FAQ based Approach to Prescription of Combination Phentermine plus Topiramate ER

인제의대 일산백병원 가정의학과
윤 영숙

Qsymia® capsule
3.75mg/23mg, 7.5mg/46mg, 11.25mg/69mg, 15mg/92mg

FAQ in a Real World

Qsymia capsule
3.75mg/23mg, 7.5mg/46mg, 11.25mg/69mg, 15mg/92mg

1. Classification of patients who can/cannot use Qsymia according to comorbidities?

AACE/ACE Guidelines 2016:

Medical Care of Patients with Obesity

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	CAD			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	Mild (50–79 mL/min)					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	Mild-Moderate (Child-Pugh 5–9)	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

AACE, The American Association of Clinical Endocrinology; ACE, American College of Endocrinology; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure, HTN, hypertension; T2DM, type 2 diabetes mellitus.

Reference. ***1.*** *Garvey WT, et al. Endocr Pract. 2016;22(7):842-884.*

1) Can patients with diabetes take Qsymia for weight loss?

AACE/ACE Guidelines 2016:

Medical Care of Patients with Obesity

TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

	DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	Clinical Component	Intervention/ Weight-Loss Goal	Clinical Goals
TERTIARY PREVENTION				
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome	10%	Prevention of T2DM
		Prediabetes	10%	Prevention of T2DM
		T2DM	5-15% or more	• Reduction in A1C • Reduction in number and/or doses of glucose-lowering medications • Diabetes remission especially when diabetes duration is short
		Dyslipidemia	5-15% or more	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension	5-15% or more	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications

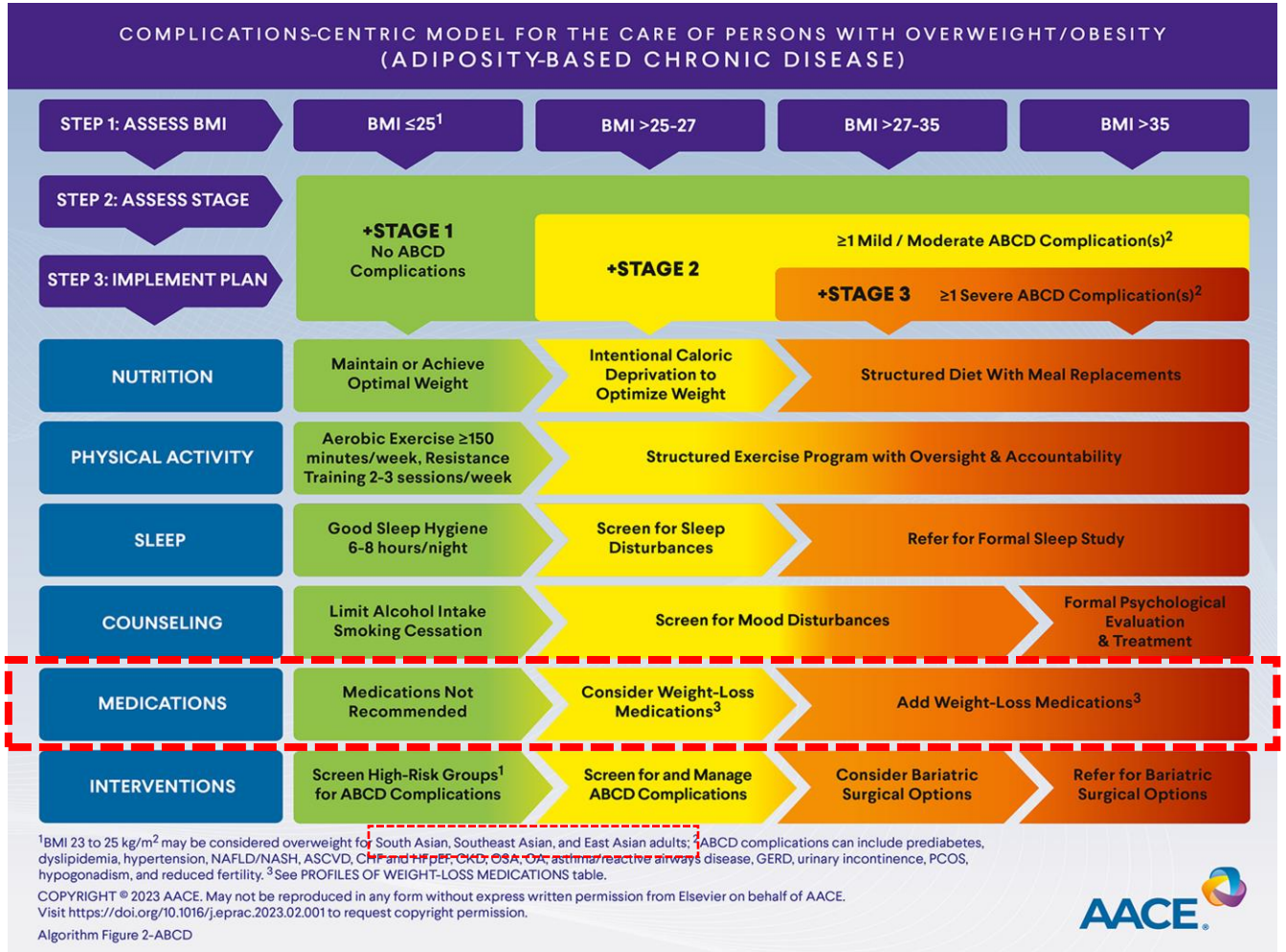
AACE, The American Association of Clinical Endocrinology; ACE, American College of Endocrinology; A1C, hemoglobin A1c; BEL, best evidence level; BMI, body mass index; BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

Reference. **1.** *Garvey WT, et al. Endocr Pract. 2016;22(7):842-884.*

Recommendations	Recommendation grade
체중 감량은 당뇨병 위험(예: 당뇨병 전증, 대사 증후군)을 치료하고 제2형 당뇨병으로의 진행을 예방하는 데 효과적입니까? 얼마나 많은 체중 감량이 필요합니까?	
• **R31.** Medication-assisted weight loss employing phentermine/topiramate ER, liraglutide 3 mg, or orlistat should be considered in patients at risk for future T2DM and should be used when needed to achieve 10% weight loss in conjunction with lifestyle therapy.	**A** (BEL 1)
제2형 당뇨병 치료에 체중 감량이 효과적인가? 얼마나 많은 체중 감량이 필요합니까?	
• **R33.** Patients with overweight or obesity and T2DM should be treated with lifestyle therapy to achieve 5 to 15% weight loss or more as needed to achieve targeted lowering of A1C. Weight-loss therapy should be considered regardless of the duration or severity of T2DM, both in newly diagnosed patients and in patients with longer-term disease on multiple diabetes medications.	**A** (BEL 1)
• **R34.** Weight-loss medications should be considered as an adjunct to lifestyle therapy in all patients with T2DM as needed for weight loss sufficient to improve glycemic control, lipids, and blood pressure.	**A** (BEL 1)

AACE Consensus Statement 2023:

Comprehensive Type 2 Diabetes Management Algorithm



Weight-loss medications should be considered, in combination with a reduced-calorie diet, to achieve and sustain weight-loss goals in patients with BMI 27 kg/m^2 to 29.9 kg/m^2 with T2D or ≥1 ABCD complication and all persons with a BMI >30 kg/m^2.

*Overweight (≥25 kg/m^2), obese (≥30 kg/m^2): noting that lower thresholds for overweight/obesity may apply for South, East, and Southeast Asian persons (≥23.5 kg/m^2 for overweight and ≥25 kg/m^2 for obese).

- ✓ ***ABCD complications*** *can include* ***prediabetes****, dyslipidemia,* ***hypertension****, ASCVD, CHF & HFpEF, and CKD.*
- ✓ *The highest* ***stage 3*** *includes patients with multiple and/or more severe complications and applies to patients already diagnosed with* ***T2D*** *as a severe ABCD complication.*

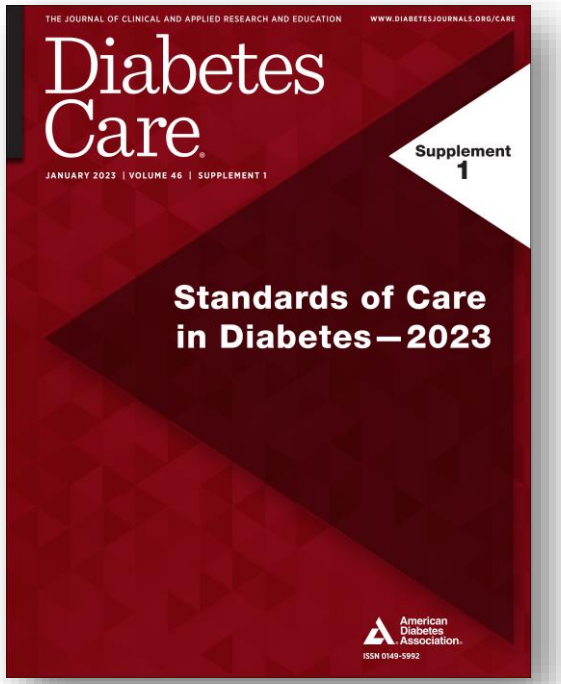
AACE, American Association of Clinical Endocrinology; ABCD, adiposity-based chronic disease; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; T2D, Type 2 Diabetes.

