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SHORT COMMUNICATION

Physician and Pharmacist Understanding of the Risk of Urinary Retention with Retigabine (Ezogabine): A REMS Assessment Survey

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Abstract

Background The Risk Evaluation and Mitigation Strategy (REMS) for retigabine/ezogabine (RTG/EZG) required an evaluation of the effectiveness of the communication plan to communicate about the risks with use of RTG/EZG.

Objective GlaxoSmithKline conducted a survey to assess understanding of the risk of urinary retention (UR) with RTG/EZG and to evaluate the effectiveness of the communication plan.

Methods This was a US-based, cross-sectional, non-interventional, observational survey, conducted from February to April 2013, of physicians who had prescribed RTG/EZG in the past year, and pharmacists who had dispensed an antiepileptic drug within the past 3 months. Thirteen primary objective questions (five specific to UR risk) were included in the survey, which assessed healthcare professionals' (HCPs') understanding of UR risk and symptoms of acute UR associated with RTG/EZG. The primary outcome was the proportion of HCPs correctly answering each question. For each question, a proportion of correct responses ≥80 % was considered to represent sufficient understanding of associated risks.

Results Of 1028 HCPs screened, 373 participated. Six of 13 questions (3/5 specific to UR risk) met the ≥80 %

Key Points

Survey results demonstrated a mixed level of understanding of aspects of UR risk associated with retigabine/ezogabine (RTG/EZG) among prescribers.

Pharmacists displayed a lower level of understanding than prescribers, probably due to the short time that RTG/EZG had been available for prescription.

A key insight from the survey was that the questions should be focused on the objective to assess specific risks and evaluate effectiveness of the communication plan, and additional questions should not be included to avoid adding complexity.

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threshold for correct responses in the physician cohort. No questions achieved this threshold in the total pharmacist group; however, four questions scored ≥80 % when stratified by pharmacists who had dispensed RTG/EZG.

Conclusions Results demonstrated a mixed level of understanding of aspects of UR risk associated with RTG/EZG, although some risk questions did not meet the 80 % threshold, especially among pharmacists. This is likely to have been due to the short time that RTG/EZG has been available and its limited use. This study provides the first evaluation of the REMS communication plan on the risk of UR with RTG/EZG.

1 Introduction

Retigabine (RTG; international nonproprietary name)/ezogabine (EZG; US adopted name) is an antiepileptic drug (AED) approved in the US (as POTIGA™, GlaxoSmithKline [GSK] and Valeant) for the adjunctive treatment of partial-onset seizures in adults who have responded inadequately to several treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity [1]. In clinical studies investigating the efficacy and safety of RTG/EZG, an increased risk of urinary retention (UR) was reported in patients receiving RTG/EZG compared with placebo [2–6].

RTG/EZG was approved in June 2011 with a US Food and Drug Administration (FDA) requirement for a Risk Evaluation and Mitigation Strategy (REMS) [7]. According to the FDA Amendments Act of 2007, the FDA may require a drug manufacturer to submit a REMS, which is intended to manage known or potential serious risks associated with a drug and to ensure that the benefits of the drug outweigh the risks [8, 9]. The REMS for RTG/EZG consisted of a communication plan for healthcare professionals (HCPs), including prescribing physicians and dispensing pharmacists, designed to disseminate information on the risk of UR with RTG/EZG and highlight the importance of advising patients to seek immediate attention for symptoms of UR, including inability to urinate and/or pain with urination. The communication plan had two elements: (i) a Dear Healthcare Professional (DHCP) letter, disseminated within 4 weeks of first retail availability (May 7, 2012) and annually for the following 2 years; and (ii) a REMS program website available at the time of launch (April 16, 2012; no longer active). The delay between the approval of the new drug application (NDA; June, 2011) and retail availability was caused by the requirement for RTG/EZG to be reviewed by the US Drug Enforcement Administration (DEA), in line with the Controlled Substances Act, in order to determine the scheduling status.

As a condition of approval, the FDA required that GSK assess this communication plan's effectiveness. Accordingly, a survey was conducted among a sample of HCPs to evaluate knowledge of UR risk with RTG/EZG [10]. The survey focused on the risks described in the DHCP letter for RTG/EZG, and assessed where HCPs prefer to seek information for RTG/EZG (e.g., DHCP letters, website, product labeling). Here we report the results of this survey.

