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SHORT COMMUNICATION

European Survey of Prescriber Understanding of Risks Associated with Retigabine

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Abstract

Background We conducted a survey to assess physicians' knowledge and understanding of key risks associated with retigabine.

Objective The survey evaluated the effectiveness of the educational plan for retigabine, as specified in the GlaxoSmithKline (GSK) European Risk Management Plan.

Methods This was a cross-sectional survey of physicians across seven European countries (Denmark, Germany, Norway, Slovakia, Spain, Switzerland, and the UK) who had prescribed an antiepileptic drug at least once within the past 3 months, and to whom a letter containing the retigabine Physician's Guide was sent. The survey included multiple-choice and closed-ended questions. Primary outcome was the proportion of physicians correctly answering questions related to retigabine-associated risks. Point estimates for the proportion of correct responses and associated confidence intervals were calculated.

Results Overall, 294 prescribers completed the survey between November 2012 and October 2013. Generally, physicians had adequate knowledge of the retigabine indication (78–92 % correct responses). Specific dose-related knowledge (57–74 %) and management of individual risks (20–77 %) were recalled less well. Subgroup analyses showed that both the 189 physicians who read the retigabine education letter and the 144 who had prescribed retigabine had better recall of the risks associated with retigabine (20–78 %) than those who did not.

Conclusions Overall, physicians were aware, to varying degrees, of the risks associated with retigabine. Subsequent to the conduct of this survey, GSK has made further changes to the product labeling for retigabine, sent an updated 'Dear Healthcare Professional' letter, and initiated another EU survey to assess how effectively specific risks associated with retigabine use are communicated.

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Key Points

Physicians were aware to varying degrees of the risks associated with retigabine.

Subgroup analyses showed that both the physicians who read the retigabine education letter and those who had prescribed retigabine had better recall of information.

To strengthen risk-minimization efforts for retigabine and following the identification of new emerging risks in 2013, GSK has since sent an updated 'Dear Healthcare Professional' letter and initiated another EU survey to assess how effectively specific risks associated with retigabine use are communicated.

1 Introduction

Retigabine (international nonproprietary name)/ezogabine (US adopted name, approved as Potiga™) is an antiepileptic drug (AED) approved in Europe [as Trobalt™, GlaxoSmithKline (GSK)] for the adjunctive treatment of drug-resistant partial-onset seizures with or without secondary generalization in patients 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated [1]. In randomized clinical studies investigating the efficacy and safety of retigabine, an increased risk of urinary retention, central nervous system (CNS) side effects (confusional state, hallucinations, and psychotic disorders), and QT prolongation was reported in patients receiving retigabine when compared with placebo [2–6].

As part of a European post-marketing commitment, GSK conducted a survey starting in November 2012 through October 2013 to assess physicians' understanding of the significant risks associated with retigabine. The goal was to evaluate the effectiveness of the educational plan as specified in the European Risk Management Plan (RMP) [7–9].

The survey, conducted among a sample of neurologists from seven European countries (Denmark, Germany, Norway, Slovakia, Spain, Switzerland, and the UK), concentrated on the risks described in the approved EU Physician's Guide (PG) for retigabine [10].

2 Methods

2.1 Study Design

This was a cross-sectional survey of physicians who had prescribed an AED at least once in the last 3 months and to whom an educational letter for retigabine had been sent (included as electronic supplementary material). This letter was intended to educate healthcare professionals about retigabine-associated risks, highlighting those described in the PG. The study design was based on risk-management evaluation studies previously completed by GSK and United BioSource Corporation (UBC) in the US and Europe, which were based on US FDA recommendations for Risk Evaluation and Mitigation Strategy (REMS) surveys [11]. The study did not include treatment intervention. Ethics Committee approval requirements were assessed by country; full review and approval were required in Slovakia and Spain, but were deemed not necessary in Denmark, Germany, Norway, Switzerland, and the UK. As risks of abnormal pigmentation of the lips, nails, skin, and/or mucosa associated with retigabine use were identified subsequent to conducting this survey, they were not included in the questionnaire.

2.2 Setting

The survey was conducted in the first European countries to launch retigabine. The rationale for selection was that issues regarding the effectiveness of the PG in communicating retigabine risks could be addressed early. Additionally, these countries were likely to have the most physicians with experience prescribing retigabine. The study started in November 2012 and completed recruitment of participants in October 2013.