Reference. ***1.*** *Samson SL, et al. Endocr Pract. 2023;29(5):305-340.*

ADA Guidelines 2023:

Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

Recommendations	Level of Evidence
8.5 Individuals with diabetes and overweight or obesity may benefit fro m modest or larger magnitudes of weight loss.	
• Relatively small weight loss (approximately **3–7%** of baseline weight) improves glycemia and other intermediate cardiovascular risk factors.	**A**
• **Larger, sustained weight losses (>10%)** usually confer greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality.	**B**



ADA, American Diabetes Association.

Reference. **1.** *ElSayed NA, et al. Diabetes Care. 2023;46(Suppl 1):S128-S139.*

Qsymia capsule

ADA Guidelines 2023:

Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

Recommendations	Level of Evidence
8.16 Obesity pharmacotherapy is effective as an adjunct to nutrition, physical activity, and behavioral counseling for selected people with type 2 diabetes and BMI ≥27 kg/m^2. Potential benefits and risks must be considered.	**A**
8.17 If obesity pharmacotherapy is effective (typically defined as ≥5% weight loss after 3 months' use), further weight loss is likely with continued use. When early response is insufficient (typically <5% weight loss after 3 months' use) or if there are significant safety or tolerability issues, consider discontinuation of the medication and evaluate alternative medications or treatment approaches.	**A**

Treatment options for overweight and obesity in type 2 diabetes

Treatment	BMI category (kg/m^2)		
	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–27.4*)	≥30.0 (or 27.5*)
Nutrition, physical activity, and behavioral counseling	†	†	†
Pharmacotherapy		†	†
Metabolic surgery			†

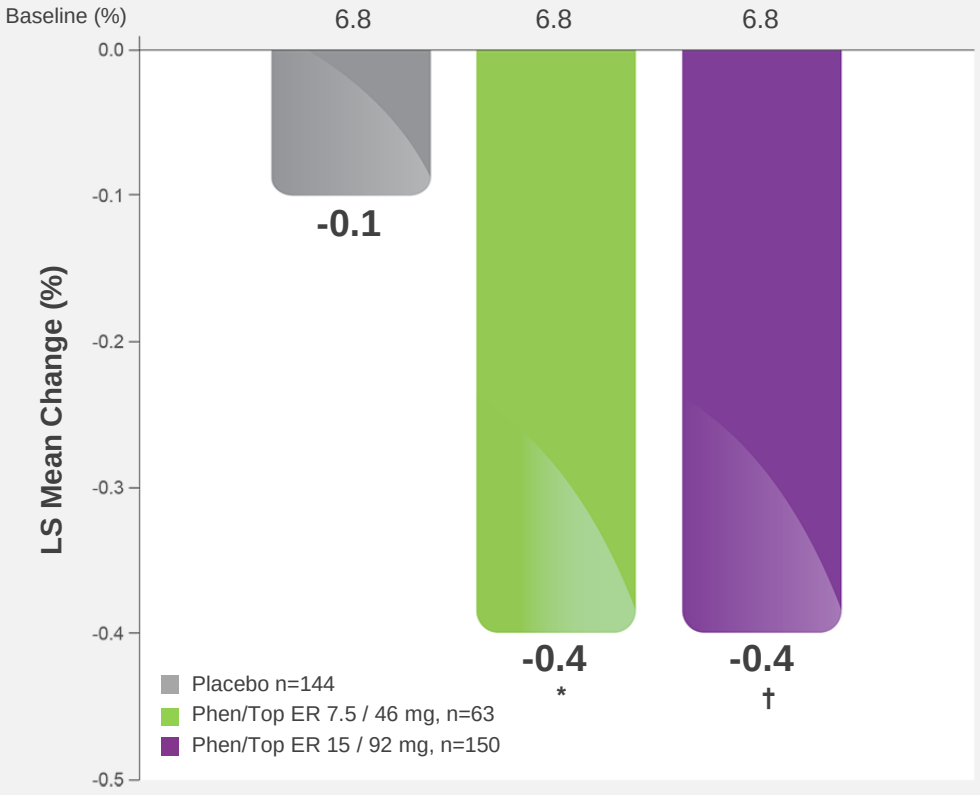
*Recommended cut points for Asian American individuals (expert opinion). †Treatment may be indicated for select motivated individuals.

ADA, American Diabetes Association; BMI, body mass index.

Reference. 1. *ElSayed NA, et al. Diabetes Care. 2023;46(Suppl 1):S128-S139.*

CONQUER Subgroup Analysis: Obese patients with Diabetes

Change in HbA1c at Week 56



Anti-Diabetic Medications

Number (%) of Patients	Placebo (n=157)	Phen/Top ER	
		7.5 / 46 mg (n=67)	15 / 92 mg (n=164)
Starting new	14.6	4.5	4.3
Discontinuing existing	2.5	3.0	3.7

HbA1c, glycated hemoglobin; LS, least-squares; Phen/Top ER, phentermine/topiramate extended-release

In Korea, topiramate in Qsymia capsule is not defined as extended-release or controlled-release formulation. Qsymia is not indicated for the treatment of type 2 diabetes.

Reference. ***1.*** *Gadde KM, et al. Lancet. 2011 Apr 16;377(9774):1341-52.*

Qsymia® capsule

2) Can patients with high blood pressure use Qsymia for weight loss?

AACE/ACE Guidelines 2016: Medical Care of Patients with Obesity

TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

	DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	Clinical Component	Intervention/ Weight-Loss Goal	Clinical Goals
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		Prediabetes	10%	Prevention of T2DM
		T2DM	5-15% or more	• Reduction in A1C • Reduction in number and/or doses of glucose-lowering medications • Diabetes remission especially when diabetes duration is short
		Dyslipidemia	5-15% or more	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension	5-15% or more	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications

Recommendations	Recommendation grade
고혈압 치료에 체중 감량이 효과적인가? 얼마나 많은 체중 감량이 필요합니까?	
• **R39.** Patients with overweight or obesity and elevated blood pressure or hypertension should be treated with lifestyle therapy to **achieve 5 to 15% weight loss or more** as necessary to achieve blood pressure reduction goals in a program that includes caloric restriction and regular physical activity.	**A** (BEL 1)
• **R40.** Patients with overweight or obesity and elevated blood pressure or hypertension should be considered for treatment with a **weight-loss medication** combined with lifestyle therapy when necessary to achieve sufficient weight loss for blood pressure reduction.	**A** (BEL 1)

AACE, The American Association of Clinical Endocrinology; ACE, American College of Endocrinology; A1C, hemoglobin A1c; BEL, best evidence level; BMI, body mass index; BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