2 Methods

2.1 Study Design

This was a cross-sectional, non-interventional, observational survey of HCPs who prescribe RTG/EZG or dispense AEDs. The study did not include intervention; therefore, institutional review board approval was not deemed necessary.

2.2 Sampling and Study Population

From a Concentrics Research market research partner's custom database of more than 668,000 geographically and therapeutically diverse US HCPs, approximately 14,000 eligible physicians and pharmacists were contacted from a demographically representative population who prescribe RTG/EZG (neurologists, neurosurgeons, epileptologists), or dispense AEDs (pharmacists). The original mailing list for the DHCP letter included prescribers, emergency room physicians and urologists, the HCPs most likely to come into contact with RTG/EZG-treated patients who may have UR symptoms. This survey focused only on recruiting potential prescribers and the overlap between the DHCP mailing list and the Concentrics database is not known.

2.3 Survey Inclusion, Exclusion, and Withdrawal Criteria

Inclusion criteria included practicing physicians who had prescribed RTG/EZG within the past year, and practicing pharmacists who had filled a prescription for at least one AED within the past 3 months. Physicians and pharmacists currently employed by, or who were representatives of, a pharmaceutical company or manufacturer of medicines or healthcare products, or who were contributors to, or editors of, published guideline committees for epilepsy or UR, were ineligible. Additionally, HCPs who previously participated in the pilot REMS study for RTG/EZG, or who were

employees of GSK or Concentrics Research, were excluded. HCPs could withdraw from the study at any time.

2.4 Screening and Baseline Assessments

HCPs were contacted initially by telephone, email, or fax with an invitation to participate in the study, conducted from February through April 2013. A standardized screening questionnaire conducted by telephone assessed eligibility, demographics, and interest in study participation. After recruitment, HCPs' understanding of the symptoms and risks of UR with RTG/EZG was evaluated by means of an online survey or telephone interview. Thirty closed-ended questions were asked to assess the following: demographics and prescribing/dispensing history of each HCP; understanding of RTG/EZG key safety messages based on US prescribing information and practices (13 primary objective questions [five specific to UR risk]); and personal experience, awareness, receipt, and dissemination of information about RTG/EZG (see electronic supplementary material).

2.5 Statistical Analysis

Baseline assessments were summarized by using proportions (%) for categorical data. The primary outcome was the proportion of HCPs correctly answering each question related to understanding of risks associated with RTG/EZG. At least 80 % of correct responses for each question was considered to represent sufficient understanding of the risks associated with RTG/EZG. This threshold was determined on the basis of experience from similar studies previously planned by GSK and approved by the FDA [11]. In a REMS workshop in July 2012, the FDA cites the 80 % threshold as a level that is generally accepted for the survey responses [12], though the discussion on setting standardized thresholds for REMS assessments is ongoing [13]. The proportion of correct answers to survey questions was summarized overall and by demographic subgroups. Data were grouped into subcategories to identify possible trends in understanding, including demographics, type of HCP, RTG/EZG prescribing/dispensing, and other practice/prescribing characteristics.

3 Results

3.1 Subject Disposition

Of 1028 HCPs who were recruited and screened, 373 physicians ($n = 168$) and pharmacists ($n = 205$) completed the survey (Fig. 1). All respondents completed the survey online, and none completed the survey by phone.

3.2 Demographics and Baseline Characteristics

Physicians reported that their primary specialty was neurology (64 %) or epileptology (36 %). Pharmacists reported community/retail (55 %) or hospital/clinic (45 %) as their primary specialty. Most HCPs had been practicing medicine/pharmacy and prescribing/dispensing AEDs for 5–35 years.

Prescribing physicians treated patients across all ages, and most reported a total number of more than 1000 patients, more than 100 of whom had epilepsy. Sixty percent of physicians had prescribed, and 41 % of pharmacists had filled prescriptions for AEDs to more than 50 patients monthly during the past year. Most pharmacists had not dispensed (77 %) RTG/EZG or answered (83 %) patients' questions about RTG/EZG in the past year. Of those who had done so, 44 % reported having dispensed RTG/EZG for only 1–3 months and most reported prescribing (physicians, 52 %) or dispensing (pharmacists, 66 %) RTG/EZG to only 1–2 patients within the past year.