2.3 Subjects

The survey aimed to recruit a random sample of 300 physicians who had prescribed an AED and who had been sent the educational letter including the PG for retigabine/ezogabine. The goal was to recruit 100 neurologists from Germany and 200 across the remaining countries. Just prior to the start of the survey, retigabine became unavailable in Germany for new patients, therefore only neurologists who had patients being treated with retigabine in November 2012 were targeted.

2.4 Screening and Baseline Assessments

The sample of neurologists who were invited to participate was a random sample of all neurologists who received the 'Educational Letter' for Trobalt. The sample of participating neurologists was self-selected since respondents voluntarily responded to the invitation to participate. However, the survey recruitment strategies were intended to recruit a heterogeneous sample of prescribers for participation. Furthermore, a subgroup of neurologists commonly referred to as 'epileptologists' who were known

from past experience to be the specialists who first initiated prescriptions of a new AED and who were therefore specifically targeted for promotional activity by GSK were the primary target of this survey. Neurologists were invited by email or mail to participate, with an introductory educational letter, a request to complete the survey, and the survey instrument. The survey used a questionnaire comprising multiple-choice and closed-ended questions (included as electronic supplementary material).

2.5 Statistical Analysis

All statistical analyses were descriptive; no formal hypotheses were tested. Confidence intervals were calculated at the 95 % level, and no adjustments were performed for multiplicity. Counts and percentages were calculated for each item in the questionnaire.

The primary outcome was the proportion of neurologists correctly answering each question related to understanding of the risks associated with retigabine. Point estimates for the proportion with correct responses, and associated confidence intervals, were calculated for each question about retigabine-associated risks. For multiple-choice questions, the number and proportion of neurologists reporting each response were recorded.

2.6 Populations and Subgroup Analysis

The primary population for the analysis included all eligible respondents who had completed the survey. Outcomes and respondent characteristics were summarized in three ways: (1) for all seven countries combined, (2) separately for Germany, and (3) for six countries combined excluding Germany. All other analyses were performed for respondents combined from all seven countries.

A subgroup analysis of prescribers who had ever prescribed retigabine versus those who had not was performed for questions related to retigabine risks and respondent characteristics. Subgroup analysis of respondents who reported reading the retigabine education letter was performed only for questions about retigabine risks.

3 Results

3.1 Study Population

A total of 8430 invitations were issued, 301 prescribers responded and were screened for participation, and 294 (97.7 %) were eligible for analysis. Of eligible prescribers, 96 were German physicians. All eligible respondents completed the survey online.

3.2 Participants

Of the 294 physicians who completed the survey, 94.9 % had prescribed AEDs within the last month. Almost half (49.0 %) had prescribed retigabine at some time point. The geographic distribution of eligible physicians was as follows: Germany 32.7 %, Spain 20.4 %, UK 18.0 %, Slovakia 9.5 %, Switzerland 7.8 %, Norway 6.5 %, and Denmark 5.1 %.

Most physicians who completed the survey (91.8 %) reported neurology as their primary specialty, and 4.8 % specialized in epileptology. Approximately two-thirds (64.3 %) of all physicians and 80.6 % of retigabine prescribers reported having read the retigabine educational letter. About half (50.7 %) of all physicians and 63.9 % of retigabine prescribers reported learning about retigabine-associated risks from the educational letter.

3.3 Survey Results

Responses by all eligible physicians to all questions related to the understanding of retigabine-associated risks are shown in Table 1.

The majority of eligible physicians (91.5 %) from all seven countries understood that retigabine is approved for use in partial-onset seizures (Q6), and 78.2 % recalled that it may be prescribed only for patients aged 18 years or older (Q11). Most (88.1 %) recalled that retigabine is not indicated for monotherapy (Q7). Specific dose-related knowledge (Q8, Q9, Q10, Q12, Q13, Q19) was recalled among 57–74 % of eligible physicians.

Between 54.1 and 66.3 % of eligible physicians recalled that patients taking retigabine had a risk of specific CNS adverse events (AEs), and 64.6 % recalled the risk of urinary retention in these patients (Q14). Fewer than half (44.6 %) recalled an association between retigabine and possible QT prolongation (Q20), although 76.5 % recalled that they should warn patients prescribed retigabine about new cardiac effects (Q23).

Awareness of many details regarding management of specific risks was low. Only 20.4 % of physicians recalled that dose titration may minimize the risk of CNS side effects (Q18), and 25.9 % recalled that an electrocardiogram (ECG) is recommended for patients with congestive heart failure (Q21).