Reference. **1.** *Garvey WT, et al. Endocr Pract. 2016;22(7):842-884.*

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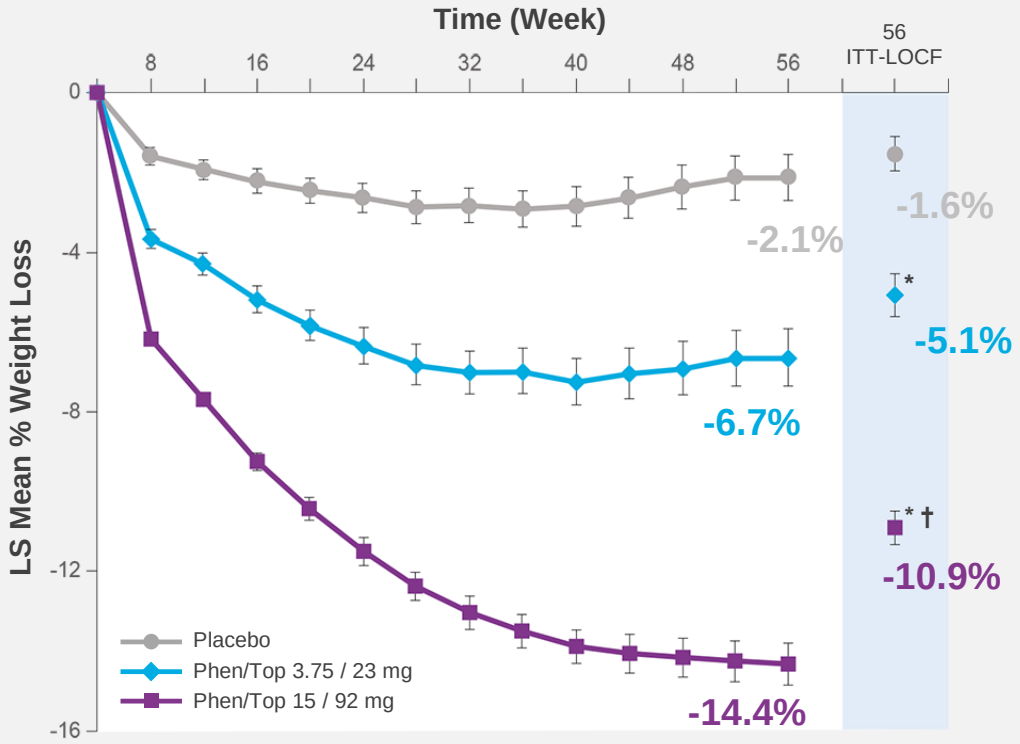
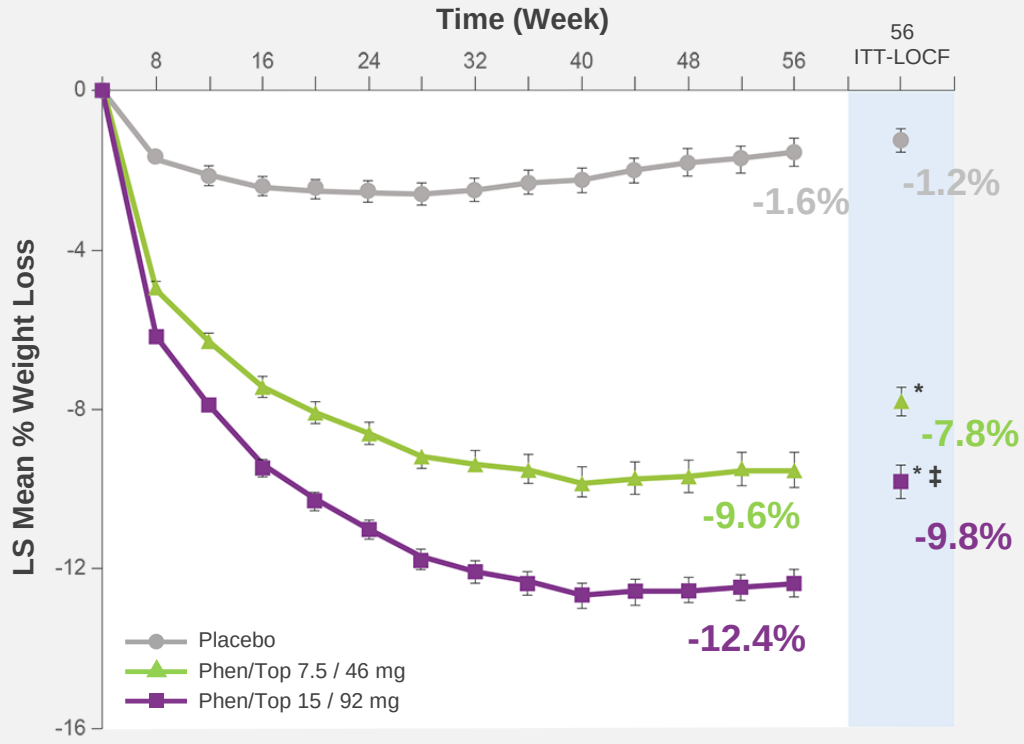
Pivotal Studies:
Weight Loss Over Time (Completers Data)

EQUIP [1]



CONQUER [2]



*p<0.0001 vs placebo; †p < 0.0001 vs Phen/Top ER 3.75 / 23 mg; ‡p < 0.0001 vs Phen/Top ER 7.5 / 46mg

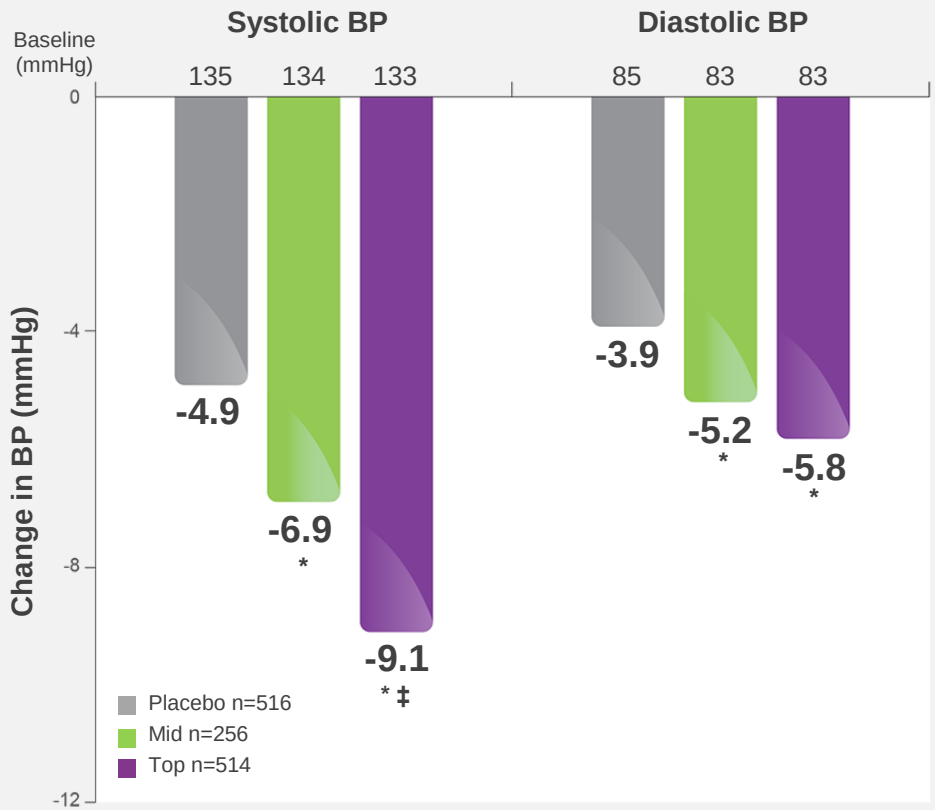
Curves are plotted for completers by visit. Error bars represent 95% confidence interval. ITT, intent-to-treat; LOCF, last observation carried forward; LS, least-squares; Phen/Top ER, phentermine/topiramate extended-release

In Korea, topiramate in Qsymia capsule is not defined as extended-release or controlled-release formulation.

References. ***1.*** *Allison DB, et al. Obesity (Silver Spring). 2012 Feb;20(2):330-42.* ***2.*** *Gadde KM, et al. Lancet. 2011 Apr 16;377(9774):1341-52.*

Qsymia® capsule

CONQUER Subgroup Analysis:
patients with obesity & Hypertension



*p<0.05 vs placebo; ‡p<0.05 vs Phen/Top ER 7.5 / 46 mg

BP, blood pressure; LS, least-squares; Phen/Top ER, phentermine/topiramate extended-release

Anti-Hypertensive Medications

Number (%) of Patients	Placebo (n=516)	Phen/Top ER	
		7.5 / 46 mg (n=256)	15 / 92 mg (n=514)
Starting new	8.1	3.9	4.3
Discontinuing existing	4.7	10.5	14.8

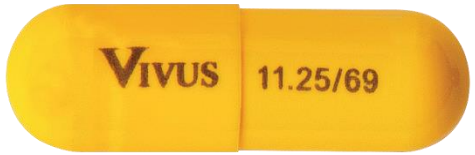
In Korea, topiramate in Qsymia capsule is not defined as extended-release or controlled-release formulation.
Qsymia is not indicated for the treatment of hypertension.

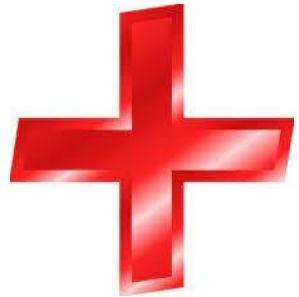
References. ***1.*** *Gadde KM, et al. Lancet. 2011 Apr 16;377(9774):1341-52.*

2. *FDA Medical Review from Drug Approval Package. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022580Orig1s000MedR.pdf (accessed on 28 Apr 2022)*

Qsymia® capsule

2. vs. Generic Phentermine and Topiramate?