3.3 Survey Results

The distribution of responses to questions assessing HCPs' understanding of the risks associated with RTG/EZG is shown in Table 1. Of the five questions related specifically to the risk of UR associated with RTG/EZG, three (Q3, Q8, Q13) were correctly answered by more than 80 % of physicians and met the pre-defined threshold, whereas two (Q7 and Q12) fell below the target threshold. Of the questions not specifically related to UR risk, Q1, Q2, and Q11.1 were answered correctly by more than 80 % of physicians (Q11 was a single question with five parts that are shown separately); the remaining questions (Q4, Q5, Q6, Q9, Q10, Q11.2, Q11.3, Q11.4, Q11.5) had an average percent correct response of 59 %.

None of the questions for the pharmacist cohort achieved the 80 % threshold. However, when stratified by pharmacists who had dispensed RTG/EZG ($n = 32$), the established threshold was met by four questions (Q1, Q3, Q8, Q11.1), two of which (Q3, Q8) were specifically related to UR risk (Table 1).

A series of profiling questions asked HCPs how they learned about the risks associated with RTG/EZG and invited them to select up to three options for how they would prefer to learn about such risks in the future. Responses to these questions are presented in Table 2. The majority of HCPs did not learn about the risks associated with RTG/EZG from a DHCP letter. Notably, 82 % of physicians and 91 % of pharmacists gave a negative response when asked if the DHCP letter was their source of information about RTG/EZG-associated risks. Most physicians reported learning about these risks from the

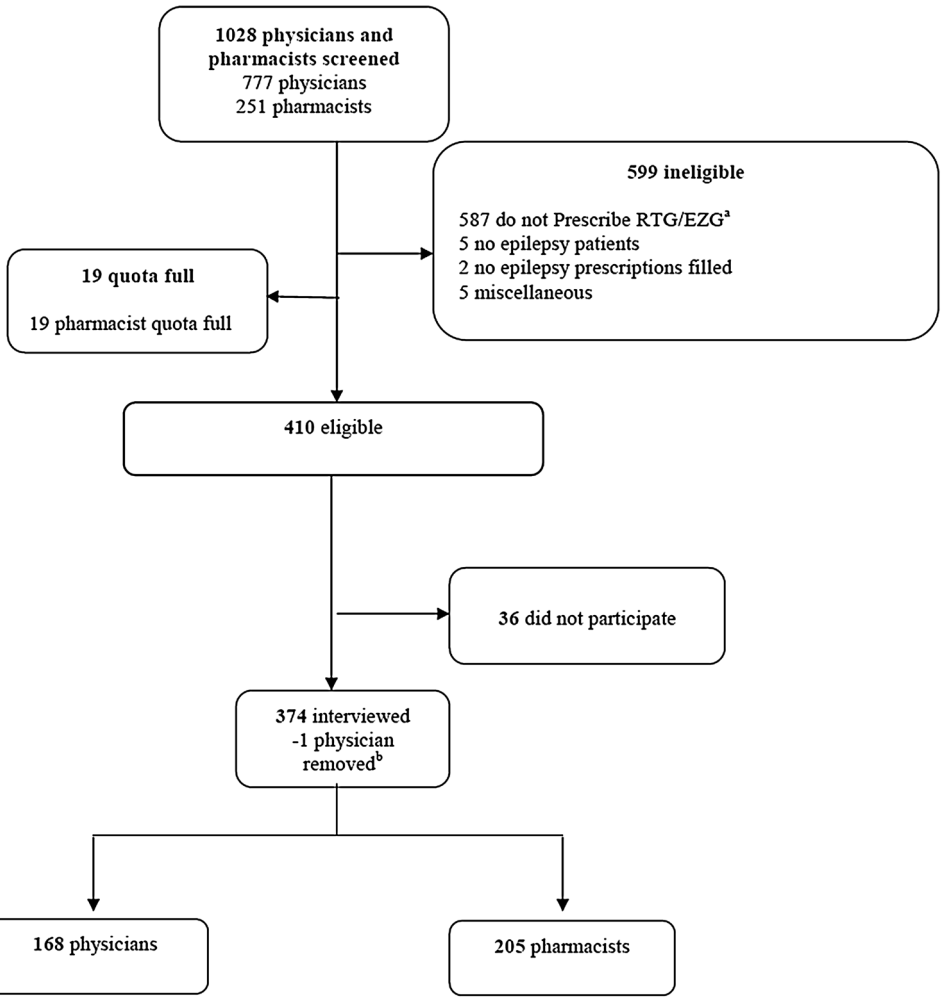

Fig. 1 Flowchart of healthcare provider screening. [a]The most common reason for termination of physicians at time of screening was not prescribing RTG/EZG. [b]One physician was removed from the study due to inconsistencies between indicated primary specialty during screening and on questionnaire. *RTG/EZG* retigabine/ezogabine