3.4 Subgroup Analyses

Compared with all physicians who completed the survey, similar but slightly higher proportions of retigabine prescribers understood the prescribing information and recalled the risks of CNS, urinary, and cardiac effects associated

Table 1 Responses to all questions related to the understanding of risks associated with retigabine (Trobalt™)

Question	All eligible physicians, all seven countries ($n = 294$)		Physicians who prescribed RTG only ($n = 144$)		Physicians who read the RTG information letter ($n = 189$)		Physicians who did not read the RTG information letter ($n = 105$)	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Question 6: For which of the following conditions is Trobalt™ approved for use?								
Migraine	2	0.7	0	0.0	1	0.5	1	1.0
Partial-onset seizures[a]	269	91.5 (87.7–94.4)	139	96.5 (92.1–98.9)	178	94.2 (89.8–97.1)	91	86.7 (78.6–92.5)
All types of seizures	11	3.7	5	3.5	7	3.7	4	3.8
All of the above	3	1.0	0	0.0	2	1.1	1	1.0
None of the above	3	1.0	0	0.0	1	0.5	2	1.9
I don't know	6	2.0	0	0.0	0	0.0	6	5.7
Question 7: Is Trobalt™ indicated for use as monotherapy?								
Yes	16	5.4	6	4.2	6	3.2	10	9.5
No[a]	259	88.1 (83.8–91.6)	136	94.4 (89.3–97.6)	178	94.2 (89.8–97.1)	81	77.1 (67.9–84.8)
I don't know	19	6.5	2	1.4	5	2.6	14	13.3
Question 8: What is the maximum recommended daily maintenance dose of Trobalt™ for most patients?[b]								
600 mg	16	5.5	12	8.4	12	6.4	4	3.8
900 mg	28	9.6	20	14.0	19	10.1	9	8.6
1200 mg[a]	200	68.3 (62.6–73.6)	104	72.7 (64.7–79.8)	146	77.7 (71.0–83.4)	54	51.4 (41.5–61.3)
2000 mg	1	0.3	0	0.0	0	0.0	1	1.0
None of the above	3	1.0	1	0.7	2	1.1	1	1.0
I don't know	45	15.4	6	4.2	9	4.8	36	34.3
Question 9: Which one of the following statements is true? (please select the best response)								
Trobalt™ should be taken once a day	16	5.4	4	2.8	7	3.7	9	8.6
Trobalt™ should be taken twice a day	33	11.2	18	12.5	19	10.1	14	13.3
Trobalt™ should be taken three times a day[a]	218	74.1 (68.7–79.1)	121	84.0 (77.0–89.6)	161	85.2 (79.3–89.9)	57	54.3 (44.3–64.0)
Trobalt™ should be taken four times a day	0	0.0	0	0.0	0	0.0	0	0.0
None of the above	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	27	9.2	1	0.7	2	1.1	25	23.8
Question 10: When increasing the dose, what is the maximum total daily dose at which Trobalt™ can be increased once every 7 days? (please select the best response)								
50 mg	30	10.2	9	6.3	17	9.0	13	12.4
150 mg[a]	214	72.8 (67.3–77.8)	114	79.2 (71.6–85.5)	152	80.4 (74.0–85.8)	62	59.0 (49.0–68.5)
300 mg	35	11.9	17	11.8	15	7.9	20	19.0
600 mg	7	2.4	4	2.8	4	2.1	3	2.9
None of the above	8	2.7	0	0.0	1	0.5	7	6.7
Question 11: Which of the following statements is true? (please select the best response)								
There are no lower age limits for Trobalt™ usage	10	3.4	3	2.1	5	2.6	5	4.8