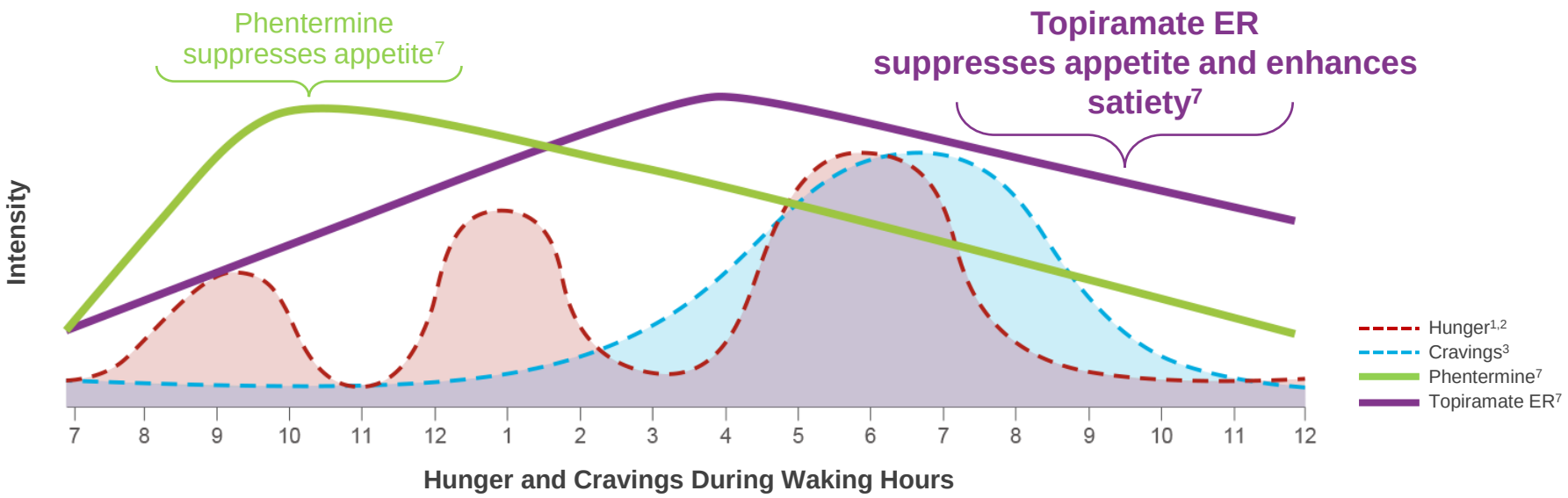




Qsymia capsule

Theoretical Rationale for Combination Therapy With Qsymia

Hypothetical representations of hunger and cravings in the average population overlaid with the release of the individual components of Phen/Top ER[1-7,a]



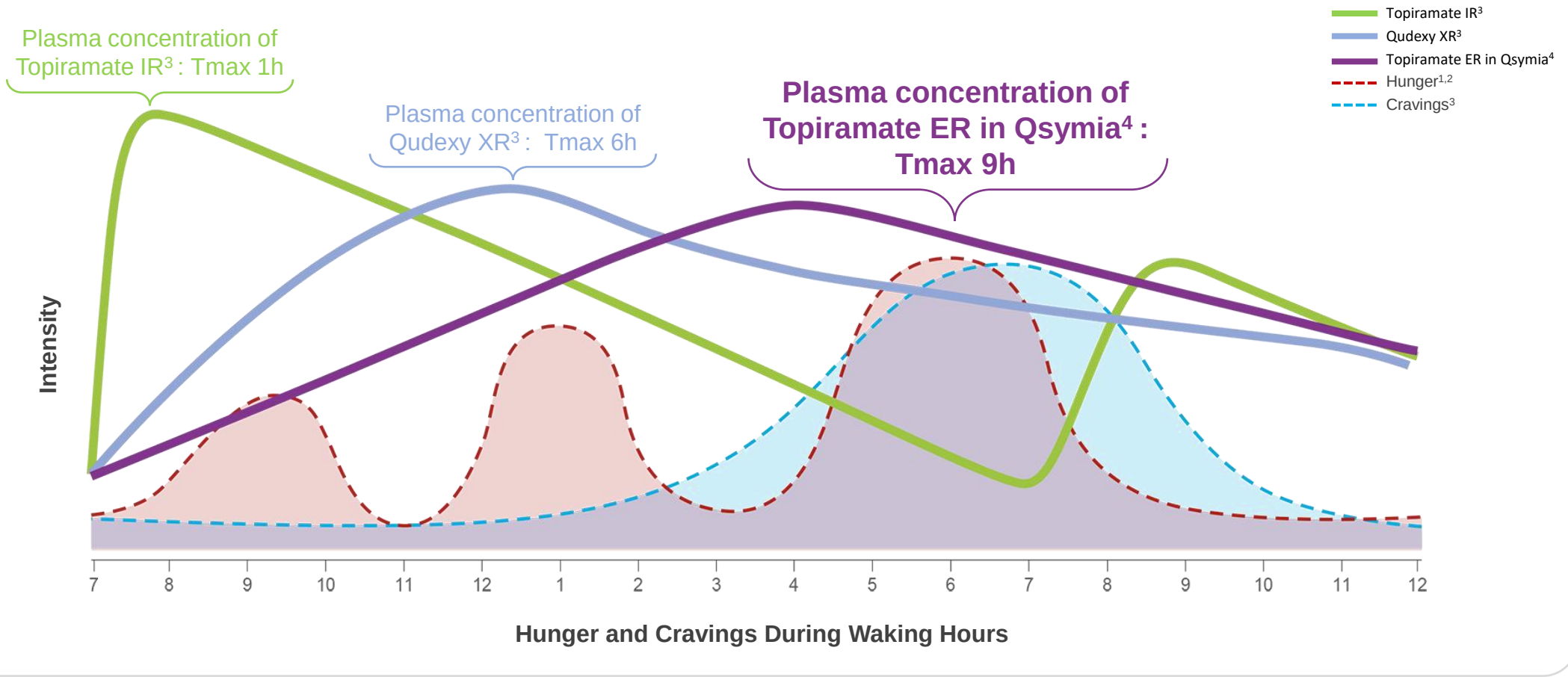
Phen/Top ER combines immediate-release and extended-release medications to help suppress appetite and enhance satiety throughout the day[7]

The precise mechanism of action of phentermine and topiramate are not known.[7]

[a]Hypothetical representation of hunger and cravings is not representative of all patients.

References. ***1.*** *Hill AJ et al. Appetite. 1991;17(3):187-197.* ***2.*** *Stubbs RJ et al. Physiol Behav. 2001;72(4):615-619.* ***3.*** *Pelchat ML. Appetite. 1997;28(2):103-113.* ***4.*** *Isaksson H et al. Food Nutr Res. 2008;52.* ***5.*** *Hill AJ. Proc Nutr Soc. 2007;66(2):277-285.* ***6.*** *Hill AJ, Heaton-Brown L. J Psychosom Res. 1994;38(8):801-814.* ***7.*** *Phen/Top ER [prescribing information]. Mountain View, CA: VIVUS, Inc; 2014.*

Theoretical Rationale for Topiramate ER in Qsymia



[a]Hypothetical representation of hunger and cravings is not representative of all patients.

References. ***1.*** *Hill AJ et al. Appetite. 1991;17(3):187-197.* ***2.*** *Stubbs RJ et al. Physiol Behav. 2001;72(4):615-619.* ***3.*** *Meir Bialer et al. Epilepsia. 2013;54(8):1444–1452* ***4.*** *Phen/Top ER [prescribing information]. Mountain View, CA: VIVUS, Inc; 2014.*

Qsymia® capsule

Compared the combination of phentermine and topiramate ER with its components as monotherapies

