Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Qsiva 7.5 mg/46 mg hard modified-release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qsiva 7.5 mg/46 mg hard modified-release capsules
Each hard modified-release capsules contains phentermine hydrochloride equivalent to 7.5 mg phentermine and 46 mg of topiramate

Excipients with known effect:

Qsiva 7.5 mg/46 mg hard modified-release capsules
sucrose (167.73 mg), tartrazine (E102, 0.10 mg), Sunset Yellow FCF (E110, 0.01 mg)

3 PHARMACEUTICAL FORM

Qsiva 7.5 mg/46 mg hard modified-release capsules
Purple cap imprinted with VIVUS, yellow body imprinted with 7.5/46

Size: 2.31 cm long, 0.73 - 0.76 cm in diameter

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Qsiva, as an adjunct to a reduced-calorie diet and physical activity, is indicated for weight management in adult patients with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obese), or
- ≥27 kg/m^2 (overweight) with weight-related co-morbidities such as hypertension, type-2 diabetes or dyslipidaemia

4.2 Posology and method of administration

Qsiva treatment should be initiated and supervised by physicians experienced with the treatment of obesity.

Posology
The recommended maintenance dose of Qsiva is 7.5 mg/46 mg, taken once daily in the morning.

Treatment should be initiated through dose titration starting with the 3.75 mg/23 mg dose for 14 days followed by the daily dose of 7.5 mg/46 mg. Patients treated with a daily dose of Qsiva 7.5 mg/46 mg for the first 3 months who do not lose at least 5% of their baseline weight should be considered non-responders and should discontinue use of Qsiva.

If a patient is a responder (i.e. ≥ 5% weight loss after 3 months treatment) and tolerating the treatment well but BMI remains 30 kg/m^2 or greater after 3 months of treatment with Qsiva 7.5 mg/46 mg, dosing with Qsiva 11.25 mg/69 mg daily for 14 days followed by dosing with Qsiva 15 mg/92 mg daily may be considered. There is a risk of seizures with abrupt cessation of Qsiva top dose. Consequently, if Qsiva 15 mg/92 mg is discontinued, this should be done gradually by taking a dose every other day for at least 1 week prior to stopping treatment altogether.

The overall incidence of adverse reactions was higher in the Qsiva 15 mg/92 mg group compared to lower dose groups (see section 4.8). A careful risk benefit evaluation should be performed before initiating Qsiva 15 mg/92 mg.

Proper nutrition, exercise and hydration are important components of a weight loss program. It is recommended that health care providers review the patient's dietary habits and recommend specific changes to reduce their daily caloric intake by about

500 kcal. Supplementation with a daily multivitamin should be considered to ensure adequate nutritional balance. Patients should consult with their physicians prior to starting any exercise program.

If the morning dose of Qsiva is missed it can still be taken up to the middle of the day, otherwise the patient should wait until the next morning to take the next daily dose as usual. A double dose should not be taken to make up for a forgotten dose. If treatment is missed for more than 7 days, consideration should be given to reinitiating treatment with the low dose.

Women of childbearing potential
Treatment with Qsiva should be initiated and supervised by a physician experienced in weight management.

Alternative therapeutic options should be considered in women of childbearing potential. The need for Qsiva treatment in this population should be reassessed at least annually (see sections 4.3, 4.4 and 4.6).

Renal impairment
Qsiva exposure is increased in patients with mild (creatinine clearance ≥ 60 - < 90 mL/min), moderate (creatinine clearance ≥ 30 - < 60 mL/min) or severe (creatinine clearance 15 - < 30 mL/min) renal impairment (see section 5.2) and treatment should be planned accordingly (see Table 1).

Table 1 Dosing recommendations for patients with renal impairment

Dosing of Qsiva	**Renal impairment:**		
	mild	**moderate**	**severe**
Starting dose	3.75 mg/23 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg every other day
Dose adjustments	Increase to 7.5 mg/46 mg daily at Month 3 is possible if well tolerated and BMI > 30 kg/m^2	none	At Day 14, increase to 3.75 mg/23 mg daily possible if well tolerated
Maintenance dose	3.75 mg/23 mg daily or 7.5 mg/46 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg every other day or 3.75 mg/23 mg daily
Maximum dose	7.5 mg/46 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg daily

Regardless of the grade of renal impairment, treatment should be discontinued in patients who do not achieve at least 5% weight loss within 3 months of first starting treatment.

Due to the lack of data, treatment with Qsiva is not recommended for patients with end stage renal disease (creatinine clearance < 15 mL/min) or on haemodialysis (see sections 4.4 and 5.2).

Hepatic impairment
Qsiva exposure is increased in patients with mild (Child-Pugh score 5 - 6) to moderate (Child-Pugh score 7 - 9) hepatic impairment and treatment should be planned accordingly:

- Mild hepatic impairment: No precautions are needed as to dosing.
- Moderate hepatic impairment: The dose of 7.5 mg/46 mg once daily should not be exceeded.
- Severe hepatic impairment (Child-Pugh score > 10): Due to the lack of data, treatment with Qsiva is not recommended (see sections 4.4 and 5.2).

Regardless of the grade of hepatic impairment, treatment should be discontinued in patients who do not achieve at least 5% weight loss within 3 months of first starting treatment.

Elderly patients
No dose adjustment is necessary when administering Qsiva to elderly patients ≤ 70 years of age.

Qsiva has not been studied in patients > 70 years of age and should be used with caution in these patients.

Paediatric population
The safety and efficacy of Qsiva in children and adolescents below the age of 18 has not been established. No data are available.

Method of administration
Qsiva can be taken in the morning with or without food. The hard modified-release capsules should be swallowed whole to make sure the entire dose is administered.

4.3 Contraindications

Hypersensitivity to the active substances, to any other sympathomimetic amine or to any of the excipients listed in section 6.1.