RTG/EZG product label (78 %) or from a GSK sales representative (60 %), whereas pharmacists reported learning from the RTG/EZG product label (46 %), other HCPs (22 %), or the GSK product website (20 %). Physicians reported interest in learning about the risks associated with RTG/EZG in the future through GSK-sponsored educational meetings (55 %), sales representatives (46 %), or product labeling (36 %). Pharmacists preferred to receive information from product labeling (49 %), GSK-sponsored educational meetings (36 %), sales representatives (35 %), or a DHCP letter (31 %).

4 Discussion

This study provides an indication of the effectiveness of the RTG/EZG REMS communication plan, as evaluated by a survey of prescribing physicians and dispensing pharmacists, to assess HCPs' recall of the risks and symptoms of UR associated with RTG/EZG. Overall, the surveyed population encompassed HCPs with 5–35 years of experience in practice; most had considerable experience in prescribing or dispensing AEDs. RTG/EZG has been available only since May 2012, and prescribing of the drug has been modest. Both of these factors explain the relatively low level of experience in prescribing and dispensing RTG/EZG among the HCPs surveyed.

The original proposal had been to survey all potential AED prescribers, but the RTG/EZG launch was delayed due to the DEA assessment of the scheduling status and sales showed that RTG/EZG uptake was low, so the sample of HCPs was enriched for those who had some experience with RTG/EZG. The selection criteria differed between prescribers and pharmacists. Prescribers were mainly specialists likely to see epilepsy patients, but pharmacists were generalists and could not be assumed to have any experience with dispensing RTG/EZG. The shorter time period for requiring dispensing of AEDs by pharmacists was selected to enrich the possibility of pharmacist experience with RTG/EZG.

Table 1 Summary of overall physician and pharmacist responses to risk questions, and pharmacist risk question responses by RTG/EZG (POTIGA™) dispensing history

