GSK Medicine: Retigabine (GW582892)
Study Number: WWE116771
Title: European Survey of Prescriber Understanding of Risks Associated with TROBALT™
Rationale: The physician respondent survey was undertaken to evaluate the understanding of the significant risks associated with retigabine and to evaluate the effectiveness of the educational plan as specified in the European Risk Management Plan (RMP).
Study Period: 18 Sep 2012 – 31 Jan 2014
Objectives: To conduct a survey of neurologists who are prescribing AEDs on their understanding of the significant risks associated with retigabine.
Indication: Epilepsy
Study Investigators/Centers: United Biosource Corporation
Research Methods: Neurologists were recruited through an invitation to participate in the survey. Invitations (that included an introductory educational letter, an invitation to complete the survey, and the survey instrument) were sent by e-mail to those neurologists for whom an e-mail address were available or by mail for those neurologists without e-mail addresses (Annex 1). The invitation directed the neurologist how to access the survey on-line on the website to complete the survey. Physicians were provided a unique code in the survey invitation letter and were asked to provide the unique code to gain access to the online survey. The code was deactivated after use to minimise the possibility for fraud. All respondents completed the survey online. The evaluation survey used a standard questionnaire.
UBC has designed and conducted assessment surveys in over 20 European countries to evaluate prescribers’ understanding of risk messages.
Data Source: This survey was conducted in the first countries to launch retigabine; United Kingdom (UK), Germany, Denmark, Sweden, Switzerland, Spain, Slovakia, and Norway
Study Design: Cross-sectional survey by self-administered on-line questionnaires.
Study Population: Physicians were recruited by selecting a random sample of neurologists from lists of all potential retigabine prescribers in each country provided by GSK.
Study Exposures, Outcomes:
The questions and statements comprising the knowledge survey were constructed to test the understanding of the significant risks associated with retigabine.
The primary outcome was the proportion of neurologists answering each question of the understanding of the risks associated with retigabine correctly.
Data Analysis Methods: Each survey was composed of multiple choice and close-ended questions. There were no open-ended questions included. For statements or questions that used “true” or “yes” vs. “false” or “no” response options, the desired response for key risk messages was generally “true” or “yes” indicating knowledge of, or behaviour in accordance with, the objectives of the program. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of “false” or “no” to avoid having the same affirmative answer for all desired responses. The Internet survey questionnaires were programmed to ensure that questions were asked in the appropriate sequence. All lists of response options were randomised to minimise the potential for positional bias. All questions were presented in a standard order. Respondents could not go back to a question once the question was answered and could not skip ahead. All questions had to be answered in order for a survey to be considered complete. Computer programming was reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.
Point estimates for the proportion with correct responses, and associated confidence intervals, were calculated for each question about the risks of retigabine. In the case of multiple choice questions, the number and proportion of neurologists reporting each response were provided.
Limitations: This was a voluntary survey and therefore, the sample while selected randomly, may not be representative of all physicians who prescribe retigabine. In addition, the survey was conducted concurrently with the educational materials being sent, and therefore could represent a possible bias to the physicians previous understanding of the risks associated with retigabine.
**Study Results:** A total of 301 prescribers responded and were screened for participation (meeting the target sample size), and 294 of these (97.7%) were considered eligible for analysis. Of those, 96 prescribers were German physicians. All eligible respondents completed the survey online.

Indication for use: Almost all (91.5%) physicians surveyed recalled that retigabine is approved for use in partial-onset seizures, but only three-quarters (78.2%) recalled that it can only be prescribed to patients who are at least 18 years of age. Most (88.1%) understood that retigabine is not indicated for monotherapy.

Dose-related questions: Approximately three-quarters (74.1%) of physicians surveyed from all countries recalled that retigabine should be taken three times/day. Almost three-quarters (72.8%) recalled that retigabine can only be increased by 150 mg/day every 7 days. Slightly more than half (56.5%) of physicians recalled that a patient can reach the minimum maintenance dose of 600 mg/day by 3 weeks using the Treatment Initiation Pack. Slightly more than two-thirds (68.3%) of physicians surveyed from all countries recalled that the maximum recommended dose of retigabine is 1200 mg.

Central Nervous System (CNS) side effects-related questions: Two-thirds (66.3%) of physicians surveyed from all countries recalled that patients taking retigabine in clinical studies had a higher risk of experiencing a confusional state. However, only slightly more than half recalled patients had a higher risk of experiencing hallucinations (55.8%) and psychotic disorders (54.1%). A small percentage (39.8%) recalled that these symptoms were reported within the first 8 weeks after starting treatment with retigabine. Fewer (20.4%) recalled that appropriate dose titration may minimise the risk of CNS side effects.

Urinary symptom-related questions: Slightly less than two-thirds of physicians surveyed from all countries recalled that patients taking retigabine in clinical studies had a higher risk of experiencing urinary retention (64.6%). About half (55.4%) of these physicians recalled that they should specifically advise their patients taking retigabine about all of the urinary symptoms (including pain when urinating, difficulty starting urination, slow stream, and inability to pass urine). Approximately the same percentage (55.1%) recalled that AEs related to voiding dysfunction were reported within the first 8 weeks after starting treatment with retigabine.

Cardiac-related questions: Overall, physicians had a less recall of information regarding the cardiac risks compared to urinary risks associated with retigabine. Less than half (44.6%) recalled that retigabine has been shown to produce a possible QT prolongation at 1200 mg. Few physicians recalled that it is recommended to perform an electrocardiogram (ECG) on patients with congestive heart failure (CHF) (25.9%), ventricular hypertrophy (26.2%), and hypokalemia (24.1%). Almost half (44.9%) recalled that the ECG should be rechecked after reaching the maintenance dose in patients who had a QTc interval of > 400 milliseconds (ms) before starting retigabine. However, more (76.5%) physicians recalled that they should warn patients to whom they prescribed retigabine about new cardiac effects of syncope, palpitations, and any other symptoms of arrhythmia.

**Conclusion:**
The survey showed that overall physicians (both prescribers and those who had never prescribed retigabine) had an adequate knowledge of indication for use of retigabine, although specific dose related knowledge, which was not a primary survey objective, was much less well recalled. Fewer eligible physicians recalled that patients taking retigabine had a higher risk of experiencing specific CNS adverse events and urinary retention and less again recalled an association between retigabine and possible QT prolongation. Knowledge was limited on much of the detail of specific management of the individual risks.