Qsiva is contraindicated:

- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential not using highly effective contraception (see sections 4.4, 4.5 and 4.6).

Qsiva is contraindicated in patients receiving treatment with monoamine oxidase inhibitors (MAOIs), such as iproniazid, isoniazid, phenelzine or tranylcypromine, used to treat depression or within 14 days of stopping MAOI treatment (see section 4.5).

Qsiva must not be used in conjunction with other medicinal products intended for weight loss.

4.4 Special warnings and precautions for use

Qsiva should not be used as a substitute for any other medicinal products containing phentermine or topiramate.

Pregnancy prevention programme
Topiramate can cause major congenital malformations and foetal growth restriction when administered to a pregnant woman.

Some data suggest an increased risk of neurodevelopmental disorders in children exposed to topiramate in utero, while other data do not suggest such an increased risk (see section 4.6).

Women of childbearing potential

Pregnancy testing should be performed before initiating treatment with topiramate/phentermine in a woman of childbearing potential.

The patient must be fully informed and understand the risks related to the use of topiramate/phentermine during pregnancy (see sections 4.3 and 4.6). This includes the need for specialist consultation if the woman is planning pregnancy to discontinue treatment with topiramate/phentermine and to discuss whether alternative treatment is needed prior to discontinuation of contraception, and for prompt contact with a specialist if she becomes pregnant or thinks she may be pregnant.

Educational materials regarding these measures are available for healthcare professionals and patients. The patient guide must be provided to all women of childbearing potential using topiramate/phentermine. A patient card is provided with the package of Qsiva.

Mood disturbance/depression
A dose-related increase in the incidence of mood disturbances and depression has been observed with Qsiva. All patients should be counselled that Qsiva contains topiramate and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behaviour and to consult a physician immediately if these occur. Patients with a history of or concurrent mood disorder or depression should be evaluated carefully to ensure treatment with Qsiva is warranted. If treatment is commenced, then these patients should be actively monitored to ensure no new or worsening of mood or depression occurs. Treatment with Qsiva is not recommended in patients with a history of recurrent major depression, bipolar disorder, or psychosis, or in patients with current depression of moderate or worse severity.

Suicide/suicide ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicinal products, such as topiramate, in several indications. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.

In the clinical studies, the incidence of suicidal ideation was low and similar for Qsiva and placebo. Reports of suicidal ideation and rare reports of suicidal attempt have been received post-marketing with Qsiva treatment.

Patients taking Qsiva should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Increases in heart rate
In clinical studies, increases in resting heart rate from baseline were observed with Qsiva compared to placebo. In an 8-week ambulatory blood pressure monitoring (ABPM) study a mean increase in 24-hr average heart rate of 3.6 beats per minutes was seen with Qsiva 15/92 mg compared to placebo. Regular measurement of resting heart rate is recommended for all patients prior to the start of treatment and while taking Qsiva. Patients should inform health care providers of palpitations or feelings of a racing heartbeat while at rest during Qsiva treatment. For any patients who experience a sustained increase in resting heart rate (e.g. greater than or equal to an absolute threshold of 90 bpm on two consecutive measurements) while taking Qsiva the dose should be reduced or Qsiva discontinued.

Patients with cardiovascular disease
Qsiva has not been studied in patients with a recent myocardial infarction (< 6 months) or in patients with congestive heart failure (NYHA class II-IV).

Use of Qsiva is not recommended for patients with a recent myocardial infarction (< 6 months) or in other patients at high cardiovascular risk including those with a history of advanced cardiovascular disease (e.g. recent [within 3 months] stroke, malignant arrhythmias, congestive heart failure [New York Heart Association - NYHA Class II-IV]).

Nephrolithiasis
Topiramate, when used for other indications, has been associated with an increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain, especially in those with a predisposition to nephrolithiasis. Nephrolithiasis was also reported under Qsiva treatment.

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. Rapid weight loss could precipitate or exacerbate gallstone formation. Metabolic acidosis could cause hypercalciuria which could contribute to calcium formation and nephrolithiasis. In addition, patients taking other medicinal products such as carbonic anhydrase inhibitors associated with nephrolithiasis may be at increased risk. Adequate hydration could reduce the risk of nephrolithiasis and is very important when using topiramate-containing medicinal products such as Qsiva.

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. Glaucoma has been reported in the clinical studies for patients treated with Qsiva. Angle closure glaucoma has been reported post-marketing in patients treated with Qsiva.

If acute myopia with secondary angle closure glaucoma develops in patients taking Qsiva, treatment should be discontinued immediately, and appropriate measures taken to reduce intraocular pressure. Discontinuing treatment with Qsiva should result in a decrease in intraocular pressure.

Metabolic acidosis
Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) has been associated with the use of topiramate. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase.

Low serum bicarbonate may be a concern in obese, diabetic patients treated with metformin, who are already at risk for lactic acidosis. No dose adjustments of either Qsiva or metformin are recommended; however, patients taking metformin should have their serum bicarbonate level measured periodically.

In general, depending on underlying conditions, periodic evaluation of serum bicarbonate levels is recommended with Qsiva therapy. Qsiva should be used with caution in patients with conditions or treatments that represent a risk factor for the appearance of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Qsiva.

Cognitive adverse events

Cognitive adverse events have been reported under Qsiva treatment (see section 4.8). In order to minimise cognitive adverse events such as attention, memory and language/word-finding difficulties due to topiramate, a rapid titration or high initial doses of Qsiva are not recommended.

Changes due to weight loss
Due to decreased food intake as a result of taking Qsiva, modification of the dose of anti-diabetic medicinal products, in particular insulin or sulphonylureas, may be required in order to reduce the risk of hypoglycaemia.

