyperammonemia and Encephalopathy Without and With Concomitant Valproic Acid Use

Topiramate treatment can cause hyperammonemia with or without encephalopathy *[see Adverse Reactions (6.1)]*. The risk for hyperammonemia increases with concomitant valproic acid related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Hyperammonemia with encephalopathy and without encephalopathy have been reported with topiramate and valproic acid in patients who tolerate each medication alone. Signs and symptoms of hyperammonemia *[7.12]*.

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemia resolved when topiramate and valproic acid were discontinued.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was approximately 2 percent (2/100) for topiramate 100 mg/day and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There was also an increased incidence of markedly increased hyperammonemia at the 100 mg dose.

Dose-related hyperammonemia was also seen in pediatric patients 1 to 24 months of age with intractable partial epilepsy treated with topiramate and valproic acid for partial-onset epilepsy and this was not due to a pharmacokinetic interaction.

In some patients, hyperammonemia can be asymptomatic.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, significant hyperammonemia in conjunction with topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and ammonia level should be measured.

5.10 Kidney Stones

Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in immediate-release topiramate-treated adults was 1.5%, in adjunctive doses of 2 to 4 times greater than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate-treated patients was higher in men. Kidney stones have also been reported in pediatric patients taking topiramate for epilepsy or migraine. During long-term (up to 1 year) topiramate-controlled clinical trials and extension study of 284 pediatric patients 1 to 24 months old with epilepsy, 7%, developed kidney or bladder stones. QUDEXY XR is not approved for treatment of epilepsy in pediatric patients less than 2 years old *[see Use in Specific Populations (8.4)]*.

Topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. *[See Warnings and Precautions (5.4)]*. The concomitant use of QUDEXY XR with any other drug that predisposes patients to metabolic acidosis, or patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

5.11 Hypothermia With Concomitant Valproic Acid Use

Hypothermia, defined as a drop in body core temperature to <35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate *[see Drug Interactions (7.1)]*. Consideration should be given to withdrawal of QUDEXY XR in patients with hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and substantial impairment of other major organ systems such as cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:
- Acute Myopia and Secondary Angle Closure Glaucoma *[see Warnings and Precautions (5.1)]*
- Visual Field Defects *[see Warnings and Precautions (5.2)]*
- Oligohydrosis and Hyperthermia *[see Warnings and Precautions (5.3)]*
- Metabolic Acidosis *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use *[see Warnings and Precautions (5.8)]*
- Kidney Stones *[see Warnings and Precautions (5.10)]*
- Hypothermia With Concomitant Valproic Acid Use *[see Warnings and Precautions (5.11)]*

The data described in section 6.1 were obtained using immediate-release topiramate tablets.

6.1 Clinical Trials Experience With Immediate-Release Topiramate

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 trials of another drug and may not reflect the rates observed in clinical practice.

Monotherapy Epilepsy

Adults 16 Years of Age and Older

The most common adverse reactions in the controlled trial (Study 1) that occurred in adults in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the placebo group were: paresthesia, anorexia, and weight loss (see Table 5).

Approximately 21% of the 159 adult patients in the 400 mg/day group who received topiramate in controlled trials in adjunctive epilepsy discontinued treatment because of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration, difficulty speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive Related Dysfunction

Impact Rates are higher with initial dose were associated with the occurrence of cognitive-related dysfunction.

In adult epilepsy add-on controlled trials, which used rapid titration (100 to 200 mg/day titration), cognitive-related dysfunction was observed in approximately 3% of the 100 mg/day, 56% of patients in the 800 mg/day and 1000 mg/day dose groups experienced cognitive-related dysfunction, compared to approximately 1% of the placebo, 6% of the 400 mg/day groups and 14% for placebo. In this rapid titration regimen, these dose-related effects appeared to begin in the titration or in the maintenance phase, and in some patients these events began during titration and persisted into the maintenance phase.

In the monotherapy epilepsy controlled trial conducted with immediate-release topiramate, the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg per day and 26% for 400 mg per day.

In the 6-month migraine prophylaxis controlled trials of immediate-release topiramate using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 4% for topiramate 50 mg/day, 22% for 100 mg/day (the recommended dose), 28% for 200 mg/day, and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (e.g., depression or mood) were dose-related for both the adjunctive epilepsy and migraine populations treated with topiramate *[see Warnings and Precautions (5.6)]*.

