Phentermine/Topiramate: Pediatric First Approval

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Abstract
Phentermine/topiramate extended-release capsule (Qsymia®) is a fixed-dose combination of phentermine (sympathomimetic amine) and topiramate being developed by VIVUS (a subsidiary of Icahn Enterprises) for the treatment of obesity, sleep apnoea syndrome, type 2 diabetes mellitus and non-alcoholic steatohepatitis (NASH). The once-daily formulation of phentermine (a sympathomimetic amine) and topiramate is designed to combat obesity by decreasing appetite and increasing satiety. In July 2022, phentermine/topiramate received its first approval in the USA, as an adjunct to a reduced-calorie diet and increased physical activity, for chronic weight management in pediatric patients aged ≥ 12 years with BMI in the 95th percentile or greater standardized for age and sex. Phentermine/topiramate is approved in the US and South Korea for obesity in adults. Clinical development of phentermine/topiramate for sleep apnoea syndrome and type-2 diabetes in obese patients and preclinical development for NASH is ongoing in the US. This article summarizes the milestones in the development of phentermine/topiramate leading to this pediatric first approval for chronic weight management in adolescents.

1 Introduction
Obesity is a serious and growing problem in adolescents worldwide. In the USA, the prevalence of obesity in 12- to 19-year-olds has increased significantly from 15.5% in 1999–2000 to 22.2% in 2017–2020 [1]. Treatment guidelines suggest pharmacotherapy if adolescents with obesity fail to limit weight gain or ameliorate comorbidities after a formal program of intensive lifestyle modification [2]. Phentermine/topiramate has established efficacy and a favourable tolerability profile in adults with obesity and is approved for chronic weight management in these patients in the USA and South Korea, as well as in in Sweden, Denmark, Finland, Iceland, Norway and Poland under a decentralised procedure, with Sweden acting as the lead Concerned Member State.

More recently, phentermine/topiramate has been assessed for use in adolescents, and in July 2022 [4], it received its pediatric first approval in the USA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in patients aged ≥ 12 years with...
body mass index (BMI) in the 95th percentile or greater standardized for age and sex [3]. Phentermine/topiramate should be taken orally once daily in the morning with or without food; administration of phentermine/topiramate in the evening should be avoided due to the possibility of insomnia. The recommended starting dosage of phentermine/topiramate is 3.75 mg/23 mg once daily for 14 days; after 14 days the dosage should be increased to 7.5 mg/46 mg once daily. After 12 weeks of treatment with phentermine/topiramate 7.5 mg/46 mg, BMI reduction should be evaluated and if the patient has not experienced a reduction of ≥ 3% of baseline BMI, phentermine/topiramate dosage should be increased to 11.25 mg/69 mg once daily for 14 days, followed by an increase to phentermine/topiramate 15 mg/92 mg once daily. After 12 weeks of treatment at this dosage, if the patient has not experienced a reduction of ≥ 5% of baseline BMI, treatment with phentermine/topiramate should be discontinued as the patient is unlikely to achieve and sustain clinically meaningful weight loss with continued treatment [3].

Clinical development of phentermine/topiramate for sleep apnoea syndrome and type-2 diabetes mellitus in obese patients and preclinical development for NASH is ongoing in the US.

1.1 Company Agreements

In October 2012, Catalent Pharma Solutions entered into an agreement with VIVUS Inc to supply phentermine/topiramate capsules. Catalent used its unique drug delivery capabilities to partner with VIVUS during the development of phentermine/topiramate, including pre-formulation and formulation, clinical supply and validation [5]. In August 2014, VIVUS acquired a group of patents from Janssen Pharmaceuticals relating to uses of topiramate as monotherapy and combination therapy [6]. In September 2017, VIVUS entered into an agreement with Alvogen under which Alvogen was to market phentermine/topiramate in the Republic of Korea for the treatment of chronic weight management or weight-related conditions [7]. Under the terms of the agreement, Alvogen was responsible for obtaining and maintaining regulatory approvals and for marketing activities in South Korea [7].

2 Scientific Summary

2.1 Pharmacodynamics

Phentermine is a sympathomimetic amine with pharmacological activity similar to amphetamine [3]. Its effect on chronic weight management is likely through the release of catecholamines in the hypothalamus, resulting in appetite suppression and decreased food consumption, although other metabolic effects may also be involved. Topiramate is thought to affect appetite suppression and satiety enhancement via a combination of pharmacologic effects, including

Chemical structure of phentermine

Chemical structure of topiramate
augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors and inhibition of carbonic anhydrase; however the exact mechanism of action of topiramate on chronic weight management remains to be determined [3].