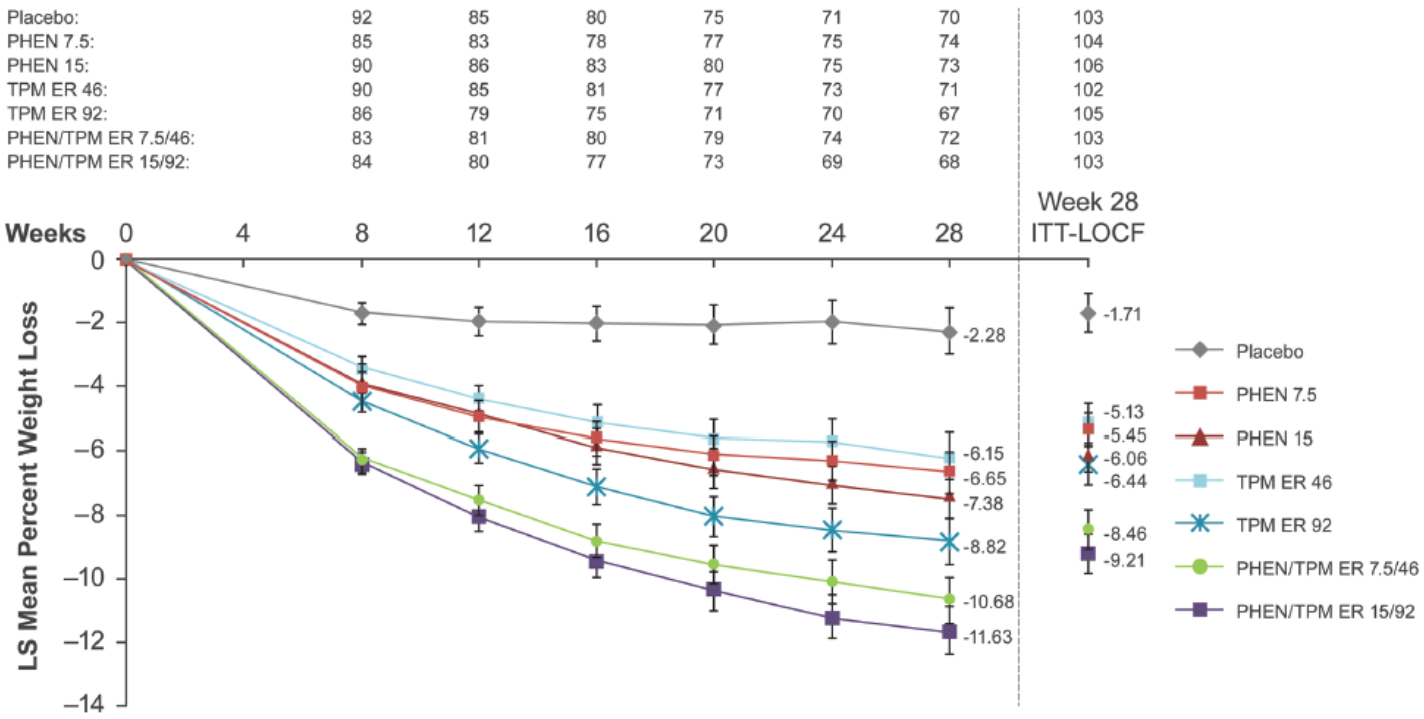


FIGURE 2 LS mean percent weight loss overtime (mITT). $P < 0.05$ vs. placebo at all time points except week 0 for all comparisons between PHEN/TPM ER and placebo or the individual components except PHEN/TPM ER 7.5/46 vs. topiramate ER 92 at weeks 20, 24, and 28 in the mITT population. All week 28 comparisons between PHEN/TPM ER and placebo or the individual components in the ITT-LOCF population were significant. LS, least squares; PHEN/TPM ER 15/92, phentermine 15 mg and topiramate extended-release 92 mg; PHEN 15, phentermine 15 mg; TPM ER 92, topiramate extended-release 92 mg; PHEN/TPM ER 7.5/46, phentermine 7.5 mg/topiramate extended-release 46 mg; PHEN 7.5, phentermine 7.5 mg; TPM ER 46, topiramate extended-release 46 mg.

Reference. ***1.*** *Obesity (2013) 21, 2163–2171 et al. Louis J. Aronne*

Qsymia capsule

3. Adolescent?

체질량지수(BMI) 95번째 백분위수로 정의되는 비만인 12세 이상 소아 환자

FDA

식품의약품안전처

NEJM Evidence

DOI: 10.1056/EV

APPROVED

NOT APPROVED

ORIGINAL ARTICLE

Phentermine/Topiramate reatn Adolescent Obesity

Aaron S. Kelly, Ph.D.,[1] Megan O. Bensignor, M.D.,[1] Daniel S. Hsia, M.D.,[2] Ashley H. Shoemaker, M.D.,[3] Winnie Shih,[4] Craig Peterson, M.S.,[4] and Santosh T. Varghese, M.D.,[4] for the Trial Investigators*

Qsymia capsule

Guideline for adolescent by KFDA

마약류통합관리시스템

식품의약품안전처 보도자료

보도시점 배포 즉시 배포 2023. 4. 27.(목)

<마약류통합관리시스템> <식욕억제제·프로포폴·졸피뎀>

마약류 오남용! 마통은 다 보고 있다… 사전알리미 시행

- 식약처, 2023년 의료용 마약류에 대한 오남용 사전알리미 시행
- 식욕억제제 2종 이상 병용 처방 등 의사 1,129명 대상 서면 통지
- 프로포폴 월 1회 초과 투약 등 의사 316명 대상 서면 통지
- 졸피뎀 1개월 초과 처방 등 의사 2,512명 대상 서면 통지

식품의약품안전처(처장 오유경)은 식욕억제제*·졸피뎀·프로포폴의 오남용 조치기준**을 벗어나 처방한 의사 3,957명(식욕억제제 1,129명, 프로포폴 316명, 졸피뎀 2,512명)에게 해당 내용을 서면으로 통지하고 개선 여부를 추적·관리하는 '사전알리미'를 시행합니다.

* 펜터민, 펜디메트라진, 디에틸프로피온(암페프라몬), 마진돌, 펜터민/토피라메이트(복합제)를 주성분으로 하는 향정신성의약품

** 「마약류 오남용 방지를 위한 조치기준」(식약처 고시) [별표] 마약류의 오남용 방지를 위한 조치사유

<마약류 오남용 방지를 위한 조치 절차(사전알리미)>

이번 조치는 2022년 9월부터 2023년 2월까지 6개월간 마약류통합관리시스템으로 수집된 의료용 마약류 처방 빅데이터를 분석한 결과를 바탕으로 실시하는 것으로, 2020년 이후 세 번째로 시행하는 것입니다.

식욕억제제·프로포폴·졸피뎀의 사전알리미 대상 의사 수는 지난 3년간 전반적으로 감소하는 추세로, 특히 올해는 지난해(4,154명) 대비 197명이 감소했습니다.

* 연도별 사전알리미(정보제공) 대상 의사 수

- 식욕억제제 : ('21년) 1,755명 → ('22년) 1,708명 → ('23년) 1,129명
- 프로포폴 : ('21년) 478명 → ('22년) 488명 → ('23년) 316명
- 졸피뎀 : ('21년) 1,720명 → ('22년) 1,958명 → ('23년) 2,512명(종전기준 적용 시 1,394명)

- 1 -

붙임 2 식욕억제제·프로포폴·졸피뎀 오남용 조치기준 주요내용

구분	조치사유
식욕억제제	가. 3개월 초과 처방·투약한 경우(단일제)
	나. 2종 이상의 식욕억제제 병용 처방·투약한 경우
	다. 청소년·어린이 처방·투약한 경우 * (단일제) 만 16세 이하 / (복합제) 만 18세 미만
프로포폴 (마취제)	가. 전신마취 수술·시술 및 진단이나 인공호흡 중환자의 진정 목적을 벗어나 사용한 경우
	나. 최대 허가용량 초과 투약한 경우 * (남성) 7,450mg, (여성) 5,960mg 기준
	다. 간단한 시술·진단에 월 1회 초과 투약한 경우
졸피뎀 (최면진정제)	가. 1개월 초과 처방·투약한 경우
	나. 만 18세 미만 처방·투약한 경우
	다. 하루 10mg(속효성) 초과 처방·투약한 경우

Qsymia capsule

4. Treatment period?

Evaluation of Phentermine and Topiramate versus Phentermine/Topiramate Extended-Release in Obese Adults

Louis J. Aronne[1], Thomas A. Wadden[2], Craig Peterson[3], David Winslow[4], Sarah Odeh[5] and Kishore M. Gadde[6]

Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)

David B. Allison[1,2], Kishore M. Gadde[3], William Timothy Garvey[2,4], Craig A. Peterson[5], Michael L. Schwiers[6], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Kishore M Gadde, David B Allison, Donna H Ryan, Craig A Peterson, Barbara Troupin, Michael L Schwiers, Wesley W Day