Somnolence/Fatigue

Somnolence and fatigue were the adverse reactions most frequently reported during clinical trials of topiramate for adjunctive epilepsy. For the adjunctive epilepsy trials, the incidence of fatigue appeared dose-related. For the monotherapy epilepsy population, the incidence of somnolence was dose-related. For the migraine population, the incidences of both somnolence and fatigue were dose-related and more common in the titration phase.

Pediatric Patients

In pediatric epilepsy trials (adjunctive and monotherapy), the incidence of cognitive/ neuropsychiatric adverse reactions was generally lower than that observed in adults. These adverse reactions included language or speech disorders/related speech problems, speech disorders/related speech problems, and language problems. The most frequently reported cognitive/neuropsychiatric adverse reactions in pediatric patients treated with topiramate therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/ neuropsychiatric adverse reactions in pediatric patients treated with QUDEXY XR add-on groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

In pediatric migraine patients, the incidence of cognitive/neuropsychiatric adverse reactions was increased in topiramate-treated patients compared to placebo.

Table 5 represents the incidence of adverse reactions that were dose-dependent and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was not observed in pediatric patients 2 to 16 years of age with epilepsy (2 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in pediatric patients treated with topiramate was difficulty with attention. Other adverse reactions in pediatric patients were dose-dependent and sometimes persisted for various durations after completing therapy.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years of age) to assess the effects of topiramate on cognitive function at baseline and at the end of the double-blind, 6-month, add-on, fixed-dose, placebo-controlled trial. Adolescents who were taking topiramate showed tasks that suggested that topiramate may result in psychomotor slowing and decreased verbal fluency.

5.7 Fetal Toxicity

QUDEXY XR can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants born to mothers who took oral clefts have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring *[see Use in Specific Populations (8.1)]*.

Consider the benefits and risks of QUDEXY XR when administering the drug in women of childbearing potential. Patients who are pregnant or planning to become pregnant should be prescribed QUDEXY XR only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

5.8 Withdrawal of Antiepileptic Drugs

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including QUDEXY XR, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In epilepsy clinical trials, QUDEXY XR was withdrawn rapid withdrawal of QUDEXY XR is medically required, appropriate monitoring is recommended.

5.9 Hyperammonemia and Encephalopathy Without and With Concomitant Valproic Acid Use

Topiramate treatment can cause hyperammonemia with or without encephalopathy *[see Adverse Reactions (6.1)]*. The risk for hyperammonemia increases with concomitant valproic acid related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Hyperammonemia with encephalopathy and without encephalopathy have been reported with topiramate and valproic acid in patients who tolerate each medication alone. Signs and symptoms of hyperammonemia *[7.12]*.

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemia resolved when topiramate and valproic acid were discontinued.

The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was approximately 2 percent (2/100) for topiramate 100 mg/day and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There was also an increased incidence of markedly increased hyperammonemia at the 100 mg dose.

Dose-related hyperammonemia was also seen in pediatric patients 1 to 24 months of age with intractable partial epilepsy treated with topiramate and valproic acid for partial-onset epilepsy and this was not due to a pharmacokinetic interaction.

In some patients, hyperammonemia can be asymptomatic.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, significant hyperammonemia in conjunction with topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop

Patients who experienced 3 to 12 migraine headaches over the 4-weeks in the baseline phase were randomized to either topiramate 50 mg/day, 100 mg/day, 200 mg/day (twice the recommended daily dosage for migraine prophylaxis), or placebo and treated for a total of 26 weeks (8-week titration period and 18-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25 mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily).

Effectiveness of treatment was assessed by the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate (according to migraines classified by IHS criteria) from the baseline phase to double-blind treatment period in each immediate-release topiramate treatment group compared to placebo in the Intent-To-Treat (ITT) population.

In Study 11, a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 48 mg/day, 88 mg/day, and 132 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches per 28 days and was similar across treatment groups. The change in the mean 4-week migraine headache frequency from baseline to the double-blind phase was −1.3, −2.1, and −2.2 in the immediate-release topiramate 50, 100, and 200 mg/day groups, respectively, versus −0.8 in the placebo group (see Figure 3). The treatment differences between the immediate-release topiramate 100 and 200 mg/day groups versus placebo were similar and statistically significant (p<0.001 for both comparisons).