Table 1 continued

Question	All eligible physicians, all seven countries ($n = 294$)		Physicians who prescribed RTG only ($n = 144$)		Physicians who read the RTG information letter ($n = 189$)		Physicians who did not read the RTG information letter ($n = 105$)	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
The youngest age at which Trobalt™ can be used is 12	18	6.1	12	8.3	11	5.8	7	6.7
The youngest age at which Trobalt™ can be used is 18[a]	230	78.2 (73.1–82.8)	120	83.3(76.2–89.0)	165	87.3 (81.7–91.7)	65	61.9 (51.9–71.2)
I don't know	36	12.2	9	6.3	8	4.2	28	26.7
Question 12: The quickest time by which the minimum maintenance dose of 600 mg should be reached is the third week								
True[a]	197	67.0 (61.3–72.4)	98	68.1 (59.8–75.6)	141	74.6 (67.8–80.6)	56	53.3 (43.3–63.1)
False	62	21.1	39	27.1	38	20.1	24	22.9
I don't know	35	11.9	7	4.9	10	5.3	25	23.8
Question 13: For the general population, the recommended total initial dosage should be 150 mg per day for 1 week								
True	89	30.3	49	34.0	62	32.8	27	25.7
False[a]	178	60.5 (54.7–66.2)	93	64.6 (56.2–72.4)	121	64.0 (56.7–70.9)	57	54.3 (44.3–64.0)
I don't know	27	9.2	2	1.4	6	3.2	21	20.0
Question 14: People taking Trobalt™ had a higher chance of experiencing which of the following risks in clinical studies (please select all that apply)								
Urinary retention[a]	190	64.6 (58.9–70.1)	107	74.3 (66.4–81.2)	140	74.1 (67.2–80.2)	50	47.6 (37.8–57.6)
Confusional state[a]	195	66.3 (60.6–71.7)	102	70.8 (62.7–78.1)	140	74.1 (67.2–80.2)	55	52.4 (42.4–62.2)
Hallucinations[a]	164	55.8 (49.9–61.5)	86	59.7 (51.2–67.8)	116	61.4 (54.0–68.4)	48	45.7 (36.0–55.7)
Psychotic disorders[a]	159	54.1 (48.2–59.9)	80	55.6 (47.1–63.8)	112	59.3 (51.9–66.3)	47	44.8 (35.0–54.8)
Myocardial infarction	8	2.7	2	1.4	5	2.6	3	2.9
Renal carcinoma	0	0.0	0	0.0	0	0.0	0	0.0
All of the above	11	3.7	6	4.2	7	3.7	4	3.8
None of the above	12	4.1	8	5.6	6	3.2	6	5.7
I don't know	37	12.6	3	2.1	7	3.7	30	28.6
Question 15: It is known from controlled studies that adverse events related to voiding dysfunction generally tend to be reported how soon after starting Trobalt™?								
Within the first week	32	10.9	16	11.1	16	8.5	16	15.2
Within the first 8 weeks[a]	162	55.1 (49.2–60.9)	96	66.7 (58.3–74.3)	127	67.2 (60.0–73.8)	35	33.3 (24.4–43.2)
After 4 months	3	1.0	1	0.7	1	0.5	2	1.9
After 12 months	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	97	33.0	31	21.5	45	23.8	52	49.5
Question 16: It is known from controlled studies that confusional state, hallucinations, and/or psychotic disorders generally tend to be reported how soon after starting Trobalt™?								
4 weeks	76	25.9	47	32.6	54	28.6	22	21.0
8 weeks[a]	117	39.8 (34.2–45.6)	60	41.7 (33.5–50.2)	92	48.7 (41.4–56.0)	25	23.8 (16.0–33.1)
12 weeks	13	4.4	9	6.3	10	5.3	3	2.9
16 weeks	2	0.7	0	0.0	0	0.0	2	1.9
I don't know	86	29.3	28	19.4	33	17.5	53	50.5