Patients being treated for hypertension may need to modify the dose of the anti-hypertensive medication as based on clinical study data, weight loss with Qsiva may reduce blood pressure. Weight loss can precipitate or exacerbate gallstone formation.

Hypokalaemia
Hypokalaemia has been reported for Qsiva. Concurrent use of Qsiva with non-potassium sparing diuretics may potentiate the potassium-wasting action of these diuretics. When prescribing Qsiva in the presence of non-potassium-sparing medicinal products patients should be monitored for hypokalaemia.

Potential for misuse
Phentermine is a weak stimulant and may have the potential for medicinal product abuse and dependence.

Hepatic impairment
There is no clinical experience in patients with severe hepatic impairment. Treatment of obesity in these patients should be avoided (see section 4.2). In patients with mild (Child-Pugh score 5 - 6) or moderate (Child-Pugh score 7 - 9) hepatic impairment, exposure to the phentermine component of Qsiva was higher compared to matched normal control subjects (see sections 4.2 and 5.2).

Renal impairment
The phentermine and topiramate components of Qsiva are primarily cleared by renal excretion and exposure is increased in patients with renal impairment (see sections 4.2 and 5.2).

Elevations in serum creatinine
Qsiva can cause an increase in serum creatinine that reflects a decrease in renal function (glomerular filtration rate). Measurement of serum creatinine prior to starting Qsiva and before increasing the Qsiva dose is recommended (see section 4.8). If persistent elevations in serum creatinine occur while taking Qsiva, the dose should be reduced or Qsiva discontinued.

Patients with hyperthyroidism
Qsiva is not recommended in patients with hyperthyroidism.

Seizures with abrupt cessation of Qsiva top dose
There is a risk of seizures with abrupt cessation of Qsiva top dose. Consequently, if Qsiva 15 mg/92 mg is discontinued, this should be done gradually as described in section 4.2.

Sucrose
Qsiva hard modified-release capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Qsiva 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg hard modified-release capsules

Tartrazine and Sunset Yellow FCF
These hard modified-release capsules colourings may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Topiramate dose-dependently induced CYP3A4 *in vitro* this could potentially lead to lower exposures and a reduced effect of CYP3A4 substrates co-administered with Qsiva. Monitoring of effect is recommended when a sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) is used concomitantly with Qsiva.

Topiramate inhibited CYP2C19 *in vitro*. This may influence other substances, which are metabolised via this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied *in vivo*.

Effect of other medicinal products on plasma levels of topiramate, a component of Qsiva

Antiepileptic drugs:
Phenytoin and carbamazepine decreased the plasma concentration of topiramate, a component of Qsiva. The addition or withdrawal of phenytoin or carbamazepine to Qsiva therapy may require an adjustment in dosage of Qsiva. This should be done by titrating to clinical effect.

Hydrochlorothiazide:
Concomitant administration of hydrochlorothiazide alone with topiramate, a component of Qsiva, alone has been shown to increase the C_{max} and AUC of topiramate by 27% and 29%, respectively.

St John's Wort (Hypericum perforatum):
A risk of decreased plasma topiramate concentrations resulting in a loss of efficacy could be observed with co-administration of Qsiva, and St John's Wort. There have been no clinical studies evaluating this potential interaction.

Effect of Qsiva on plasma levels of other medicinal products

Systemic hormonal contraceptives:
Co-administration of multiple-dose Qsiva 15 mg/92 mg once daily with a single dose of oral contraceptive containing 35 µg ethinylestradiol (oestrogen component) and 1 mg norethisterone (progestin component), in obese otherwise healthy volunteers, decreased the exposure of ethinylestradiol by 16% and increased the exposure of norethisterone by 22%.

The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking systemic hormonal contraceptive products with Qsiva. Patients should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding. Women using systemic hormonal contraceptives should be advised to also use a barrier method.

Antiepileptic drugs:
The addition of topiramate to antiepileptic drugs (carbamazepine, valproic acid, phenobarbital, primidone or lamotrigine) had no clinically significant effect on their steady-state plasma concentrations. In some patients, treatment with Qsiva and phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of CYP2C19 by topiramate. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored.

Antidiabetic drugs:

Metformin

Metformin C_{max} and $AUC_{0-\tau}$ were increased by approximately 16% and 23%, respectively, in healthy obese patients following co-administration of multiple once-daily doses of Qsiva (15 mg/92 mg) with multiple twice-daily doses of 500 mg metformin. Patients receiving metformin should be monitored appropriately. No dosage adjustment of metformin or Qsiva is recommended.

Low serum bicarbonate due to excess bicarbonate excretion related to topiramate administration may be a concern in obese, diabetic patients treated with metformin, who are already at risk for lactic acidosis. No dose adjustments of either Qsiva or metformin are recommended; however, patients taking metformin should have their serum bicarbonate level measured periodically.

Pioglitazone
A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and topiramate in a clinical trial. The clinical relevance of these observations is unknown; however, when Qsiva is added to pioglitazone therapy or pioglitazone is added to Qsiva therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Sitagliptin
The pharmacokinetics of sitagliptin were not altered in healthy obese patients following co-administration of Qsiva (15 mg/92 mg) with sitagliptin (100 mg).

Glibenclamide
A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide. When Qsiva is added to glibenclamide therapy or glibenclamide is added to Qsiva therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Digoxin:
In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of topiramate. The clinical relevance of this observation has not been established. When Qsiva is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

Lithium:
In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. Lithium levels should be monitored when co-administered with topiramate.

Risperidone:
Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with psychotic disorders, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100 and 200 mg/day there was no significant change in risperidone exposure (administered at doses ranging from 1 to 6 mg/day) between treatment with risperidone alone and combination treatment with topiramate. There was also no significant change in the systemic exposure of topiramate.