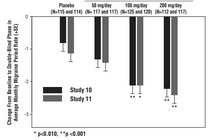
In Study 12, a total of 468 patients (406 females, 62 males), ranging in age from 12 to 65 years, were randomized and provided efficacy data. Two hundred fifty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 47 mg/day, 86 mg/day, and 150 mg/day in the target dose groups of immediate-release topiramate 50, 100, and 200 mg/day, respectively.

The mean migraine headache frequency rate at baseline was approximately 5.5 migraine headaches per 28 days and was similar across treatment groups. The change in the mean 4-week migraine headache period frequency from baseline to the double-blind phase was −1.4, −2.1, and −2.4 in the immediate-release topiramate 50, 100, and 200 mg/day groups, respectively, versus −1.1 in the placebo group (see Figure 3). The differences between the immediate-release topiramate 100 and 200 mg/day groups versus placebo were similar and statistically significant (p=0.008 and p <0.001, respectively).

In both studies, there were no apparent differences in treatment effect within age or gender subgroups. Because most patients were Caucasian, there were insufficient numbers of patients from different races to make a meaningful comparison of race.

For patients withdrawing from immediate-release topiramate, daily dosages were decreased in weekly intervals by 25 to 50 mg/day.

Figure 3: Reduction in 4-Week Migraine Headache Frequency (Studies 11 and 12 for Adults and Adolescents)



Pediatric Patients 12 to 17 Years of Age

The effectiveness of immediate-release topiramate as prophylaxis for migraine headache in pediatric patients 12 to 17 years of age was established in a multicenter, randomized, double-blind, parallel-group trial (Study 13). The study enrolled 103 patients (46 male, 63 female) 12 to 17 years of age with episodic migraine headaches with or without aura. Patient selection was based on IHS criteria for migraines (using proposed revisions to the 1988 IHS pediatric migraine criteria [IHS-R criteria]).

Patients who experienced 3 to 12 migraine headache attacks (according to migraines classified by patient reported diaries) and ≤14 headache days (migraine and non-migraine) during the 4-week prospective baseline period were randomized to either immediate-release topiramate 50 mg/day, 100 mg/day, or placebo and treated for a total of 16 weeks (4-week titration period followed by a 12-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25 mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily). Approximately 80% or more patients in each treatment group completed the study. The median average daily dosages were 45 and 79 mg/day in the target dose groups of immediate-release topiramate 50 and 100 mg/day, respectively.

Effectiveness of treatment was assessed by comparing each immediate-release topiramate treatment group to placebo (ITT population) for the percent reduction from baseline to the last 12 weeks of the double-blind phase in the monthly migraine attack rate (primary endpoint). The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate is shown in Table 15. The 100 mg immediate-release topiramate dose produced a statistically significant treatment difference relative to placebo of 28% reduction from baseline in the monthly migraine attack rate.

The mean reduction from baseline to the last 12 weeks of the double-blind phase in average monthly attack rate, a key secondary efficacy endpoint in Study 3 (and the primary efficacy endpoint in Studies 1 and 2, of adults) was 3.0 for 100 mg immediate-release topiramate dose and 1.7 for placebo. This 1.3 treatment difference in mean reduction from baseline of monthly migraine rate was statistically significant (p = 0.0087).

Table 15: Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate: Study 13 (Intent-to-Treat Analysis Set)

Category	Placebo (N=33)	Topiramate 50 mg/day (N=35)	Topiramate 100 mg/day (N=35)
Baseline			
Median	3.6	4.0	4.0
Last 12 Weeks of Double-Blind Phase			
Median	2.3	2.3	1.0
Percent Reduction (%)			
Median	44.4	44.6	72.2
P-value versus Placebo[1,2]		0.7875	0.0164[1]

[1]P-values (two-sided) for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.

[2]P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.