Q#	Objective	Physicians	Pharmacists		
		Overall $N = 168$ *n* (%)	Overall $N = 205$ *n* (%)	Have dispensed POTIGA™ $N = 32$ *n* (%)	Have not dispensed POTIGA™ $N = 173$ *n* (%)
Q1	According to US prescribing information, what is the FDA-approved indication for POTIGA™?[a]				
	Migraine	2 (1.2)	1 (0.5)	1 (3.1)	–
	Partial-onset seizures[b]	164 (97.6)	127 (62.0)	29 (90.6)	98 (56.6)
	Generalized tonic clonic seizures	9 (5.4)	6 (2.9)	3 (9.4)	3 (1.7)
	None of the above	–	–	–	–
	I don't know	2 (1.2)	74 (36.1)	2 (6.3)	72 (41.6)
Q2	True or False: According to US prescribing information, POTIGA™ can be used as monotherapy				
	True	8 (4.8)	29 (14.1)	9 (28.1)	20 (11.6)
	False[b]	153 (91.1)	82 (40.0)	20 (62.5)	62 (35.8)
	I don't know	7 (4.2)	94 (45.9)	3 (9.4)	91 (52.6)
Q3	According to US prescribing information, which of the following are potential risks associated with POTIGA™?[a]				
	Urinary retention[b]	143 (85.1)	117 (57.1)	26 (81.3)	91 (52.6)
	Pancreatitis	9 (5.4)	5 (2.4)	3 (9.4)	2 (1.2)
	Ischemic colitis	3 (1.8)	1 (0.5)	1 (3.1)	–
	I don't know	19 (11.3)	85 (41.5)	4 (12.5)	81 (46.8)
Q4	According to US prescribing information, what is the maximum recommended daily maintenance dose of POTIGA™ for the general population?[a]				
	600 mg	11 (6.5)	10 (4.9)	4 (12.5)	6 (3.5)
	900 mg	13 (7.7)	4 (2.0)	2 (6.3)	2 (1.2)
	1200 mg[b]	114 (67.9)	105 (51.2)	24 (75.0)	81 (46.8)
	2000 mg	1 (0.6)	–	–	–
	None of the above	4 (2.4)	6 (2.9)	–	6 (3.5)
	I don't know	27 (16.1)	84 (41.0)	4 (12.5)	80 (46.2)
Q5	According to US prescribing information, which of the following statements, if any, is true?[a]				
	The oldest age at which POTIGA™ can be used is 65 y	6 (3.6)	2 (1.0)	1 (3.1)	1 (0.6)
	There are no lower age limits for POTIGA™	11 (6.5)	4 (2.0)	1 (3.1)	3 (1.7)
	The youngest age at which POTIGA™ can be used is 12 y	22 (13.1)	11 (5.4)	5 (15.6)	6 (3.5)
	The youngest age at which POTIGA™ can be used is 18 y[b]	104 (61.9)	85 (41.5)	18 (56.3)	67 (38.7)
	None of the above	9 (5.4)	10 (4.9)	1 (3.1)	9 (5.2)
	I don't know	25 (14.9)	94 (45.9)	7 (21.9)	87 (50.3)
Q6	According to US prescribing information, which of the following statements, if any, is true?				
	POTIGA™ should always be taken with food	6 (3.6)	5 (2.4)	2 (6.3)	3 (1.7)
	POTIGA™ should always be taken on its own, without food	2 (1.2)	3 (1.5)	3 (9.4)	–
	POTIGA™ can be taken with or without food[b]	116 (69.0)	120 (58.5)	24 (75.0)	96 (55.5)
	None of the above	2 (1.2)	1 (0.5)	–	1 (0.6)
	I don't know	42 (25.0)	77 (37.6)	4 (12.5)	73 (42.2)

Table 1 continued

Q#	Objective	Physicians	Pharmacists		
		Overall $N = 168$ *n* (%)	Overall $N = 205$ *n* (%)	Have dispensed POTIGA™ $N = 32$ *n* (%)	Have not dispensed POTIGA™ $N = 173$ *n* (%)
Q7	Which of the following urinary symptoms, if any, should you specifically advise patients taking POTIGA™ to watch out for?[a]				
	Pain when urinating[b]	38 (22.6)	47 (22.9)	14 (43.8)	33 (19.1)
	Difficulty starting urination[b]	98 (58.3)	97 (47.3)	24 (75.0)	73 (42.2)
	Renal colic	17 (10.1)	10 (4.9)	3 (9.4)	7 (4.0)
	Inability to urinate[b]	129 (76.8)	88 (42.9)	22 (68.8)	66 (38.2)
	None of the above	1 (0.6)	1 (0.5)	–	1 (0.6)
	I don't know	12 (7.1)	73 (35.6)	2 (6.3)	71 (41.0)
Q8	If a patient on POTIGA™ experiences inability to pass urine, what would you advise them to do?[a]				
	Report the issue at their next doctor's appointment	6 (3.6)	25 (12.2)	6 (18.8)	19 (11.0)
	Drink more water	6 (3.6)	6 (2.9)	2 (6.3)	4 (2.3)
	Seek immediate medical attention[b]	139 (82.7)	138 (67.3)	26 (81.2)	112 (64.7)
	Stop taking POTIGA™	68 (40.5)	26 (12.7)	6 (18.8)	20 (11.6)
	None of the above	2 (1.2)	1 (0.5)	–	1 (0.6)
	I don't know	3 (1.8)	44 (21.5)	–	44 (25.4)
Q9	According to US prescribing information, when increasing the dose, what is the maximum total daily dose at which POTIGA™ can be increased once every 7 days?				
	Total daily dose increased by 50 mg/day	21 (12.5)	26 (12.7)	6 (18.8)	20 (11.6)
	Total daily dose increased by 150 mg/day[b]	100 (59.5)	88 (42.9)	19 (59.4)	69 (39.9)
	Total daily dose increased by 200 mg/day	8 (4.8)	–	–	–
	Total daily dose increased by 300 mg/day	13 (7.7)	2 (1.0)	1 (3.1)	1 (0.6)
	None of the above	4 (2.4)	1 (0.5)	–	1 (0.6)
	I don't know	22 (13.1)	88 (42.9)	6 (18.8)	82 (47.4)
Q10	True or False: According to US prescribing information, for the general population, the recommended total initial dosage should be 150 mg per day for one week				
	True	54 (32.1)	24 (11.7)	9 (28.1)	15 (8.7)
	False[b]	92 (54.8)	102 (49.8)	22 (68.8)	80 (46.2)
	I don't know	22 (13.1)	79 (38.5)	1 (3.1)	78 (45.1)
Q11	The label for POTIGA™ recommends caution when prescribing for patients with which of the following conditions, if any?				
11.1	Moderate to severe renal or hepatic impairment				
	Yes[b]	147 (87.5)	133 (64.9)	28 (87.5)	105 (60.7)
	No	8 (4.8)	9 (4.4)	2 (6.3)	7 (4.0)
	I don't know	13 (7.7)	63 (30.7)	2 (6.3)	61 (35.3)
11.2	Moderate to severe Crohn's disease				
	Yes	18 (10.7)	20 (9.8)	6 (18.8)	14 (8.1)
	No[b]	87 (51.8)	62 (30.2)	18 (56.3)	44 (25.4)
	I don't know	63 (37.5)	123 (60.0)	8 (25.0)	115 (66.5)