Table 1 continued

Question	All eligible physicians, all seven countries ($n = 294$)		Physicians who prescribed RTG only ($n = 144$)		Physicians who read the RTG information letter ($n = 189$)		Physicians who did not read the RTG information letter ($n = 105$)	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Question 17: Which of the following urinary symptoms, if any, should you specifically advise patients taking Trobalt™ to watch out for? (please select the best response)								
Pain when urinating	4	1.4	1	0.7	1	0.5	3	2.9
Difficulty starting urination	51	17.3	22	15.3	33	17.5	18	17.1
Slow stream	1	0.3	1	0.7	1	0.5	0	0.0
Inability to pass urine	46	15.6	24	16.7	32	16.9	14	13.3
All of the above[a]	163	55.4 (49.6–61.2)	90	62.5 (54.1–70.4)	118	62.4 (55.1–69.4)	45	42.9 (33.2–52.9)
None of the above	1	0.3	0	0.0	0	0.0	1	1.0
I don't know	28	9.5	6	4.2	4	2.1	24	22.9
Question 18: According to the Trobalt™ Physician's Guide, appropriate dose titrations may minimize the risk of which of the following adverse events? (please select the best response)								
QT prolongation	35	11.9	17	11.8	20	10.6	15	14.3
CNS side effects such as hallucinations[a]	60	20.4 (16.0–25.5)	29	20.1 (13.9–27.6)	44	23.3 (17.5–30.0)	16	15.2 (9.0–23.6)
Urinary retention	21	7.1	11	7.6	11	5.8	10	9.5
All of the above	128	43.5	70	48.6	94	49.7	34	32.4
None of the above	10	3.4	7	4.9	9	4.8	1	1.0
I don't know	40	13.6	10	6.9	11	5.8	29	27.6
Question 19: Using the Treatment Initiation Pack, by which week can the patient reach a dose of 600 mg/day?								
2 weeks	34	12.5	16	11.6	23	13.0	11	11.7
3 weeks[a]	153	56.5 (50.3–62.4)	85	61.6 (52.9–69.7)	111	62.7 (55.1–69.9)	42	44.7 (34.4–55.3)
4 weeks	60	22.1	30	21.7	33	18.6	27	28.7
5 weeks	7	2.6	1	0.7	3	1.7	4	4.3
None of the above	17	6.3	6	4.3	7	4.0	10	10.6
Switzerland[c]	23							
Question 20: At what dose has Trobalt™ been shown to produce a possible QT prolonging effect?								
600 mg	18	6.6	10	7.2	17	9.6	1	1.1
900 mg	16	5.9	9	6.5	8	4.5	8	8.5
1200 mg[a]	121	44.6 (38.6–50.8)	70	50.7 (42.1–59.3)	96	54.2 (46.6–61.7)	25	26.6 (18.0–36.7)
1800 mg	14	5.2	9	6.5	10	5.6	4	4.3
I don't know	102	37.6	40	29.0	46	26.0	56	59.6
Switzerland[b]	23							
Question 21: For which patients is it recommended that an ECG is recorded before initiating Trobalt™? (please select all that apply)								
Patients with hypertension	5	1.7	4	2.8	3	1.6	2	1.9
Patients with congestive heart failure[a]	76	25.9 (20.9–31.3)	36	25.0 (18.2–32.9)	55	29.1 (22.7–36.1)	21	20.0 (12.8–28.9)
Patients with ventricular hypertrophy[a]	77	26.2 (21.3–31.6)	39	27.1 (20.0–35.1)	61	32.3 (25.7–39.4)	16	15.2 (9.0–23.6)

Table 1 continued

Question	All eligible physicians, all seven countries ($n = 294$)		Physicians who prescribed RTG only ($n = 144$)		Physicians who read the RTG information letter ($n = 189$)		Physicians who did not read the RTG information letter ($n = 105$)	
	n	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)	*n*	% (95 % CI)
Patients with hypokalemia[a]	71	24.1 (19.4–29.5)	34	23.6 (16.9–31.4)	57	30.2 (23.7–37.2)	14	13.3 (7.5–21.4)
All of the above	178	60.5	95	66.0	118	62.4	60	57.1
None of the above	2	0.7	1	0.7	0	0.0	2	1.9
I don't know	24	8.2	4	2.8	3	1.6	21	20.0
Question 22: What should you do in a patient with a QTc of more than 400 ms before starting Trobalt™? (please select the best response)								
Recheck the ECG 1 week after the first dose	105	35.7	56	38.9	62	32.8	43	41.0
Recheck the ECG at monthly intervals	18	6.1	8	5.6	11	5.8	7	6.7
Recheck the ECG after reaching the maintenance dose[a]	132	44.9 (39.1–50.8)	67	46.5 (38.2–55.0)	106	56.1 (48.7–63.3)	26	24.8 (16.9–34.1)
I don't know	39	13.3	13	9.0	10	5.3	29	27.6
Question 23: Which new cardiac effects in particular should you warn your patients about after prescribing Trobalt™? (please select all that apply)								
Syncope	20	6.8	10	6.9	11	5.8	9	8.6
Palpitations	16	5.4	11	7.6	8	4.2	8	7.6
Any other symptoms of arrhythmia	23	7.8	12	8.3	15	7.9	8	7.6
All of the above[a]	225	76.5 (71.3–81.3)	111	77.1 (69.3–83.7)	148	78.3 (71.7–84.0)	77	73.3 (63.8–81.5)
None of the above	25	8.5	8	5.6	15	7.9	10	9.5

The European branded name for retigabine (Trobalt™) was used throughout the survey

CI confidence interval, *CNS* central nervous system, *ECG* electrocardiogram, *RTG* retigabine

[a] Indicates correct response

[b] Question 8 was answered by 293 physicians from all 7 countries, 143 physicians who prescribe retigabine, 188 physicians who had read the retigabine information letter, and 105 physicians who did not read the retigabine information letter

[c] Questions 19 and 20 were not presented to respondents whose main residence was Switzerland owing to labeling variation in that country

with retigabine, as well as the appropriate management of individual risks (Table 1).