Other forms of interactions

Monoamine oxidase inhibitors (MAOIs):
Qsiva is contraindicated in patients receiving treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping MAOI treatment (see section 4.3).

Central nervous system depressants:
Concomitant administration of Qsiva and alcohol or other central nervous system (CNS) depressant medicinal products has not been evaluated in clinical studies. It is recommended that Qsiva not be used concomitantly with alcohol or other CNS depressant medicinal products.

Carbonic anhydrase inhibitors:
Concomitant use of topiramate, a component of Qsiva, with any other carbonic anhydrase inhibitor (e.g. zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation (see section 4.4).

Non-potassium sparing diuretics:
Concurrent use of Qsiva with non-potassium sparing diuretics may potentiate the potassium-wasting action of these diuretics. When prescribing Qsiva in the presence of non-potassium-sparing medicinal products, patients should be monitored for hypokalaemia (see section 4.4).

Valproic acid:
Concomitant administration of topiramate, a component of Qsiva, and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction.

Hypothermia, defined as an unintentional drop in body core temperature to < 35 °C, has been reported in association with concomitant use of topiramate and valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate.

4.6 Fertility, pregnancy and lactation

Pregnancy
Qsiva is contraindicated during pregnancy (see section 4.3 and 4.4).

Topiramate is known to be teratogenic in animals (see section 5.3) and humans. In humans, topiramate crosses the placenta and similar concentrations have been reported in the umbilical cord and maternal blood.

Clinical data from pregnancy registries indicate that infants exposed in utero to topiramate monotherapy have:

Major congenital malformation and foetal growth restriction

- An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher prevalence of major congenital malformations (4.3%), compared with a reference group not taking AEDs (1.4%). Data from an observational population-based registry study from the Nordic countries showed a 2 to 3-fold higher prevalence of major congenital malformations (up to 9.5 %), compared with a reference group not taking AEDs (3.0%). In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.
- A higher prevalence of low birth weight (<2500 grams) compared with a reference group.
- An increased prevalence of being small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex). In the North American Antiepileptic Drug Pregnancy Registry, the risk of SGA in children of women receiving topiramate was 18 %, compared with 5 % in children of women without epilepsy not receiving an AED. The long-term consequences of the SGA findings could not be determined.

Neurodevelopmental disorders

- Data from two observational population-based registry studies undertaken in largely the same dataset from the Nordic countries suggest that there may be a 2-to-3-fold higher prevalence of autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD) in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED. A third observational cohort study from the U.S.A did not suggest an increased cumulative incidence of these outcomes by 8 years of age in approximately 1000 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED.

Women of childbearing potential
Qsiva is contraindicated in women of childbearing potential not using highly effective contraception. At least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method should be used (see sections 4.3, 4.4 and 4.5) during treatment and for at least 4 weeks after stopping treatment with Qsiva.

Alternative therapeutic options should be considered in women of childbearing potential.
Pregnancy testing should be performed before initiating treatment with topiramate/phentermine in a woman of childbearing potential.

The patient must be fully informed and understand the risks related to the use of Qsiva during pregnancy. This includes the need for specialist consultation if the woman is planning pregnancy, and for prompt contact with a specialist if she becomes pregnant or thinks she may be pregnant and is taking Qsiva.

Breast-feeding
Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Effects that have been observed in breastfed newborns/infants of treated mothers include diarrhea, drowsiness, irritability and inadequate weight gain.

It is unknown whether phentermine is excreted in human milk.

Qsiva should not be used during breast feeding.

Fertility
An effect of topiramate on human fertility has not been established.

There is no published information on potential adverse effects of phentermine on fertility.

4.7 Effects on ability to drive and use machines

Qsiva has moderate influence on the ability to drive and use machines. Cognitive effects, primarily attention deficits may occur. Drowsiness, dizziness, visual disturbances and/or blurred vision have been reported with use of topiramate.

No specific studies on the effects on the ability to drive and use machines have been performed. Caution should be exercised when driving a car or using heavy machines until the effects of Qsiva on the individual are determined.

4.8 Undesirable effects

In the most relevant 1-year cohort, the safety of Qsiva was evaluated from a clinical trial database consisting of 3,879 patients (2,318 treated with Qsiva, 1,561 with placebo) who participated in the clinical trial program for Qsiva as a weight-loss treatment in overweight and obese adult patients for 1 year of treatment. The 2-year cohort consisted of one study and included 675 subjects of which 448 were treated with Qsiva.

The most commonly reported adverse reactions for Qsiva treatment in the 1-year cohort were dry mouth (15%), paraesthesia (15%) and constipation (10% of patients).

The following table lists the adverse reactions observed for Qsiva during clinical trials that occurred more often in Qsiva treated patients than in placebo treated patients in clinical trials of 1 year duration. Within each frequency grouping, adverse reactions are presented in order of decreasing reporting rate. The frequency terms are listed as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000). Adverse reactions reported during post-marketing surveillance are included with frequency unknown.

Table 2 Qsiva adverse reactions with an incidence higher than with placebo treatment in clinical trials*