[1]Indicates p-value is < 0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

QUDEXY® XR (topiramate) extended-release capsules contain beads of topiramate in a capsule and are available in the following strengths and colors:

25 mg: light pink and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "25 mg" on the body in black ink. 25 mg capsules are available in the following package configurations:

- Bottle of 30 count with desiccant (NDC 0245-1071-30)
- Bottle of 90 count with desiccant (NDC 0245-1071-90)

50 mg: golden yellow and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "50 mg" on the body in black ink. 50 mg capsules are available in the following package configurations:

- Bottle of 30 count with desiccant (NDC 0245-1072-30)
- Bottle of 90 count with desiccant (NDC 0245-1072-90)

100 mg: reddish brown and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "100 mg" on the body in black ink. 100 mg capsules are available in the following package configurations:

- Bottle of 30 count with desiccant (NDC 0245-1074-30)
- Bottle of 90 count with desiccant (NDC 0245-1074-90)

150 mg: pale yellow and gray capsules, printed with "UPSHER-SMITH" on the cap in black ink and "150 mg" on the body in black ink. 150 mg capsules are available in the following package configurations:

- Bottle of 30 count with desiccant (NDC 0245-1075-30)
- Bottle of 90 count with desiccant (NDC 0245-1075-90)

200 mg: brown and gray capsules, printed with "UPSHER-SMITH" on the cap in white ink and "200 mg" on the body in black ink. 200 mg capsules are available in the following package configurations:

- Bottle of 30 count with desiccant (NDC 0245-1073-30)
- Bottle of 90 count with desiccant (NDC 0245-1073-90)

16.2 Storage and Handling

QUDEXY XR (topiramate) extended-release capsules should be stored in a tightly closed container 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]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Administration Instructions

Counsel patients to swallow QUDEXY XR capsules whole or carefully open and sprinkle the entire contents on a spoonful of soft food. This drug/food mixture should be swallowed immediately and not chewed. Do not store drug/food mixture for future use *[see Dosage and Administration (2.6)]*.

Eye Disorders

Advise patients taking QUDEXY XR to seek immediate medical attention if they experience blurred vision, visual disturbances or periorbital pain *[see Warnings and Precautions (5.1 and 5.2)]*.

Oligohydrosis and Hyperthermia

Closely monitor QUDEXY XR-treated patients, especially pediatric patients, for evidence of decreased sweating and increased body temperature, especially in hot weather. Counsel patients to contact their healthcare professionals immediately if they develop a high or persistent fever, or decreased sweating *[see Warnings and Precautions (5.3)]*.

Metabolic Acidosis

Warn patients about the potential significant risk for metabolic acidosis that may be asymptomatic and may be associated with adverse effects on kidneys (e.g., kidney stones, nephrocalcinosis), bones (e.g., osteoporosis, osteomalacia, and/or rickets in children), and growth (e.g., growth delay/retardation) in pediatric patients, and on the fetus *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.4)]*.

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and families that AEDs, including QUDEXY XR, may increase the risk of suicidal thoughts and behavior and they should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, behavior or thoughts about self-harm. Instruct patients to immediately report behaviors of concern to their healthcare providers *[see Warnings and Precautions (5.5)]*.

Interference With Cognitive and Motor Performance

Warn patients about the potential for somnolence, dizziness, confusion, difficulty concentrating, visual effects, and advise patients not to drive or operate machinery until they have gained sufficient experience on QUDEXY XR to gauge whether it adversely affects their mental performance, motor performance, and/or vision *[see Warnings and Precautions (5.6)]*.

Even when taking QUDEXY XR, or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Therefore, advise all patients taking QUDEXY XR for epilepsy to exercise appropriate caution when engaging in any activities where loss of consciousness could result in serious danger to themselves or those around them (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Discuss the appropriate level of caution with patients, before patients with epilepsy engage in such activities.

Fetal Toxicity

Inform pregnant women and women of childbearing potential that use of QUDEXY XR during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), which occur early in pregnancy before many women know they are pregnant. Also inform patients that infants exposed to topiramate monotherapy *in utero* may be small for their gestational age. There may also be risks to the fetus from chronic metabolic acidosis with use of QUDEXY XR during pregnancy *[see Warnings and Precautions (5.4, 5.7), Use in Specific Populations (8.1)]*.

When appropriate, counsel pregnant women and women of childbearing potential about alternative therapeutic options. Advise women of childbearing potential who are not planning a pregnancy to use effective contraception while using QUDEXY XR, keeping in mind that there is a potential for decreased contraceptive efficacy when using estrogen-containing birth control with topiramate *[see Drug Interactions (7.4)]*.

Encourage pregnant women using QUDEXY XR to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The registry is collecting information about the safety of antiepileptic drugs during pregnancy *[see Use in Specific Populations (8.1)]*.