Overall, physicians who had read the retigabine education letter recalled more correct information regarding the use of retigabine and its associated risks than those who had not (Table 1). More physicians who had read the retigabine education letter recalled that retigabine should be taken three times a day [85.2 vs. 54.3 % (Q9)], that retigabine is associated with a risk of urinary retention [74.1 vs. 47.6 % (Q14)], that urinary AEs were generally reported within 8 weeks after starting retigabine [67.2 vs. 33.3 % (Q15)], and that the ECG should be re-evaluated after achievement of the maintenance dose in patients with congestive heart failure [56.1 vs. 24.8 % (Q22)].

Slightly higher percentages of retigabine prescribers understood the prescribing information and recalled the risks associated with retigabine when compared with all physicians who completed the survey (data not shown).

4 Discussion

The results of this survey, which assessed understanding of the risks associated with retigabine by neurologists across seven countries, provide an indication of the effectiveness of risk-minimization measures for retigabine in Europe.

Generally, physicians had adequate knowledge of the indication for retigabine use, but weaker recall of dose-related information and management of specific risks. Subgroup analyses showed that both the physicians who read the retigabine education letter and those who had prescribed retigabine had better recall of information regarding the use of retigabine in patients with partial-onset seizures and the associated risks than did physicians who had not read the education letter or prescribed retigabine. Responses from physicians in Germany were analyzed separately due to the change in availability of retigabine in that country at the time of the survey, but the results largely paralleled those from physicians in the other six countries.

Although the original study design included patient and prescriber surveys, the patient survey was not conducted because of lack of patient recruitment by retigabine prescribers, the relatively low uptake of retigabine in Europe, and confidentiality regulations restricting direct contact with patients. The original survey protocol was amended to exclude Sweden because of delays in ethics committee submissions.

This study was not based on retigabine prescribing volume but, rather, targeted a geographically diverse population of physicians across Europe. The survey was conducted online, which facilitated physicians' responses. The study design was based on GSK's and UBC's experience in designing RMPs and conducting similar surveys in the EU. Further, a similar US survey had been previously performed by GSK to evaluate REMS for retigabine [12]. Further guidance on risk-minimization measures was not available at the time of the survey [13, 14].

This was a voluntary survey in which the respondents were self-selected; therefore, the sample, although random, may not be representative of all physicians who prescribe retigabine. The survey focused on the risks described for retigabine in the PG, although this is not the only source of information about risks associated with medication use. While taking the survey, physicians were not restricted from referencing educational materials, which could have introduced a possible bias in the prior understanding of risks associated with retigabine. However, it was purposely not indicated which materials could be referenced to find the responses. Additionally, subsequent to data collection, retigabine was withdrawn in Germany. Therefore, the survey results may not represent the current prescribing population, as approximately one-third of respondents were practicing in Germany.

Overall, results indicate mixed physician understanding, ranging from adequate to limited recall, of the main risks associated with retigabine. To strengthen risk-minimization efforts for retigabine and following the identification of new emerging risks in 2013 [15], GSK has since sent an updated 'Dear Healthcare Professional' letter and initiated another EU survey to assess how effectively specific risks associated with retigabine use are communicated [16].

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Author contributions All authors met the International Committee for Medical Journal Editors criteria for authorship, were fully involved in manuscript development, and assume responsibility for the direction and content. Lianna Ishihara had a major role in the concept and study design, data analysis, and data interpretation; Anne Lewis, Sathish Kolli, and Neil Brickel were involved in concept and study design, data analysis, and data interpretation.

Compliance with Ethical Standards

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Conflicts of interest Lianna Ishihara was an employee and shareholder in GSK at the time of the study. She is currently employed by Lundberg SAS. Neil Brickel is an employee and shareholder of GSK. Anne Lewis is an employee of UBC. Sathish Kolli was an employee of GSK as European Medical Advisor at the time of the survey. He is currently employed by LEO Pharma.

Ethical approval This was a cross-sectional, non-interventional, observational survey. The study did not include intervention. The survey was approved by the European Medicines Agency (EMA) for implementation in all EU countries. Local regulations in each country were also followed.

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