System Organ Class	**Frequency:** Adverse reaction
Infections and infestations	**Uncommon:** Urinary tract infection, **Rare:** Respiratory tract infection,Sinusitis, Influenza, Bronchitis, Candidiasis, Ear infection **Not known:** Viral gastroenteritis
Blood and lymphatic system disorders	**Uncommon**: Anaemia
Metabolism and nutrition disorders	**Common:** Anorexia **Uncommon:** Hypokalaemia, Hypoglycaemia, Fluid retention, Dehydration, Increased appetite **Rare:** Metabolic acidosis, Gout
Psychiatric disorders	**Common:** Insomnia, Depression, Anxiety **Uncommon:** Nervousness, Libido altered, Mood altered, Agitation, Confusional state, Sleep disorder (including abnormal dreams and nightmares), Restlessness, Crying, Stress, Affect lability, Emotional disorder, Apathy, Anger, Panic attack, Paranoia **Rare:** Suicidal ideation, Aggression, Anhedonia, Bereavement reaction, Bruxism, Food aversion, Hallucination, Disorientation, Dysphemia **Not known:** Suicide attempt, Logorrhoea
Nervous system disorders	**Very common:** Paraesthesia **Common:** Headache, Dysgeusia, Dizziness, Disturbance in attention, Hypoaesthesia, Memory impairment **Uncommon:** Amnesia, Lethargy, Somnolence, Aphasia, Tremor, Cognitive disorder, Hypogeusia, Migraine, Poor quality sleep, Syncope, Neuropathy, Psychomotor hyperactivity, Parosmia, Restless leg syndrome, Burning sensation, Dysarthria, Coordination abnormal **Rare:** Formication

	Not known: Seizure, Neuralgia
Eye disorders	**Common:** Vision blurred, Dry eye **Uncommon:** Eye pain, Blepharospasm, Photophobia, Photopsia, Diplopia, Eye pruritus **Rare:** Lacrimation increased,Glaucoma, Conjunctival haemorrhage **Not known:** Angle closure glaucoma, Transient blindness, Cataract, Mydriasis, Macular degeneration, uveitis
Ear and labyrinth disorders	**Uncommon:** Tinnitus, Vertigo **Rare:**Deafness, Ear pain **Not known:** Hypoacusis, Middle ear effusion
Cardiac disorders	**Common:** Palpitations **Uncommon:** Tachycardia **Rare:** Atrial fibrillation, Arrhythmia **Not known:** Cardiac failure
Vascular disorders	**Uncommon:** Flushing, Hypotension, Hypertension **Rare:** Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	**Uncommon:** Cough, Epistaxis, Dyspnoea, Pharyngolaryngeal pain, Sinus congestion, Nasal congestion, Postnasal drip **Rare:** Dry throat, Rhinorrhoea **Not known:** Nasal polyps, Acute respiratory failure
Gastrointestinal disorders	**Very common:** Dry mouth; Constipation **Common:** Nausea, Diarrhoea, Abdominal pain, Dyspepsia **Uncommon:** Flatulence, Gastroesophageal reflux, Vomiting, Eructation **Rare:** Breath odour, Gingival pain, Glossitis, Glossodynia, Haemorrhoids, Infrequent bowel movements **Not known:** Dysphagia, Oral discomfort, Retching
Hepatobiliary disorders	**Rare:** Cholelithiasis, Cholecystitis
Skin and subcutaneous tissue disorders	**Common:** Alopecia **Uncommon:** Pruritus, Rash, Dry skin, Hyperhidrosis, Acne, Skin odour abnormal, Urticaria, Erythema, Hair texture abnormal **Rare:** Onychoclasis **Not known:** Angioedema
Musculoskeletal and connective tissue disorders	**Uncommon:** Muscle spasms, Pain in extremity, Myalgia, Arthralgia, Back pain, Muscular weakness, Muscle twitching **Rare:** Muscle tightness
Renal and urinary disorders	**Uncommon:** Nephrolithiasis, Pollakiuria, Urinary hesitation, Nocturia **Rare:** Urine odour abnormal **Not known:** Acute kidney injury
Reproductive system and breast disorders	**Uncommon:** Erectile dysfunction, Menstrual disorders
General disorders and administration site conditions	**Common:** Fatigue, Irritability, Thirst, Feeling jittery **Uncommon:** Asthenia, Feeling abnormal, Feeling cold, Oedema peripheral, Chest pain, Energy increased, Feeling hot **Rare:** Gait disturbance **Not known:** Sensation of foreign body
Investigations	**Uncommon:** Heart rate increased,Blood bicarbonate decreased, Blood potassium decreased, Liver function test abnormal, Creatinine renal clearance decreased **Rare:** Blood creatinine increased, Blood glucose increased **Not known:** Blood glucose decreased, Blood thyroid stimulating hormone increased, Blood triglycerides increased, Glycosylated haemoglobin increased
Injury, poisoning and procedural complications	**Rare:** Fall
Immune system disorders	**Not known:** Hypersensitivity

*Adverse reactions were not included if only 1 event was reported for Qsiva treatment. Adverse reactions were also included in the table if the incidence for Qsiva treatment was not higher than with placebo treatment but > 3 post-marketing reports were documented. Adverse reactions labelled "not known" were reported post-marketing only.

Description of selected adverse reactions/adverse events:

Paraesthesia
In clinical studies (1-year cohort), the incidence of adverse reactions of paraesthesia was dose-dependently increased with treatment with Qsiva compared with placebo: 3.3%, 11.8% and 17.3% vs 1.2% for 3.75/23 mg, 7.5/46 mg and 15/92 mg Qsiva vs placebo. Symptoms were typically characterized as tingling in hands and feet. No serious adverse reactions of paraesthesia were reported, and symptoms were mild in severity in the majority of patients (80-86%). Symptoms of paraesthesia persisted for approximately 3 months and resolved spontaneously in approximately 75-80% of the patients with continued treatment

Psychiatric disorders
In clinical studies (1-year cohort), there was a dose-dependent increased risk of adverse events indicative of psychiatric disorders with treatment with Qsiva (15.8%, 14.5% and 20.6% for 3.75/23 mg, 7.5/46 mg and 15/92 mg Qsiva, respectively) as compared with placebo (10.3%). Psychiatric disorders were mostly sleep disorders, depression-related, or anxiety-related. The majority (94%) of adverse reactions were of mild to moderate intensity. No serious events were reported.