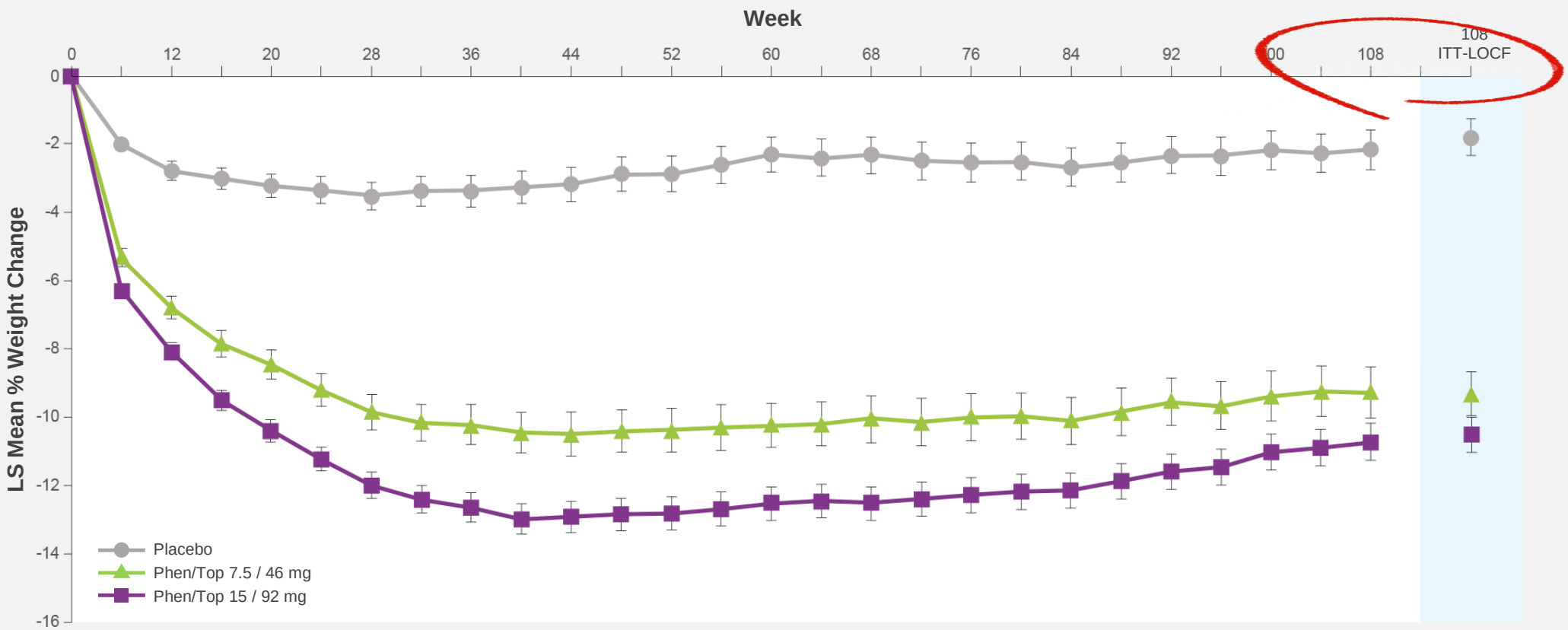
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1–3]

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden

Phase 3 : 4 trials

Qsymia capsule

2-Year Cohort (Completers Data)
LS Mean Percent Weight Change Over time



Completers & ITT-LOCF, p < 0.0001 vs placebo at all time points assessed.
Error bars represent 95% confidence interval. ITT, intent-to-treat; LOCF, last observation carried forward; LS, least-squares; Phen/Top ER, phentermine/topiramate extended-release

In Korea, topiramate in Qsymia capsule is not defined as extended-release or controlled-release formulation.

Reference. ***1.*** *Garvey WT, et al. Am J Clin Nutr. 2012 Feb;95(2):297-308.*

Qsymia capsule

Guideline by KFDA

의료용 마약류 식욕억제제 안전사용을 위한 기준(안)

2020. 8.

식품의약품안전처 마 약 관 리 과

Ⅰ 의료용 마약류 식욕억제제 안전사용을 위한 기준

< 주요 내용 >

- ◆ 의료용 마약류 식욕억제제는 비만 치료 목적으로 사용하여야 한다.
- ◆ 의료용 마약류 식욕억제제 사용 시 남용 및 의존 가능성을 항상 염두에 두어야 한다.
- ◆ "펜터민, 펜디메트라진, 디에틸프로피온, 마진돌" 은 허가용량 내 4주 이내 단기처방하며, 최대 3개월 이내 사용한다.
- ◆ 의료용 마약류 식욕억제제는 다른 의료용 마약류 식욕억제제와 병용하지 않는다.
- ◆ 의료용 마약류 식욕억제제는 어린이 및 청소년에게 사용하지 않는다.

1 국내 허가된 의료용 마약류 식욕억제제 종류

연번	주성분	허가사항	작용기전
1	펜터민	단기사용	Sympathomimetic amine
2	펜디메트라진	단기사용	Sympathomimetic amine
3	디에틸프로피온	단기사용	Sympathomimetic amine
4	마진돌	단기사용	Sympathomimetic amine
5	펜터민/토피라메이트	장기사용	Sympathomimetic amine/ antiepileptic drug

※ '로카세린' 성분 제제는 국내에서 향정신성의약품 식욕억제제로 2015년에 허가되었으나, 2019년 2월 암 발생 가능성 증가 위험으로 인하여 처방·복용 중단 및 회수 진행

5. Discontinued?

Dosing & Administration

Take Qsymia once daily in the morning with or without food. Avoid dosing with Qsymia in the evening due to the possibility of insomnia.

- **Start treatment with Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topirmate 23 mg) daily for 14 days; after 14 dats increase to the recommended dose of Qsymia 7.5 mg/46 mg (phentermine 7.5 mg/topiramate 46 mg) once daily.**
- **Evaluate weight loss after 12 weeks of treatment with Qsymia 7.5 mg/46 mg.**

  If a patient has not lost at least 3% of baseline body weight on Qsymia. 7.5 mg/46 mg, discontinue Qsymia or escalate the dose, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss at the Qsymai 7.5 mg/46 mg dose.

  To escalate the dose: Increase to Qsymia 11.25 mg/69 mg (phentermine 11.25 mg/topiramate 69 mg extended-release) daily for 14 days; followed by dosing Qsymia 15 mg/92 mg (phentermine 15 mg/ topiramate 92 mg extended-release) once daily.
- **Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after an additional 12 weeks of treatment.**

  If a patient has not lost at least 5% of baseline body weight on Qsymia 15 mg/92 mg, discontinue Qsymia as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss woth continued treatment.
- **Qsymia 3.75 mg/23 mg and Qsymia 11.25 mg/69 mg are for titration purposes only.**

Discontinue 15 mg / 92 mg gradually by taking a dose every other day for at least 1 week prior to stopping treatment altogether, due to the possibility of precipitating a seizure

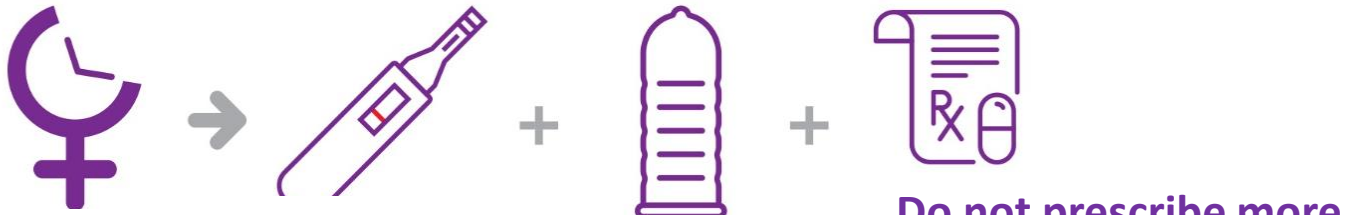
Reference. **1.** *Qsymia Product Information, Available at https://nedrug.mfds.go.kr, accessed on May 31, 2022*

Qsymia capsule

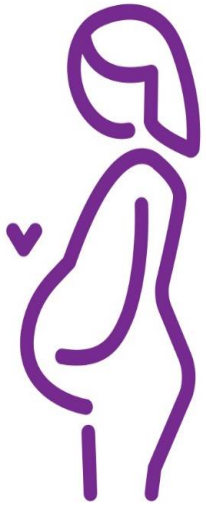
6. Pregnancy?

Fetal toxicity

- **Qsymia can cause fetal harm.**
  Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to **topiramate**, a component of Qsymia, has an increased risk of **cleft lip and cleft palate** (cleft lip with or without cleft palate).
- **If Qsymia is used during pregnancy or if a patient becomes pregnant while taking Qsymia,** treatment should be discontinued immediately, and the patient should be apprised of the potential hazard to a fetus.
- **Woman of childbearing potential should have a negative pregnancy test before starting Qsymia and monthly thereafter during Qsymia therapy**.
  To do this, do not prescribe more than one month's supply of medicine. Woman of childbearing potential should use effective contraception during Qsymia therapy.