Hyperammonemia and Encephalopathy

Warn patients about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/ or cognitive function with lethargy and/or vomiting. This hyperammonemia and encephalopathy can develop with topiramate treatment alone or with topiramate treatment with concomitant valproic acid (VPA). Instruct patients to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status *[see Warnings and Precautions (5.8)]*.

Kidney Stones

Instruct patients, particularly those with predisposing factors, to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation *[see Warnings and Precautions (5.10)]*.

Hypothermia

Counsel patients that QUDEXY XR can cause a reduction in body temperature, which can lead to alterations in mental status. If they note such changes, they should call their health care professional and measure their body temperature. Patients taking concomitant valproic acid should be specifically counseled on this potential adverse reaction *[see Warnings and Precautions (5.11)]*.

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UPSHER-SMITH LABORATORIES, LLC
Maple Grove, MN 55369

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MEDICATION GUIDE
QUDEXY® XR (cue-DEKS-ee ex-arr) (topiramate) Extended-Release Capsules

What is the most important information I should know about QUDEXY XR?

QUDEXY XR may cause eye problems. Serious eye problems include:

- any sudden decrease in vision with or without eye pain and redness,
- a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).

These eye problems can lead to permanent loss of vision if not treated. You should call your healthcare provider right away if you have any new eye symptoms, including any new problems with your vision.

QUDEXY XR may cause decreased sweating and increased body temperature (fever). People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition. If you have a high fever, a fever that does not go away, or decreased sweating develops, call your healthcare provider right away.

QUDEXY XR can increase the level of acid in your blood (metabolic acidosis). If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones, can slow the rate of growth in children, and may possibly harm your baby if you are pregnant. Metabolic acidosis can happen with or without symptoms. Sometimes people with metabolic acidosis will:

- feel tired
- not feel hungry (loss of appetite)
- feel changes in heartbeat
- have trouble thinking clearly

Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with QUDEXY XR.

If you are pregnant, you should talk to your healthcare provider about whether you have metabolic acidosis.

Like other antiepileptic drugs, QUDEXY XR may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

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

- thoughts about suicide or dying
- feeling agitated or restless
- acting aggressive, being angry, or violent
- attempts to commit suicide
- panic attacks
- acting on dangerous impulses
- new or worse depression
- trouble sleeping (insomnia)
- an extreme increase in activity and talking (mania)
- new or worse anxiety
- new or worse irritability
- other unusual changes in behavior or mood

Do not stop QUDEXY XR without first talking to a healthcare provider.

- Stopping QUDEXY XR suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

QUDEXY XR can harm your unborn baby.

- If you take QUDEXY XR during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.
- Cleft lip and cleft palate may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- There may be other medicines to treat your condition that have a lower chance of birth defects.
- All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of QUDEXY XR. If the decision is made to use QUDEXY XR, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your healthcare provider about the best kind of birth control to use while you are taking QUDEXY XR.
- Tell your healthcare provider right away if you become pregnant while taking QUDEXY XR. You and your healthcare provider should decide if you will continue to take QUDEXY XR while you are pregnant.
- If you take QUDEXY XR during pregnancy, your baby may be smaller than expected at birth. The long term effects of this are not known. Talk to your healthcare provider if you have any questions about this risk during pregnancy.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if QUDEXY XR has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking QUDEXY XR, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of QUDEXY XR and other antiepileptic drugs during pregnancy.

What is QUDEXY XR?

QUDEXY XR is a prescription medicine used:

- to treat certain types of seizures (partial-onset seizures and primary generalized tonic-clonic seizures) in adults and children 2 years of age and older.
- with other medicines to treat certain types of seizures (partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years of age and older.
- to prevent migraine headaches in adults and adolescents 12 years of age and older.

What should I tell my healthcare provider before taking QUDEXY XR?

Before taking QUDEXY XR, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems, kidney stones or are getting kidney dialysis
- have a history of metabolic acidosis (too much acid in the blood)
- have liver problems
- have weak, brittle or soft bones (osteomalacia, osteoporosis, osteopenia, or decreased bone density)
- have lung or breathing problems
- have eye problems, especially glaucoma
- have diarrhea
- have a growth problem
- are on a diet high in fat and low in carbohydrates, which is called a ketogenic diet
- are having surgery
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed. QUDEXY XR passes into breast milk. Breastfed babies may be sleepy or have diarrhea. It is not known if the QUDEXY XR that passes into breast milk can cause other serious harm to your baby. Talk to your healthcare provider about the best way to feed your baby if you take QUDEXY XR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. QUDEXY XR and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- Valproic acid (such as DEPAKENE® or DEPAKOTE®)
- any medicines that impair or decrease your thinking, concentration, or muscle coordination
- birth control pills. QUDEXY XR may make your birth control pills less effective. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and QUDEXY XR.