Adverse events indicative of depression were reported for 5.0%, 3.8% and 7.7% of the patients treated with 3.75/23 mg, 7.5/46 mg and 15/92 mg Qsiva, respectively, compared with 3.4% in the placebo group. Anxiety and related events were reported in 4.6%, 4.8% and 7.9% of the patients treated with 3.75/23 mg, 7.5/46 mg and 15/92 mg Qsiva, respectively, versus 2.6% in placebo. In addition, one case each of suicidal ideation of moderate intensity was reported in the Qsiva and the placebo group.

Cognitive disorders
In clinical studies (1-year cohort), the incidence of adverse events indicative of cognitive disorders was increased in the Qsiva 3.75/23 mg, 7.5/46 mg and 15/92 mg groups (2.1%, 5.0% and 7.6%, respectively) as compared with placebo (1.5%) Cognitive disorders were mostly attention disorders and memory impairment. The majority (97%) of cognitive disorder events were of mild to moderate intensity. No serious events were reported.

Cardiac disorders
In clinical studies (1-year cohort), adverse events indicative of cardiac disorders were reported with an incidence of 1.7%, 3.8% and 3.5% vs 1.8% for Qsiva 3.75/23 mg, 7.5/46 mg and 15/92 mg vs placebo. Cardiac adverse events were mostly related to cardiac arrhythmia. Adverse events indicative of cardiac arrhythmia (mostly events of palpitations, heart rate increased, tachycardia) were reported in 1.3%, 4.2% and 4.7% of the patients treated with Qsiva 3.75/23 mg, 7.5/46 mg and 15/92 mg as compared with 1.8% in the placebo group. Serious arrhythmia events were reported for 0.2% of the patients treated with Qsiva compared with 0.3% in the placebo group. All adverse reactions were mild or moderate in intensity.

Serum Creatinine
Qsiva can cause an increase in serum creatinine that reflects a decrease in renal function (glomerular filtration rate). Effects of Qsiva 15/92 mg on GFR was evaluated in study OB-404, a 4-week study in healthy overweight obese adults. Treatment with Qsiva 15/92 mg was associated with a decrease in GFR as measured by iohexal clearance (iGFR); -14.9 mL/min/1.73 m^2 (-15.8%) vs 1.08 mL/min/1.73 m^2 (1.2%) in the placebo group at the end of treatment. At the *end of study* (4 weeks after treatment discontinuation) mean change in iGFR from baseline was -3.8 mL/min/1.73 m^2 (-4.0%) for Qsiva vs 2.34 mL/min/1.73 m^2 (2.6%) for placebo.

In phase 3 trials, peak increases in serum creatinine of approximately 15% were observed after 4 to 8 weeks of treatment. On average, serum creatinine subsequently declined gradually but remained elevated over baseline creatinine values. In this population, mean estimated GFR using the MDRD equation was reduced after 4 weeks of treatment by a similar percentage. On average e-GFR subsequently increased gradually but remained below baseline values (-5.4 mL/min/1.73 m^2). In the 1-year controlled studies of Qsiva, the incidence of increases in serum creatinine of greater than or equal to 0.3 mg/dL at any time during treatment was 7.2% and 8.4% vs 2.0% for Qsiva 7.5/46 mg and 15/92 mg vs placebo. Increases in serum creatinine of ≥ 50% over baseline occurred in 2.0% and 2.8% for Qsiva 7.5/46 mg and 15/92 mg compared to 0.6% for placebo. On average, serum creatinine gradually declined over time, but remained elevated over baseline creatinine values.

The effect of chronic treatment on renal function is not known. Therefore, measurement of serum creatinine prior to starting Qsiva and during Qsiva treatment is recommended.

In clinical studies (1-year cohort), adverse reactions of creatinine renal clearance decreased, urine albumin/creatinine ratio increased, or blood creatinine increased were each reported for 0.1% of the patients in the Qsiva treatment groups. Only urine albumin/creatinine ratio increased was reported in 1 placebo patient (0.1%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance website: www.hpra.ie .

4.9 Overdose

In the case of a significant overdose with Qsiva, treatment is largely symptomatic. Treatment with activated charcoal can be utilised.

Phentermine
Experience with an acute overdose of the approved single agent phentermine may include signs such as restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggressiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute phentermine intoxication is largely symptomatic. A barbiturate to mitigate excessive CNS stimulation can be utilised. Acidification of the urine increases phentermine excretion. Intravenous phentolamine has been suggested for possible acute, severe hypertension, if this complicates phentermine overdose.

Topiramate
Topiramate overdose has resulted in severe metabolic acidosis. Other signs and symptoms include convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-medicinal product overdoses involving gram amounts of topiramate. A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

Activated charcoal has been shown to adsorb topiramate *in vitro*. Haemodialysis is an effective means of removing topiramate from the body.

One case of overdose has been reported during post-marketing surveillance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiobesity preparations, excluding diet products; centrally acting antiobesity products. ATC code: A08AA51.

Mechanism of action
Qsiva is a combination of phentermine and topiramate. Both drugs suppress appetite, but do so by different mechanisms.

Phentermine is in a class of drugs that treat obesity primarily through appetite suppression. The mechanism of action of phentermine for weight loss is an anorectic effect occurring through the release of norepinephrine in the hypothalamus. The clinical doses of phentermine in Qsiva stimulate the release of norepinephrine (NE) with negligible effects on dopamine and no central or peripheral effect on serotonin (5-HT).

Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety due to decreased gastrointestinal motility, increased energy expenditure and decreased caloric intake.

A primary pharmacological mechanism of topiramate is carbonic anhydrase enzyme inhibition that has been shown to be involved in lipid biosynthesis, diuresis and blood pressure lowering. In addition, topiramate has been shown to modulate hepatic genes including genes that encode for the expression of metabolic enzymes and signalling proteins involved in lipid metabolism.