Woman of childbearing potential → **Pregnancy test (Monthly)** + **Contraception** + **Do not prescribe more than one month's supply of medicine.**



STOP

Treatment discontinuation + Apprise to patient

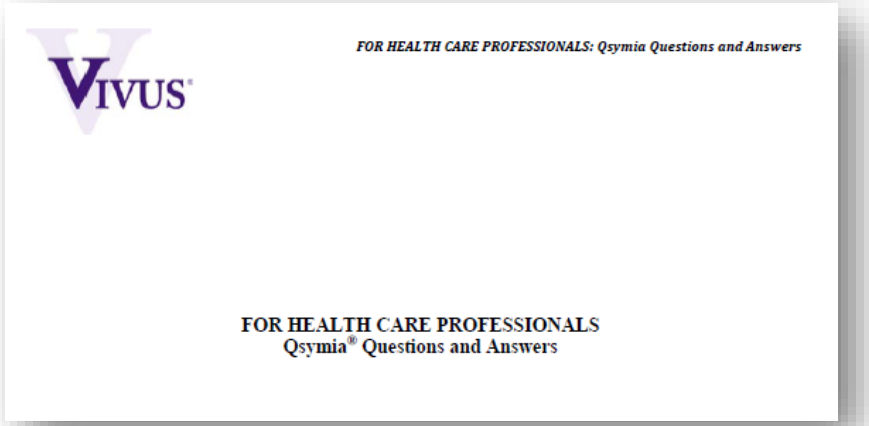
Qsymia capsule

Pregnancy?

Table 1. Current FDA Pregnancy Categories

Category	Description
A	Well-controlled studies in humans show no risk to the fetus
B	No well-controlled studies have been conducted in humans; animal studies show no risk to the fetus
C	No well-controlled studies have been conducted in humans; animal studies have demonstrated an adverse effect on the fetus
D	Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations
X	Controlled studies in animals or humans demonstrate fetal abnormalities; the risk in pregnant women clearly outweighs any possible benefit

Source: Reference 1.



11. Once Qsymia is discontinued, how long should a woman wait to get pregnant? The mean phentermine terminal half-life is about 20 hours and the mean topiramate terminal half-life is about 65 hours. The rule of thumb is to wait at least 5 times the half-life number for complete clearance. Additionally, to remove any concern for pregnancy-related issues, this half-life number should be doubled. Thus, the recommendation is to wait 28 days post-discontinuation of Qsymia before discontinuing contraception and attempting to become pregnant. Please note that

Qsymia capsule

7. Blurred vision?

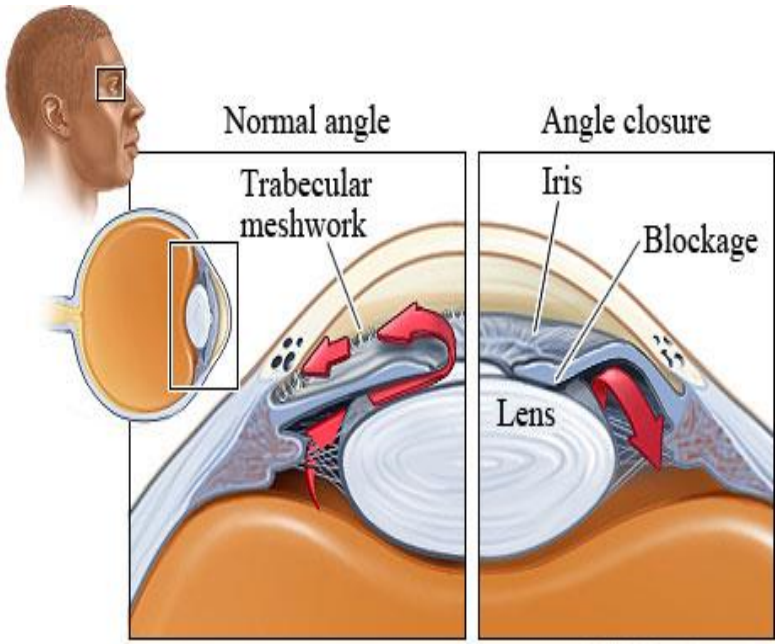
Table 3. Adverse Reactions Reported in ≥2% of QSYMIA-Treated Adults with Overweight or Obesity and More Frequently than Placebo in Overall Study Population of 1 Year Duration

Preferred Term	Placebo (N = 1561) %	QSYMIA 3.75 mg/23 mg (N = 240) %	QSYMIA 7.5 mg/46 mg (N = 498) %	QSYMIA 15 mg/92 mg (N = 1580) %
Paraesthesia	2	4	14	20
Dry Mouth	3	7	14	19
Constipation	6	8	15	16
Upper Respiratory Tract Infection	13	16	12	14
Headache	9	10	7	11
Dysgeusia	1	1	7	9
Insomnia	5	5	6	9
Nasopharyngitis	8	13	11	9
Dizziness	3	3	7	9
Sinusitis	6	8	7	8
Nausea	4	6	4	7
Back Pain	5	5	6	7
Fatigue	4	5	4	6
Diarrhea	5	5	6	6
Vision Blurred	4	6	4	5

EXTERNAL EMAIL

SOC	PREFERREDTERM	Count of PREFERREDTERM		
Eye disorders	Angle closure glaucoma	29	0.397	% of angle closure glaucoma out of 7305 from the beginning to Dec 31, 2021.
	Glaucoma	7	0.096	% of glaucoma out of 7305
Grand Total		7305		

We cannot assume the 'glaucoma' was 'open angle' since the report only mentions glaucoma.



Qsymia capsule

Blurred vision and angle-closure glaucoma

- **Blurred vision**
  - **The first presenting symptom of acute secondary angle-closure glaucoma** in many patients was blurring o f vision.[1]
- **Secondary angle closure glaucoma**
  - **Acute myopia** associated with secondary angle closure glaucoma has been reported in patients treated with topiramate.[2]
  - Symptoms typically occur **within 1 month of initiating treatment** with topiramate.[2]
  - Overall, topiramate-induced angle-closure glaucoma is **rare**.[3]
  - **The mechanism is not well-known**. One theory proposes that topiramate may cause excessive fluid accum ulation within the ciliary body and choroid.[3]
  - It has been suggested that supraciliary effusion and ciliary body swelling may displace the lens and iris ant eriorly, secondarily resulting in angle closure glaucoma.[2,4]

References. ***1.*** *Fraunfelder FW, et al. Ophthalmology. 2004;111(1):109-111.* ***2.*** *FDA-Approved Drugs: QSYMIA®. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/ (accessed on Jul 2023).* ***3.*** *Mechrgui M, et al. 2022;14(8):e28513.* ***4.*** *Hilton EJ, et al. Seizure. 2004;13(2):113-128.*

Qsymia® capsule

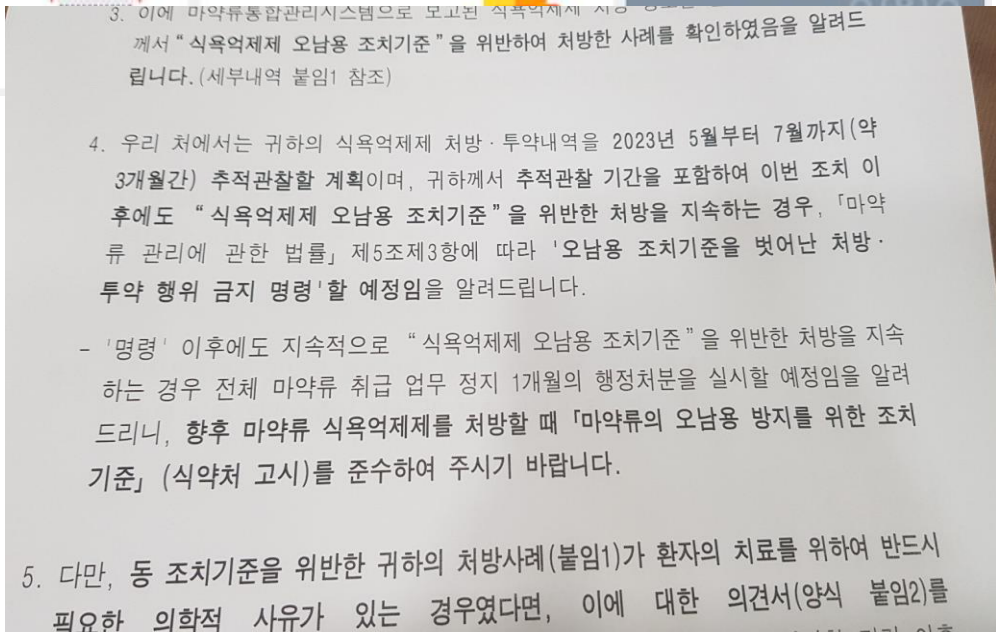
Management of angle-closure glaucoma

- The primary treatment to reverse symptoms is **discontinuation of QSYMIA** as rapidly as possible.[1]
- In most cases of topiramate-induced angle-closure glaucoma, symptoms **resolved soon after cessation of the drug**.[2]
- **The prognosis is favorable** if the medicine is discontinued early and proper treatment is provided.[3]
- **Intraocular pressure, refractive error, and visual acuity** usually return to normal as the ciliochoroidal effusions resolve.[3]

References. ***1.*** *FDA-Approved Drugs: QSYMIA®. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/ (accessed on Jul 2023).* ***2.*** *Abtahi MA, et al. Clin Ophthalmol. 2012;6:117-131.* ***3.*** *Mechrgui M, et al. 2022;14(8):e28513.*

Qsymia® capsule

8. NIMS? (Narcotics Information Management System: 마약류통합관리시스템)



게서 "식욕억제제 오남용 조치기준"을 위반하여 처방한 사례를 확인하였음을 알려드립니다.(세부내역 붙임1 참조)

4. 우리 처에서는 귀하의 식욕억제제 처방·투약내역을 2023년 5월부터 7월까지(약 3개월간) 추적관찰할 계획이며, 귀하께서 추적관찰 기간을 포함하여 이번 조치 이후에도 "식욕억제제 오남용 조치기준"을 위반한 처방을 지속하는 경우, 「마약류 관리에 관한 법률」 제5조제3항에 따라 '오남용 조치기준을 벗어난 처방·투약 행위 금지 명령'할 예정임을 알려드립니다.