A supra-therapeutic dose of phentermine/topiramate (22.5 mg/138 mg) resulting in phentermine and topiramate maximum concentrations (C\text{max}) 4- and 3-times higher than that with phentermine/topiramate 7.5 mg/46 mg did not have a significant effect on the corrected QT interval [3]. Glomerular filtration rate is generally decreased during treatment with phentermine/topiramate and returns to baseline levels within 4 weeks of treatment discontinuation [3].

### 2.2 Pharmacokinetics

The pharmacokinetics of phentermine/topiramate were assessed in 37 adolescents (aged 12–17 years) with obesity in a randomized, double-blind, placebo-controlled phase 4 study (NCT02714062) [8]. After administration of phentermine/topiramate 7.5 or 15 mg/92 mg once daily in adolescents with obesity, the exposure to phentermine and topiramate was consistent with that observed previously in adults with obesity [3]: the mean apparent clearance and apparent central volume of distribution of phentermine were within 10% and of topiramate were within 30% of those observed previously in adults with obesity [8].

The mean time to peak plasma concentration in adolescents with obesity was \( \approx 3.6 \) h for phentermine and \( \approx 5.1 \) h for topiramate following administration of phentermine/topiramate 7.5 mg/46 mg or 15 mg/92 mg [8]. In adults with obesity, at steady state, the mean accumulation ratios for area under the concentration-time curve from time zero to infinity and peak plasma concentration were both \( \approx 2.5 \) for phentermine and both \( \approx 4.0 \) for topiramate following a phentermine/topiramate dose of 15 mg/100 mg [3]. A high fat meal in adults with obesity did not affect the pharmacokinetics of phentermine or topiramate after a phentermine/topiramate 15 mg/92 mg dose [3].

Phentermine is 17.5% plasma protein bound; topiramate is 15–41% plasma protein bound over the blood concentration range of 0.5–250 μg/mL [3]. The bound fraction of topiramate decreases as the concentration of topiramate in blood increases. In adolescents with obesity, the mean apparent central volume of distribution of phentermine was \( \approx 290 \) L and that of topiramate was \( \approx 46 \) L [8].

Phentermine is primarily metabolized by CYP3A4 via p-hydroxylation of the aromatic ring and N-oxidation of the aliphatic side chain; monoamine oxidase (MAO)-A and MAO-B do not metabolize phentermine [3]. Topiramate is metabolized via hydroxylation, hydrolysis and glucuronidation into six metabolites, none of which constitute more than 5% of an administered dose [3]. Both phentermine and topiramate are not metabolized extensively, with 70–80% of a phentermine dose and 70% of a topiramate dose eliminated as unchanged drug in the urine [3]. In adolescents with obesity, the mean terminal elimination half-life of phentermine is \( \approx 31 \) h and that of topiramate is \( \approx 36 \) h; phentermine and topiramate estimated oral clearance is \( \approx 6.7 \) and \( \approx 1.2 \) L/h, respectively [8].

Exposure to phentermine and topiramate is higher in patients with moderate [creatinine clearance (CL\text{CR}) \( \geq 30 \) to < 50 mL/min] or severe (CL\text{CR} <50 mL/min) renal impairment, and exposure to phentermine (but not topiramate) is higher in patients with mild (Child–Pugh 5–6) or moderate (Child–Pugh 7–9) hepatic impairment [3]. Therefore, the maximum recommended dosage of phentermine/topiramate in patients with moderate or severe renal impairment and moderate hepatic impairment is 7.5 mg/46 mg. No dosage adjustment is required for patients with mild renal impairment (CL\text{CR} \geq 50 to < 80 mL/min) or mild hepatic impairment. The pharmacokinetics of phentermine/topiramate have not been assessed in patients with end-stage renal disease or severe hepatic impairment (Child–Pugh score 10–15); therefore, phentermine/topiramate use should be avoided in these patients [3].