Clinical efficacy

The effect of Qsiva on weight loss after 1 year of treatment was studied in obese patients (the EQUIP study; OB-302) and in obese and overweight patients with significant co-morbidities (the CONQUER study; OB-303). An additional Phase 3 study in obese patients evaluated the safety and efficacy of Qsiva during 6 months of treatment (OB-301). All studies demonstrated that patients treated with Qsiva experienced greater weight loss than those treated with phentermine or topiramate alone.

Data from 3,678 patients in the ITT population of the individual 1-year studies showed that treatment with Qsiva in conjunction with a hypocaloric diet and increased physical activity resulted in a mean (SD) weight loss at 1 year of 5.1%, 7.8%, and 9.8-10.9% for Qsiva 3.75 mg/23 mg, 7.5 mg/46 mg and 15 mg/92 mg, respectively. This compared to a mean weight loss of 1.2-1.6% for placebo. Differences compared to placebo were statistically significant for all Qsiva doses. The percentage of patients achieving 5%, 10% or 15% weight loss at 1 year was greater for all dose levels of Qsiva compared to placebo (Table 3).

Table 3 Percentage of patients (ITT population) achieving 5%, 10% and 15% weight loss at 1 year

Percent weight loss	Treatment group	Number patients achieving percent weight loss/number exposed (%) [p-value (Qsiva vs placebo)]	
		OB-302	OB-303
5%	Placebo	86/498 (17.3)	204/979 (20.8)
	3.75 mg/23 mg	105/234 (44.9)*	-
	7.5 mg/46 mg	-	303/488 (62.1)*
	15 mg/92 mg	332/498 (66.7)*	687/981 (70.0)*
10%	Placebo	37/498 (7.4)	72/979 (7.4)
	3.75 mg/23 mg	44/234 (18.8)*	-
	7.5 mg/46 mg	-	182/488 (37.3)*
	15 mg/92 mg	235/498 (47.2)*	467/981 (47.6)*
15%	Placebo	17/498 (3.4)	28/979 (2.9)
	3.75 mg/23 mg	17/234 (7.3)	-
	7.5 mg/46 mg	-	94/488 (19.3)*
	15 mg/92 mg	161/498 (32.3)*	283/981 (28.8)*

*p-value (Qsiva vs placebo): < 0.001

The effects of Qsiva on weight loss were observed across subgroups by gender, age, race, baseline BMI and diabetic status. At 1 year, Qsiva therapy resulted in statistically significant decreases from baseline in systolic and diastolic blood pressure. In the CONQUER study the 7.5 mg/46 mg and 15 mg/92 mg doses reduced systolic blood pressure by 4.7 and 5.6 mm Hg, respectively, compared with a 2.4 mm Hg reduction obtained with placebo. In an 8-week 24-hour ambulatory blood pressure monitoring (ABPM) study, the change in systolic blood pressure from baseline was -3.3 mmHg for Qsiva 15/92 mg and -0.1 mmHg for placebo and the change in diastolic blood pressure from baseline for Qsiva was +0.8 mmHg and -0.4 mmHg for placebo. Triglycerides, and high-density lipoprotein cholesterol (HDL-C) were each significantly improved from baseline compared with placebo across the Phase 3 trials.

Haemoglobin A1c (HbA1c) and fasting glucose were also consistently and significantly reduced from baseline, compared with placebo across Phase 3 trials. In the CONQUER study, fasting serum glucose levels were also reduced from baseline in diabetic patients treated with the 7.5 mg/46 mg and 15 mg/92 mg dose by 9.7 and 11.9 mg/dL, respectively, compared with a reduction 5.6 mg/dL with placebo.

Qsiva treatment (15 mg/92 mg) over 1 year resulted in a 58% decrease in the annualised incidence of type 2 diabetes in obese patients compared to placebo. Among non-diabetic patients evaluated in the CONQUER study, progression to type 2 diabetes

occurred in 4.5% of patients treated with placebo, 3.1% of patients treated with the 7.5 mg/46 mg dose of Qsiva and 1.9% of patients treated with the 15 mg/92 mg dose of Qsiva.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of phentermine (75% to 85%) and topiramate (81% to 95%) is high. After oral administration of Qsiva, peak plasma concentrations of phentermine and topiramate occurred at a median (range) T_{max} of 6 hours (2 - 10) and 10 hours (7 - 16) post dose, respectively. There was no clinically significant effect of food on the bioavailability of phentermine or topiramate.

Distribution
The fraction of phentermine (17.5%) or topiramate (13-17%) reversibly bound to plasma proteins is low. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/mL has been observed. The mean oral volume of distribution (V/F) of phentermine and topiramate following a single oral dose of Qsiva 7.5 mg/46 mg was 369 litres and 76.4 litres, respectively.

Biotransformation
Topiramate and phentermine are not extensively metabolised and are eliminated primarily unchanged in the urine. Six metabolites of topiramate formed via hydroxylation, hydrolysis and glucuronidation have been identified in humans, none of which constitutes more than 5% of an administered dose. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of phentermine is CYP3A4. Topiramate is a weak inducer of CYP3A4 and a weak inhibitor of CYP2C19 *in vitro*.

Elimination
The terminal elimination half-life ($t_{1/2}$) of phentermine and topiramate were 21 hours and 49 hours, respectively. The apparent total clearance /CL/F) of phentermine and topiramate from plasma after oral administration was 7.84 L/h. and 1.35 L/h for phentermine and topiramate, respectively. Approximately 75 - 85% and 70% of an administered phentermine or topiramate dose is excreted unchanged in urine, respectively. For phentermine, 3 - 4% and < 5% of the administered dose was excreted in human urine as p-hydroxylated and N-oxidation products, respectively.