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take QUDEXY XR?

- Take QUDEXY XR exactly as your healthcare provider tells you to.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- QUDEXY XR capsules may be swallowed whole or, if you cannot swallow the capsule whole, you may carefully open the QUDEXY XR capsule and sprinkle the medicine on a spoonful of soft food like applesauce.
  - Swallow the food and medicine mixture right away. **Do not** store the food and medicine mixture to use later.
  - Do not crush or chew QUDEXY XR before swallowing.
- Drink plenty fluids during the day. This may help prevent kidney stones while taking QUDEXY XR.
- If you take too much QUDEXY XR, call your healthcare provider right away or go to the nearest emergency room.
- QUDEXY XR can be taken before, during, or after a meal.
- If you miss a single dose of QUDEXY XR, take it as soon as you can. If you have missed more than one dose, you should call your healthcare provider for advice.
- Do not stop taking QUDEXY XR without talking to your healthcare provider. Stopping QUDEXY XR suddenly may cause serious problems. If you have epilepsy and you stop taking QUDEXY XR suddenly, you may have seizures that do not stop. Your healthcare provider will tell you how to stop taking QUDEXY XR slowly.
- Your healthcare provider may do blood tests while you take QUDEXY XR.

What should I avoid while taking QUDEXY XR?

- You should not drink alcohol while taking QUDEXY XR. QUDEXY XR and alcohol can effect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate machinery until you know how QUDEXY XR affects you. QUDEXY XR can slow your thinking and motor skills and may affect vision.

What are the possible side effects of QUDEXY XR?

QUDEXY XR may cause serious side effects, including:

See "What is the most important information I should know about QUDEXY XR?"

- **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when QUDEXY XR is taken with a medicine called valproic acid (DEPAKENE® and DEPAKOTE®).
- **Kidney stones.** Drink plenty of fluids when taking QUDEXY XR to decrease your chances of getting kidney stones.
- **Low body temperature.** Taking QUDEXY XR when you are also taking valproic acid can cause a drop in body temperature to less than 95°F, or can cause tiredness, confusion, or coma.
- **Effects on thinking and alertness.** QUDEXY XR may affect how you think, and cause confusion, problems with concentration, attention, memory, or speech. QUDEXY XR may cause depression or mood problems, tiredness, and sleepiness.
- **Dizziness or loss of muscle coordination.**

Call your healthcare provider right away if you have any of the symptoms above.

The most common side effects of QUDEXY XR include:

- tingling of the arms and legs (paresthesia)
- not feeling hungry
- weight loss
- nervousness
- nausea
- speech problems
- tiredness
- dizziness
- sleepiness/drowsiness
- a change in the way foods taste
- upper respiratory tract infection
- decreased feeling or sensitivity, especially in the skin
- slow reactions
- difficulty with memory
- fever
- abnormal vision
- diarrhea
- pain in the abdomen

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of QUDEXY XR. For more information, ask your healthcare provider or pharmacist.

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

You may also report side effects to Upsher-Smith Laboratories, LLC at 1-855-899-9180.

How should I store QUDEXY XR?

- Store QUDEXY XR capsules at room temperature between 68° to 77°F (20° to 25°C).
- Keep QUDEXY XR in a tightly closed container.
- Keep QUDEXY XR dry and away from moisture.
- **Keep QUDEXY XR and all medicines out of the reach of children.**

General information about the safe and effective use of QUDEXY XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use QUDEXY XR for a condition for which it was not prescribed. Do not give QUDEXY XR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about QUDEXY XR that is written for health professionals.

What are the ingredients in QUDEXY XR?

Active ingredient: topiramate

Inactive ingredients: microcrystalline cellulose, hypromellose 2910, ethylcellulose, diethyl phthalate, titanium dioxide, black iron oxide, red iron oxide and/or yellow iron oxide, black pharmaceutical ink, and white pharmaceutical ink (200 mg only).

Distributed by: **UPSHER-SMITH LABORATORIES, LLC**, Maple Grove, MN 55369

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

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