Phentermine is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 enzymes or of monoamine oxidases [3]. Phentermine is not an inducer of CYP1A2, CYP2B6 and CYP3A4 enzymes. Concomitant use of phentermine with monoamine oxidase inhibitors (MAOI) increases the risk of hypertensive crisis; therefore, the concomitant use of these drugs is and the use of phentermine/topiramate within 14 days of stopping an MAOI is contraindicated. Topiramate is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 enzymes; however, it is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. Phentermine and topiramate are not P-glycoprotein substrates [3].

### 2.3 Therapeutic Trials

Phentermine/topiramate, in conjunction with reduced caloric intake and increased physical activity, significantly reduced BMI in adolescents with obesity who were participating in the pivotal, 56-week, randomized, double-blind, phase 4 trial (NCT03922945) [9]. Eligible patients were aged 12 to < 17 years with a BMI in the 95th percentile or greater for age and sex. Patients were randomized to receive phentermine/topiramate 7.5 mg/46 mg \( (n = 54) \) or 15 mg/92 mg \( (n = 113) \) or placebo \( (n = 56) \) taken orally once daily in the morning and stratified by age group (12–14 vs 15–16 years) and sex. All patients were to follow a well-balanced reduced-calorie diet within 4 weeks of treatment discontinuation [3].
Features and properties of phentermine/topiramate

Alternative names
Phentermine and topiramate extended-release capsules-VIVUS; phentermine/CR topiramate—VIVUS; Qnexa; Qsiva; Qsymia; topiramate/phentermine; VI-0521

Class
Amphetamines; anorectics; anti-hyperglycaemics; dioxolanes; hepatoprotectants; hexoses; ketoses; sleep disorder therapies; small molecules; sulfonic acids

Mechanism of action
Phentermine likely acts via the release of catecholamines in the hypothalamus resulting in reduced appetite and food consumption
Topiramate may affect appetite suppression and satiety enhancement via a combination of pharmacologic effects

Route of administration
Oral

Pharmacodynamics
Suppresses appetite, decreases food consumption and enhances satiety
Supratherapeutic dose does not significantly affect corrected QT interval
Glomerular filtration rate is generally decreased during treatment and returned to baseline levels within 4 weeks of treatment discontinuation

Pharmacokinetics (adolescents)
Exposure to phentermine and topiramate consistent with that in adults with obesity
Phentermine and topiramate mean time to peak plasma concentration ≈ 3.6 and ≈ 5.1 h, respectively
Phentermine and topiramate mean Vc/F ≈ 290 L and ≈ 46 L, respectively
Phentermine and topiramate mean t1/2 ≈ 31 h and ≈ 36 h, respectively, and oral clearance ≈ 6.7 and ≈ 1.2 L/h

Adverse events (adolescents)
Most frequent
Depression, nausea, pyrexia, dizziness, arthralgia, influenza, ligament sprain

Serious
Bile duct stone, depression, suicidal ideation

ATC codes
WHO ATC code A08A-A01 (phentermine); N03A-X11 (topiramate)
EphMRA ATC code A8A (antiobesity preparations, excluding dietetics); N7X (all other CNS drugs)
Chemical name 2-methyl-1-phenylpropan-2-amine/[1R,2S,6S,9R)-4,4,11,11-tetramethyl-3,5,7,10,12-pentaaxtricyclo[7.3.0.02,6]dodecan-6-yl]methyl sulfamate

Pharmacokinetic data are for adolescents aged 12–17 years with obesity

CL/F apparent clearance, t1/2 terminal elimination half-life, Vc/F apparent central volume of distribution

diet resulting in ≈ 500 kcal/day decrease in caloric intake and to implement a family-based lifestyle modification program, including physical activity, behaviour change and family support. At baseline, the BMI was 37.8 kg/m² in the overall population [9].

At week 56, BMI was significantly reduced in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group, with a least-squares mean (LSM) percent change in BMI of −4.78% and −7.11% versus 3.34% [primary endpoint; difference from placebo −8.11 (95% CI −11.92 to −4.31) and −10.44 (95% CI −13.89 to −6.99), respectively; both p < 0.001] [9]. There was no significant difference between the two phentermine/topiramate dose groups in terms of the percentage change from baseline in BMI (LSM difference −2.33%; 95% CI −5.27% to 0.62). Significantly greater proportions of patients in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group had BMI reductions of ≥5% (38.9% and 46.9% vs 5.4%), ≥10% (31.5% and 42.5% vs 0%) or ≥15% (13.0% and 28.3% vs 0%) (all p < 0.01) [9].