Linearity/non-linearity
Following single and multiple dose administration of Qsiva, plasma C_{max} and AUC of topiramate and phentermine increased linearly with increasing doses. Plasma C_{max} and AUC of phentermine and topiramate increased approximately 2.5- to 2.9-fold and 3.7- to 5.2-fold, respectively following multiple doses of Qsiva.

Renal impairment
Compared to subjects with normal renal function, increases of 150%, 59%, and 24% in plasma AUCss of exposure to phentermine and 134%, 59%, and 25% in plasma AUCss of topiramate were predicted in patients with severe, moderate and mild renal impairment, respectively, based on the population pharmacokinetics analysis at all dose levels. There is no information on the pharmacokinetics of Qsiva in patients with end stage renal disease (see section 4.2).

Monte-Carlo simulations were performed using the final population pharmacokinetics models of phentermine and topiramate to predict the exposure levels in obese subjects with different degrees of renal functions (See Table 4).

Table 4 Average concentrations of phentermine and topiramate at steady-state predicted for patients with normal renal function and with renal impairment at the recommended dose levels

Dosing Frequency	Dose levels	Mean (coefficient of variation) Average concentrations (Phentermine [ng/mL], Topiramate [µg/mL])			
		Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment
Every other day	Phentermine 3.75 mg				24.2 (36.8%)
	Topiramate 23 mg				0.843 (27.2%)
Once daily	Phentermine 3.75 mg	19.0 (35.4%)	23.6 (33.8%)	30.3 (34.7%)	47.5 (37.2%)
	Topiramate 23 mg	0.706 (29.0%)	0.883 (28.9%)	1.13 (28.5%)	1.66 (27.6%)
	Phentermine 7.5 mg	38.0 (35.4%)	47.2 (33.8%)		
	Topiramate 46 mg	1.41 (29.0%)	1.77 (28.9%)		
	Phentermine 11.25 mg	57.0 (35.4%)			
	Topiramate 69 mg	2.12 (29.0%)			
	Phentermine 15 mg	76.1 (35.4%)			
	Topiramate 92 mg	2.83 (29.0%)			

Hepatic impairment
In patients with mild (Child-Pugh score 5 - 6) or moderate hepatic insufficiency (Child-Pugh score 7 - 9), exposure to phentermine was 37% and 60% higher compared to healthy matched controls. The pharmacokinetics of topiramate were not affected in patients with mild or moderate hepatic dysfunction compared with healthy matched controls. There is no information on the pharmacokinetics in patients with severe hepatic impairment (Child-Pugh score ≥ 10) (see section 4.2).

Elderly
Age (18 - 70 years) did not seem to have any clinically meaningful effect on the pharmacokinetics of Qsiva based on a population pharmacokinetic analysis.

Other special populations
BMI generally did not appear to have a clinically meaningful effect on the pharmacokinetics of Qsiva based on a population pharmacokinetic analysis.

5.3 Preclinical safety data

Non-clinical data on phentermine or topiramate alone revealed no special hazard for humans based on genotoxicity and carcinogenicity studies.

Topiramate is well known to be teratogenic in animals, including mice, rats and rabbits as well as in humans (see section 4.6). In embryo-foetal development studies in rats and rabbits, topiramate or phentermine were tested either alone or in combination during the period of organogenesis. Topiramate or phentermine administered alone did not cause maternal or embryofoetal toxicity in rats or rabbits. Treatment with topiramate and phentermine in combination caused decreased foetal weights in rats, but teratogenicity was not seen at doses that produced no maternal toxicity. In rabbits, no maternal or embryofoetal toxicity was observed. The exposure margin in rats from the no observed adverse effect level (NOAEL) to the clinical dose was estimated to < 1 for phentermine and 2× for topiramate. In rabbits, the exposure margins to the clinical dose from the maximum tested dose were < 1 for phentermine and 2× for topiramate.

In a pre- and postnatal development study in rats, topiramate or phentermine were administered either alone or in combination starting on day 6 of pregnancy and continued until day 20 of lactation. Treatment with phentermine alone was associated with lower gestation and lactation weights, lower gestation body weight gain, decreased food consumption during gestation, poor pup survival and maternal neglect early in lactation, as well as lower pup body weights through to weaning and postnatal day 28.Treatment with topiramate alone was associated with lower pup body weights during lactation and until postnatal day 28.Treatment with phentermine and topiramate in combination was associated lower gestation and lactation weights, lower gestation weight gain, decreased food consumption during gestation and lactation, poor pup survival and maternal neglect early in lactation, as well as lower pup body weights at birth and throughout lactation, delays in the onset of several physical developmental parameters (pinna detachment and eye opening), and delays in sexual maturation. Margin of exposure from NOAEL to the clinical dose was estimated as < 1 for phentermine and 2× for topiramate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sucrose
Maize starch
Hypromellose
Microcrystalline cellulose
Methylcellulose
Ethylcellulose
Povidone
Talc

Capsule
Qsiva 7.5 mg/46 mg hard modified-release capsuless
Gelatin
Titanium dioxide (E171)
Brilliant Blue FCF (E133)
Erythrosine (E127)
Tartrazine (E102)
Sunset Yellow FCF (E110)
black printing ink: iron oxide black (E172), shellac, propylene glycol
white printing ink: titanium dioxide (E171), shellac, propylene glycol, simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30 °C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Qsiva hard modified-release capsules are packaged in a HDPE bottle with a silica gel desiccant, containing fourteen (14) or thirty (30) hard modified-release capsules, closed with a tamper-evident, child resistant white polyethylene screw-cap.

Do not swallow the desiccant.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Vivus B.V.
Office 03-106
Strawinskylaan 4117
Amsterdam
Noord-Holland
1077 ZX

Netherlands

8 MARKETING AUTHORISATION NUMBER

PA25222/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th October 2024
Date of last renewal: 22nd December 2025

10 DATE OF REVISION OF THE TEXT

June 2026