Effect of Co-administration of Qsymia® (Phentermine and Topiramate Extended-release) With Metformin, Sitagliptin, or Probenecid

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BACKGROUND
It is estimated that approximately 120 million adults in the United States are clinically overweight or obese1,2. In recent years, there has been a dramatic increase in obesity in both children and adults.3 Obesity is associated with numerous comorbidities including diabetes, cardiovascular disease, hypertension, stroke, and type 2 diabetes mellitus (T2DM).4,5 Epidemiological data indicate that obesity is associated with increased mortality and a recent study5 concluded that excess body weight during midlife was associated with an increased risk of death.4 A modest weight loss (5-10%) can result in a marked reduction in obesity-related metabolic and cardiovascular risk factors.6,7 Diet, exercise, and behavior modification are the mainstays of treatment, however, most obese individuals do not achieve substantial weight reduction without supplemental pharmacotherapy.

Qsymia® (PHEN/TPM ER) is a fixed-dose combination of phentermine hydrochloride (lipotropic suppressant) and extended-release (ER) topiramate (anti-epileptic with weight loss efficacy), approved for once-daily (QD) combination treatment with reduced-calorie diet and exercise for chronic weight management in individuals with body mass index (BMI) of at least 30 kg/m² or a BMI between 27 and 29.9 kg/m² with at least 1 comorbidity.8 PHEN/TPM ER is taken once a day, with patients starting at the lowest dose of 0.75 mg phentermine/23 mg topiramate, then increasing to the recommended dose (1.5 mg/kg per day). In some circumstances, patients may have their doses increased to the highest dose (5 mg/kg per day).

PURPOSE
This study examined the effect of PHEN/TPM ER co-administration with metformin or sitagliptin, drugs commonly prescribed for T2DM and likely to be co-administered with PHEN/TPM ER. Co-administration of probenecid was also examined, due to evidence of renal tubular re-absorption of topiramate in non-clinical studies.

METHODS
An open-label, non-randomised, fixed-sequence, crossover, Phase 1 study was conducted at a single center.

A total of 20 subjects were enrolled, and 19 completed the study.

- All 20 subjects who were enrolled in the study were included in the analyses, where applicable.
- Only 19 subjects were included in the pharmacokinetic (PK) analyses on Day 34 and only 19 subjects were included in the PK analyses on Day 39.

Subjects were administered oral doses of 1 × 500 mg metformin tablet BID, 1 × 100 mg sitagliptin tablet QD, and 15 mg/92 mg PHEN/TPM ER capsules (days 19–39) plus one dose of 2 g probenecid (PHEN/TPM ER + Probenecid; Days 19–39) doses of 100 mg sitagliptin (Test Treatment on Day 39) with meals (N = 19). Sitagliptin alone was administered with 240 mL of water.

Phenformin + PHEN/TPM ER: Multiple BID doses of 500 mg metformin (Days 30–34) plus multiple QD doses of PHEN/TPM ER capsules (15 mg/92 mg) (Days 19–39)

PHEN/TPM ER Alone: Multiple QD doses of PHEN/TPM ER capsules (15 mg/92 mg) (Days 19–39) [Reference Treatment on Day 28]

Phenformin Alone: Multiple BID doses of 500 mg metformin (Days 1–5) [Reference Treatment on Day 5]

Topiramate Cmax was not evaluable for the one subject on Day 28, one subject on Day 29 and 2 subjects on Day 39.

Nonparametric statistical comparisons of plasma sitagliptin Cmax and AUC parameters following PHEN/TPM ER + sitagliptin and PHEN/TPM ER + probenecid versus PHEN/TPM ER alone are presented in Table 2.

The PK parameters for sitagliptin, metformin, and topiramate in the present study were comparable to previously reported values.31

RESULTS

- The geometric mean plasma phenformin, topiramate, metformin, and sitagliptin concentrations versus time profiles are presented in Figures 1, 2, 3, and 4, respectively.

- The statistical comparisons of plasma phenformin and topiramate Cmax and AUC parameters following PHEN/TPM ER + sitagliptin, and PHEN/TPM ER + probenecid versus PHEN/TPM ER alone are presented in Table 2.

- The statistical comparisons of plasma phenformin and topiramate Cmax and AUC, after multiple doses PHEN/TPM ER suggested phenformin and topiramate concentrations were unaffected by metformin, sitagliptin, or probenecid co-administrations (90% CIs for each comparison were within 80-125%).

- The statistical comparisons of plasma metformin Cmax and AUC, and parameters following metformin + PHEN/TPM ER versus metformin alone are presented in Table 3.

- The statistical comparisons of plasma sitagliptin PK parameters after multiple doses of metformin demonstrated mean maximum (Cmax) and overall (AUC) sitagliptin exposure increased by approximately 15% and 23%, respectively, following PHEN/TPM ER co-administration.

- Nonparametric statistical comparisons of plasma Cmax and AUC values are presented in Table 5 for phenformin and topiramate, Table 6 for metformin, and Table 7 for sitagliptin.

- The nonparametric statistical comparisons of plasma phenformin, topiramate, sitagliptin, and metformin Cmax and AUC values did not show any significant drug-drug interaction effect following PHEN/TPM ER co-administration.

CONCLUSION
No clinically significant drug interactions were observed between PHEN/TPM ER and metformin or sitagliptin nor does no dose adjustment is recommended. Phenformin and topiramate exposures when dosed as a PHEN/TPM ER combination were unaffected by the blocking of renal tubular re-absorption.

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REFERENCES