In another 56-week, randomized, double-blind, phase 4 trial (NCT02714062), phentermine/topiramate significantly reduced bodyweight in adolescents with obesity [8]. Eligible patients were aged 12–17 years with a BMI in the 95th percentile or greater for age and sex. Patients were randomized to receive phentermine/topiramate 7.5 mg/46 mg (n = 15) or 15 mg/92 mg (n = 13) or placebo (n = 14) taken orally once daily in the morning and stratified by age group (12–14 vs 15–16 years) and sex. At baseline, bodyweight was 97.8, 99.4 and 111.3 kg in the phentermine/topiramate 7.5 mg/46 mg, phentermine/topiramate 15 mg/92 mg and placebo groups, respectively.
At week 56, bodyweight was significantly reduced in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group, with a LSM percent change from baseline of −3.72% and −4.96% vs 1.06% [difference from placebo −4.78 (95% CI −7.09 to −2.48) and −6.02 (95% CI −8.43 to −3.61), respectively; both \( p < 0.05 \)]. Numerically greater proportions of patients in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group had BMI reductions of ≥5% [13.3% and 50.0% vs 0%; difference from placebo 13.3% (95% CI −24.5 to 47.9) and 50% (95% CI 9.5–78.9), respectively] [8].

### 2.4 Adverse Events

The tolerability profile of phentermine/topiramate, in conjunction with reduced caloric intake and increased physical activity, in adolescents with obesity participating in the pivotal phase 4 study (NCT03922945) was generally consistent that seen previously in clinical trials in adults with obesity [9]. Treatment-emergent AEs occurred in 37.0, 52.2 and 51.8% of patients in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg and placebo groups, respectively. Treatment-emergent AEs occurring at an incidence of >3% and more commonly with phentermine/topiramate 7.5 mg/46 mg or 15 mg/92 mg than placebo were depression (1.9% and 4.4% vs 0%), nausea (3.7% and 4.4% vs 3.6%), pyrexia (1.9% and 4.4% vs 1.8%), dizziness (1.9% and 3.5% vs 0%), arthralgia (1.9% and 3.5% vs 0%), influenza (3.7% and 1.8% vs 0%) and ligament sprain (3.7% and 1.8% vs 0%) [9].

Three serious AEs (bile duct stone, depression and suicidal ideation occurred in two patients receiving phentermine/topiramate 15 mg/92 mg [9]. Across treatment groups, no clinically relevant differences were observed in terms of mental health (mental health questionnaire (Patient Health Questionnaire-9 and Columbia Suicide Severity Rating Scale) or cognition (Cambridge Neuropsychological Test Automated Battery) [9].

In adolescents (aged 12–17 years) with obesity, heart rate elevations occurred at numerically higher incidences in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group [e.g. >5 beats per minute (bpm) 70.4% and 81.4% vs 66.1%; >10 bpm 55.6% and 64.6% vs 46.4%] [3]. Height velocity was lower (by −1.3 to −1.4 cm/year) in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups than in the placebo group [3]. Phentermine/topiramate was associated with less bone mineral acquisition. In a substudy evaluating bone mineral density in adolescents (aged 12–17 years), declines in bone mineral density Z scores of −0.5 or greater from baseline for total body less head occurred in 9 and 30% of patients in the phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg groups compared with 0% of patients in the placebo group [3].

### 2.5 Ongoing Clinical Trials

Recruitment is underway for a phase 2 study (NCT04298203) that will evaluate the role of pharmacotherapy in counteracting weight regain in ≈143 adolescents (aged 12–18 years) with severe obesity. The primary outcome measure is the change in BMI over 58 weeks and secondary outcome measures include changes in total body fat, visceral fat and lipids over 52 weeks.

A pilot, early phase 1 study (NCT04881799) is planned that will evaluate the effects of phentermine/topiramate on BMI, insulin sensitivity and B cell function versus placebo plus standard treatment in patients aged (12–20 years) with obesity and type 2 diabetes. The study plans to enrol ≈30 patients and the primary outcome measure is the change in BMI over 6 months.

### 3 Current Status

Phentermine/topiramate combination received its pediatric first approval in the USA on 20 July 2022 [4] as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in patients aged ≥12 years with BMI in the 95th percentile or greater standardized for age and sex [3].
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