**Risk Minimization Physician Survey Protocol**

| | |
|---|---|
| Drug Substance | Quetiapine fumarate |
| Study Code | D1443C000127 |
| Edition Number | 1 |
| Date | 19 December 2012 |

# Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended Release Tablets in selected countries in the European Union (EU)

*Requesting AZ department: Regulatory*
*Therapeutic area: Neuroscience*
*Name of Requester: John McGuire (European Regulatory Affairs Director)*

**Sponsor:**
**AstraZeneca AB, 151 85 Södertälje, Sweden**

*RWE Engagement Lead: Soheil Chavoshi; 1800 Concord Pike, Wilmington, DE USA 19850-5437*
*RWE Design and Analytics core member: Robert S. Brody; 1800 Concord Pike, Wilmington, DE USA 19850-5437*

**The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:**

| Amendment No. | Date of Amendment | Local Amendment No: | Date of Local Amendment |
|---|---|---|---|
| | | | |

| Administrative Change No. | Date of Administrative Change | Local Administrative Change No. | Date of Local Administrative Change |
|---|---|---|---|
| | | | |
| | | | |

**Principal Investigators:**

Robert S. Brody, MPH
Director, Global Epidemiology
Payer & Real World Evidence
Global Medicines Development
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

Matt Wilhelm
Business Insight Director
Global Commercial
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

**Co-Investigator**

Dhaval Desai, MD
Medical Science Director
Global Clinical Development
Global Medicines Development
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

## TABLE OF CONTENTS PAGE



## LIST OF TABLES



## LIST OF APPENDICES

# 1. BACKGROUND

The MEB, as the Reference Member State (RMS) for SEROQUEL and SEROQUEL XR, requested AstraZeneca to update the education materials in scope of the EU Risk Management Plan (RMP) and Summary of Product Characteristics (SmPC) changes with respect to hyperglycaemia and metabolic monitoring. The content and the messages for these educational materials have been agreed and distribution in the individual member states is ongoing.

AstraZeneca was also requested to provide a plan for assessing the effectiveness of these educational materials. During discussion with the MEB, it was communicated that there are 2 components to the assessment of effectiveness: process indicators (receipt and understanding of materials) and outcome indicators (changes in behaviour and effect on patients). To realize these 2 indicators, AstraZeneca is proposing 2 components for the evaluation of the effectiveness of the metabolic education: an objective, easy to understand and complete healthcare provider survey and the use of an Electronic Medical Records approach, as a potential means to assess the monitoring of patients.

This protocol describes the evaluation of the effectiveness of the distribution of metabolic educational materials sent to healthcare providers in the EU. It will be conducted via an evaluation survey that uses a questionnaire to assess the receipt of the educational material, whether the material was read, and to assess healthcare provider behaviour regarding the conduct of monitoring of metabolic parameters for patients treated with SEROQUEL and SEROQUEL XR. The survey will be conducted among healthcare providers who were targeted to receive the educational materials following local guidance and directives.

A companion proposal describes the evaluation of electronic medical record (EMR) data including details on objectives, the source of data, and the target healthcare provider-base for the database assessment.

# 2. OBJECTIVES OF THE EVALUATION SURVEY

The healthcare provider survey is a questionnaire that will document the receipt of educational materials and assess the behaviour of healthcare providers around the following key metabolic monitoring messages communicated through the educational materials.

The key messages communicated in the educational materials are presented below.

**Information on weight and hyperglycaemia has been updated in the "Special Warnings and Precautions" section of the label:**

***Weight:***

Weight gain has been reported in patients who have been treated with Seroquel® or Seroquel® XR, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines*.

***Hyperglycaemia:***

Hyperglycaemia and/or development or exacerbation of diabetes mellitus occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including Seroquel® or Seroquel® XR, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Existing information on other metabolic parameters include the following:**

***Lipids:***

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with Seroquel® or Seroquel® XR. Lipid changes should be managed as clinically appropriate.

***Metabolic Risk***

Given the observed changes in weight, blood glucose (see hyperglycaemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate.