Table 1 continued

Q#	Objective	Physicians	Pharmacists		
		Overall $N = 168$ *n* (%)	Overall $N = 205$ *n* (%)	Have dispensed POTIGA™ $N = 32$ *n* (%)	Have not dispensed POTIGA™ $N = 173$ *n* (%)
11.3	Moderate to severe asthma				
	Yes	6 (3.6)	12 (5.9)	3 (9.4)	9 (5.2)
	No[b]	106 (63.1)	72 (35.1)	21 (65.6)	51 (29.5)
	I don't know	56 (33.3)	121 (59.0)	8 (25.0)	113 (65.3)
11.4	Patients over the age of 65 years				
	Yes	93 (55.4)	90 (43.9)	24 (75.0)	66 (38.2)
	No[b]	39 (23.2)	22 (10.7)	6 (18.8)	16 (9.2)
	I don't know	36 (21.4)	93 (45.4)	2 (6.3)	91 (52.6)
11.5	Moderate to severe glaucoma				
	Yes	20 (11.9)	31 (15.1)	9 (28.1)	22 (12.7)
	No[b]	79 (47.0)	52 (25.4)	12 (37.5)	40 (23.1)
	I don't know	69 (41.1)	122 (59.5)	11 (34.4)	111 (64.2)
Q12	True or False: It is known from controlled studies that adverse events related to voiding dysfunction generally tend to be reported within the first 6 months after starting POTIGA™				
	Yes	124 (73.8)	94 (45.9)	25 (78.1)	69 (39.9)
	No[b]	8 (4.8)	8 (3.9)	2 (6.3)	6 (3.5)
	I don't know	36 (21.4)	103 (50.2)	5 (15.6)	98 (56.6)
Q13	Which of the following patient groups are recommended to have closer monitoring (including comprehensive evaluation of urologic symptoms) for urinary retention?[a]				
	Patients with benign prostatic hyperplasia (BPH)[b]	144 (85.7)	137 (66.8)	26 (81.3)	111 (64.2)
	Patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients)[b]	134 (79.8)	99 (48.3)	21 (65.6)	78 (45.1)
	Patients who use concomitant medications that may affect voiding (e.g., anti-cholinergics)[b]	138 (82.1)	129 (62.9)	26 (81.3)	103 (59.5)
	Patients who use non-steroidal anti-inflammatory drugs (NSAIDs)	13 (7.7)	33 (16.1)	5 (15.6)	28 (16.2)
	Patients who are obese	4 (2.4)	12 (5.9)	3 (9.4)	9 (5.2)
	None of the above	1 (0.6)	2 (1.0)	–	2 (1.2)
	I don't know	11 (6.5)	57 (27.8)	2 (6.3)	55 (31.8)

The US branded name for RTG/EZG (POTIGA™) was used throughout the survey

FDA US Food and Drug Administration, *RTG/EZG* retigabine/ezogabine, – indicates a percentage that does not round to 1 or is zero

[a] Respondents could select more than one response

[b] Indicates correct responses

Generally, among physicians, the survey results revealed a mixed level of understanding of several aspects of the UR risk associated with RTG/EZG, although a number of risk questions did not meet the pre-defined 80 % correct response threshold. The lower understanding of RTG/EZG-associated UR risk within the pharmacist group can be explained by a lack of familiarity and experience with dispensing RTG/EZG among retail and hospital pharmacists due to the short time that RTG/EZG has been available and its low rate of prescribing.