- '명령' 이후에도 지속적으로 "식욕억제제 오남용 조치기준"을 위반한 처방을 지속하는 경우 전체 마약류 취급 업무 정지 1개월의 행정처분을 실시할 예정임을 알려드리니, 향후 마약류 식욕억제제를 처방할 때 「마약류의 오남용 방지를 위한 조치기준」(식약처 고시)를 준수하여 주시기 바랍니다.

5. 다만, 동 조치기준을 위반한 귀하의 처방사례(붙임1)가 환자의 치료를 위하여 반드시 필요한 의학적 사유가 있는 경우였다면, 이에 대한 의견서(양식 붙임2)를

< 사전알리미 운영 절차>

사전알리미 (정보제공) ⇨ 의사면허원토 및 추적관찰 ⇨ 사전통지 ⇨ 행정조치 ⇨ 조치이행 확인 ⇨ 후속조치 (감시·처분)

※ **근거법령**

「마약류 관리에 관한 법률」 제5조(마약류 등의 취급 제한) ③ 식품의약품안전처장은 공익을 위하여 필요하다고 인정하는 때에는 (생략) **사용을 금지 또는 제한하거나 그 밖의 필요한 조치를 할 수 있다.**

3. **마약류 품목허가증에 기재된 용량 이상의 마약 또는 향정신성의약품을 남용하였다고 인정하는 경우**
4. 마약 또는 향정신성의약품에 대한 **신체적·정신적 의존성을 야기하게 할 염려가 있을 정도로 마약 또는 향정신성의약품을 장기 또는 계속 투약하거나 투약하기 위하여 제공하는 경우**
5. **그 밖에 대통령령으로 정하는 경우**

「마약류 관리에 관한 법률 시행령」 제5조(마약류 취급의 금지 및 제한) ③ 법 제5조제3항에 따른 조치의 세부기준은 식품의약품안전처장이 정하여 고시한다.

「마약류의 오남용 방지를 위한 조치기준」 제2조(조치사유 등) ① 식품의약품안전처장이 마약류취급의료업자를 대상으로 「마약류 관리에 관한 법률」 제5조제3항 및 같은 법 시행령 제5조제3항에 따른 조치를 취할 수 있는 사유는 별표와 같다.(붙임2 참조)

3. 이에 따라 마약류통합관리시스템으로 보고된 의료용 마약류(식욕억제제, 프로포폴, 졸피뎀)을 분석하여 오남용 조치기준을 벗어난 오남용 의심 사례에 대하여 해당 마약류취급의료업자에게 서면으로 정보제공하여 기준 준수를 요청하였으나('22.4.),

- 이후 3개월간('22.5.1.~7.31.)의 추적관찰 결과, 219명의 마약류취급의료업자가 반복하여 조치기준을 벗어나 마약류를 처방한 사례가 있음을 확인하였습니다.

4. **(행정조치 사항)** 이에 우리 처에서는 「마약류 관리에 관한 법률」 제5조제3항에 따라 **부적정한 마약류 처방을 지속한 해당 마약류취급의료업자(219명)에게 '오남용 조치기준을 위반한 행위에 대한 처방·투약(투약을 위한 제공 포함) 금지'를 명령**하였음을 알려드리니,

NIMS? (Narcotics Information Management System:
마약류통합관리시스템)

의료용 마약류 식욕억제제 안전사용 기준

2020. 8.

식품의약품안전처
마 약 관 리 과

< 주요 내용 >

◆ 의료용 마약류 식욕억제제는 비만 치료 목적으로 사용하여야 한다.

◆ 의료용 마약류 식욕억제제 사용 시 남용 및 의존 가능성을 항상 염두에 두어야 한다.

◆ "펜터민, 펜디메트라진, 디에틸프로피온, 마진돌" 은 허가용량 내 4주 이내 단기처방하며, 최대 3개월 이내 사용한다.

◆ 의료용 마약류 식욕억제제는 다른 의료용 마약류 식욕억제제와 병용하지 않는다.

◆ 의료용 마약류 식욕억제제는 어린이 및 청소년에게 사용하지 않는다.

9. Use with psychiatric drugs?

AACE/ACE Guidelines 2016:

Medical Care of Patients with Obesity

Depression & Anxiety

- **Avoid maximum dose : 15mg/92mg per day**

  (Not exceeding 7.5mg/46mg per day in Korea)

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	CAD			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	Mild (50–79 mL/min)					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	Mild-Moderate (Child-Pugh 5–9)	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	
Anxiety				Avoid max dose: 15 mg/92 mg per day		

Reference. **1.** *Garvey WT, et al. Endocr Pract. 2016;22(7):842-884.*

AACE, The American Association of Clinical Endocrinology; ACE, American College of Endocrinology; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure, HTN, hypertension; T2DM, type 2 diabetes mellitus.

Qsymia capsule

10. Interactions with other drugs

Monoamine Oxidase Inhibitor (MAO Inhibitor)

: Class of antidepressants, currently rarely used. Interacts with most drugs.

Central nervous system depressants including alcohol

: Concomitant administration may cause **central nervous system depression**. (ex. barbiturates, benzodiazepines, sleeping pills, etc.)

Non-potassium-sparing diuretics

: **Hypokalemia** monitoring is required when co-prescribing (ex. hydrochlorothiazide)

Other anticonvulsants

: phenytoin, carbamazepine reduced by 40%, concomitant administration of valproic acid may cause hyperammonemia.

Carbonic anhydrase inhibitors

: Concomitant use of topiramate with carbonic anhydrase inhibitors may increase the risk of **kidney stone** formation (ex. zonisamide, acetazolamide, methazolamide)

Oral contraceptives

: Taking birth control pills containing estrogen or progestin reduces exposure to estrogen and increases exposure to progestin, which can cause **irregular bleeding** more often.

Reference. **1.** *Qsymia Product Information, Available at https://nedrug.mfds.go.kr, accessed on May 31, 2022*

Take home message

- 큐시미아는 동반 질환이 있는 환자에서도 체중 감량에 효과적입니다. 당뇨병이나 고혈압이 동반된 환자에서도 혈당 및 혈압 강하와 함께 해당 약물 치료를 감소시킬 수 있습니다.
- 큐시미아에는 각 약물의 고정 용량 조합이 포함되어 있으며 1일 1회 투여로 하루종일 장시간 효과를 기대할 수 있습니다. 이러한 효과는 단순히 펜터민/ 토피라메이트 병합만으로는 기대하기 어렵습니다.
- 큐시미아는 임상연구에서 2년간 사용하였을 때 환자들은 well-toterable 하였고, 체중 감량을 잘 유지하였습니다. 따라서 다른 식욕억제제 (펜터민, 펜디메트라진, 디에틸프로피온, 마진돌) 과 달리 장기간 사용할 수 있습니다.
- 환자의 내약성과 효과를 고려하여 점진적 용량 증가가 필요하며, 발작의 위험을 감소시키기 위해 중단시에도 이틀에 한 번 복용하면서 1주일에 걸쳐서 끊어야 합니다.
- 큐시미아는 미국에서는 12세 이상 소아청소년에 허가 되었지만, 한국에서는 소아청소년에 허가 되어 있지 않습니다. 우울증이 있는 경우 최대용량 (15/92 mg)은 피하는 것이 좋습니다.
- 가임기 여성에서 태아 독성에 대한 설명 및 반드시 피임하도록 교육이 필요합니다.
- 큐시미아는 녹내장 환자에서 금기이며, 복용 중 시야 흐림이 발생하면 바로 중단하도록 하여야 합니다.

Thank you