Although the survey included a considerable number of physicians and pharmacists, the sample may not be fully representative of HCPs who prescribe or dispense RTG/

Table 2 Healthcare provider profiling questions

Q#	Objective	Physicians $N = 168$ n (%)	Pharmacists $N = 205$ n (%)
Q29	Have you learned about the risks associated with the use of POTIGA™ from any of the following sources?		
29.1	POTIGA™ Dear HCP letter		
	Yes	14 (8.3)	10 (4.9)
	No	137 (81.5)	186 (90.7)
	Don't know	17 (10.1)	9 (4.4)
29.2	GlaxoSmithKline medical information		
	Yes	58 (34.5)	21 (10.2)
	No	98 (58.3)	177 (86.3)
	Don't know	12 (7.1)	7 (3.4)
29.3	GlaxoSmithKline promotional materials		
	Yes	67 (39.9)	28 (13.7)
	No	90 (53.6)	171 (83.4)
	Don't know	11 (6.5)	6 (2.9)
29.4	GSK website: POTIGA.com		
	Yes	39 (23.2)	41 (20.0)
	No	118 (70.2)	159 (77.6)
	Don't know	11 (6.5)	5 (2.4)
29.5	GlaxoSmithKline sales representatives		
	Yes	100 (59.5)	9 (4.4)
	No	64 (38.1)	190 (92.7)
	Don't know	4 (2.4)	6 (2.9)
29.6	GlaxoSmithKline-sponsored educational meeting		
	Yes	30 (17.9)	4 (2.0)
	No	130 (77.4)	195 (95.1)
	Don't know	8 (4.8)	6 (2.9)
29.7	POTIGA™ product labeling (including prescribing information, medication guide)		
	Yes	131 (78.0)	95 (46.3)
	No	30 (17.9)	104 (50.7)
	Don't know	7 (4.2)	6 (2.9)
29.8	Other healthcare professionals		
	Yes	74 (44.0)	45 (22.0)
	No	85 (50.6)	154 (75.1)
	Don't know	9 (5.4)	6 (2.9)
Q30	How would you prefer to learn about the risks associated with the use of POTIGA™ in the future? (Select up to 3 options)		
	GlaxoSmithKline-sponsored educational meeting	92 (54.8)	74 (36.1)
	GlaxoSmithKline sales representatives	77 (45.8)	71 (34.6)
	POTIGA™ product labeling (including prescribing information, medication guide)	60 (35.7)	101 (49.3)
	Other healthcare professionals	60 (35.7)	36 (17.6)
	GlaxoSmithKline medical information	41 (24.4)	48 (23.4)
	GSK website: POTIGA.com	37 (22.0)	61 (29.8)
	GlaxoSmithKline promotional materials	28 (16.7)	60 (29.3)
	POTIGA™ Dear HCP letter	21 (12.5)	64 (31.2)

The US branded name for RTG/EZG (POTIGA™) was used throughout the survey. Among the 30 survey questions, questions Q29.1 through Q30 pertained to HCP profiling

HCP healthcare provider, *RTG/EZG* retigabine/ezogabine

EZG. To limit this potential bias, HCPs were recruited from a large online database of geographically and demographically diverse US HCPs, rather than by targeting only high prescribers of RTG/EZG. Because the small sample size in certain subgroups may have resulted in low precision, data were grouped into appropriate subcategories to identify possible trends in understanding. As this was an online survey, it was not possible to detect whether or not HCPs used any reference materials while taking the survey.

Overall, in this first evaluation of the REMS communication plan to disseminate information on the risks of UR associated with RTG/EZG treatment, physicians demonstrated a mixed level of understanding of the symptoms and of risks associated with RTG/EZG use. Pharmacists displayed a lower level of understanding, probably due to the short time that RTG/EZG has been available for prescription. One key insight gained from the survey was that the questions should be focused on the specific risks, and the addition of extra questions to mask the intent of the survey from respondents may have added complexity and confusion. The EU survey was modified accordingly following the REMS survey experience [14]. The results of the survey did not indicate a need for alternative or additional measures, beyond the originally proposed REMS measures, to enhance the understanding of the risk of UR with POTIGA™. The FDA announcement on pigmentation in retigabine patients was released on 26 April 2013 [15]. At the start the survey, these risks were not yet known. After the safety issues emerged, the planned distribution of annual DHCP letters as part of the original REMS was delayed in agreement with the FDA and ongoing discussions took place with the FDA on the next steps.

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Compliance with Ethical Standards

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Conflict of interest Neil Brickel is an employee of, and a shareholder in, GSK. Melissa Beck and Sara Travis are employees of Concentrics Research LLC. Concentrics Research LLC has conducted other studies under contract with GSK. At the time of the study, Lianna Ishihara and Olusegun Akintayo were employees of and shareholders in GSK. Lianna Ishihara is currently employed by Lundberg SAS. Olusegun Akintayo is currently employed by Apotex Inc.

Ethical approval This was a cross-sectional, non-interventional, observational study. The study did not include intervention; therefore, institutional review board approval was not deemed necessary.

References

1. GlaxoSmithKline. POTIGA (retigabine) package insert. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022345s006lbl.pdf. Accessed 23 Mar 2015.
2. Brickel N, Gandhi P, VanLandingham KE, Hammond J, DeRossett S. The urinary safety profile and secondary renal effects of retigabine (ezogabine): a first-in-class antiepileptic drug that targets KCNQ (Kv7) potassium channels. Epilepsia. 2012;53(4):606–12.
3. Brodie MJ, Lerche H, Gil-Nagel A, Elger C, Hall S, Shin P, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. Neurology. 2010;75(20):1817–24.
4. Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM. Randomized, multicenter, dose-ranging trial of retigabine for partial-onset seizures. Neurology. 2007;68(15):1197–204.
5. Porter RJ, Burdette DE, Gil-Nagel A, Hall ST, White R, Shaikh S, et al. Retigabine as adjunctive therapy in adults with partial-onset seizures: integrated analysis of three pivotal controlled trials. Epilepsy Res. 2012;101(1–2):103–12.
6. French JA, Abou-Khalil BW, Leroy RF, Yacubian EM, Shin P, Hall S, et al. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. Neurology. 2011;76(18):1555–63.
7. GlaxoSmithKline. NDA 22-345 POTIGA™ (ezogabine) Tablets Appendix A-REMS. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM261933.pdf. Accessed 23 June 2015.
8. Fox JL. New law broadens FDA safety authority, renews user fees. Nat Biotechnol. 2007;25(11):1189–90.
9. Shane R. Risk evaluation and mitigation strategies: impact on patients, health care providers, and health systems. Am J Health Syst Pharm. 2009;66(24 Suppl 7):S6–12.
10. US National Institutes of Health. REMS Retigabine Study. https://clinicaltrials.gov/ct2/show/NCT01938560. Accessed 4 June 2015.
11. DiSantostefano RL, Beck M, Yeakey AM, Raphiou I, Stempel DA. Patient comprehension of medication guides for asthma and chronic obstructive pulmonary disease medications. Ther Innov Regul Sci. 2014;48(5):574–82.
12. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) Assessments: social science methodologies to assess goals related to knowledge: public workshop in

June 2012. http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm. Accessed 4 June 2015.
13. Engelberg Center for Health Care Reform at Brookings. Strengthening Risk Evaluation and Mitigation Strategies (REMS) Through Systematic Analysis, Standardized Design, and Evidence-Based Assessment http://www.brookings.edu/~/media/events/2013/9/25-engelberg-strengthening-rems/rems_summary_final.pdf. Accessed 23 June 2015.
14. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). WEUKBRE5744: European Survey of Patient and Prescriber Understanding of Risks Associated with TROBALT™. http://www.encepp.eu/encepp/viewResource.htm?id=9225. Accessed 23 June 2015.
15. U.S. Food and Drug Administation. FDA Drug Safety Podcast: anti-seizure drug Potiga (ezogabine) linked to retinal abnormalities and blue skin discoloration. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm350120.htm. Accessed 23 June 2015.