# 3. METHODOLOGY

This protocol and the accompanying physician survey were designed by AstraZeneca.

## 3.1 Study Design

This survey will be completed by a sample of healthcare providers who were targeted to receive the metabolic educational materials and either currently prescribe or have the potential to prescribe SEROQUEL or SEROQUEL XR. A sample of healthcare providers who were targeted for the educational materials will be approached to participate in the survey.

The survey will be administered using the following modality:

- Self-administered and Internet-based questionnaire accessed through a secure website instructing the participant to enter a unique code provided in the invitation.

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take less than 10 minutes.

The survey included in Appendix B is written to reflect the wording and screen-by-screen presentation of questions for an Internet-based survey administration.

All respondents who complete the survey and who provide their contact information will be mailed a fee consistent with approved market value for the physician's time for completing the survey.

The questions related to having received the educational materials and having read the information (measures of process) are closed-ended questions (answered affirmatively as yes/no/unsure response options). Questions related to physician behavior regarding monitoring of patients (measures of outcome) are percentage estimates provided by the physician.

### 3.1.1 Questions Regarding Key Monitoring Behavior

**Question 1:**

What is your medical specialty*? Please select one from the drop-down list below.

- ○ General Medicine/General Practice
- ○ Neurology
- ○ Psychiatry
- ○ Other SPECIFY:_____

* NOTE – OTHER SPECIALTIES TO BE INCLUDED BASED ON AUDIENCES TO WHOM MATERIAL WAS SENT

**Question 2**

Please think about your patients with schizophrenia, bipolar disorder, and/or major depressive disorder who are treated with Seroquel® or Seroquel® XR. Describe the "monitoring" of metabolic factors* potentially related to treatment with Seroquel® or Seroquel® XR.

A. What proportions of your patients are being monitored by you, someone else in your practice or are referred to other healthcare providers? ____ %

B. What proportion of your patients is referred to other healthcare providers for monitoring? ____%

*Monitoring of metabolic factors includes: weight at initiation and during continuing treatment, ordering or reviewing lipid panel tests, observing patients for signs or symptoms associated with hyperglycaemia, ordering or reviewing tests for blood glucose measurement for patients with diabetes mellitus or in patients with risk factors for diabetes mellitus for worsening of glycaemic control, and counseling on nutrition, exercise and maintaining a healthy lifestyle

**Question 3**

Thinking now of the patients that you (or someone in your practice) monitor for metabolic issues potentially related to treatment with Seroquel® or Seroquel® XR, which of the following activities do you do? Please check all that apply.

- ▫ I counsel patients taking Seroquel® or Seroquel® XR on healthy eating, exercise, and healthy lifestyle improvements
- ▫ I monitor patients' weight at the initiation of treatment with Seroquel® or Seroquel® XR
- ▫ I monitor patients' weight on a regular basis after initiating treatment with Seroquel® or Seroquel® XR
- ▫ I monitor tests for hyperlipidemia in patients who are taking Seroquel or Seroquel® XR
- ▫ I observe for signs and symptoms of hyperglycaemia in patients who are taking Seroquel® or Seroquel® XR
- ▫ I monitor patients with diabetes mellitus or with risk factors for diabetes mellitus for worsening of glucose control if they are taking Seroquel® or Seroquel® XR

**Question 4**

The following question has two parts; please respond to both parts of the question.

A. Did you receive educational information relevant to the issues in this survey from AstraZeneca, either as a mailing or from a company representative, in (INSERT LOCAL MARKET REFERENCE MONTH) 2012 regarding the Product Label for Seroquel® or Seroquel® XR?

- ○ Yes
- ○ No
- ○ Unaware/not sure

B. Did you read the educational information?

- ○ Yes
- ○ No
- ○ Unaware/not sure

## 3.2 Study Population

### 3.2.1 Inclusion Criteria

Health Care Professionals who were targeted to receive the metabolic educational materials and either currently prescribe or have the potential to prescribe SEROQUEL or SEROQUEL XR.

Each physician should meet all inclusion criteria and none of the exclusion criteria to be eligible for this survey. Under no circumstances can there be any exceptions to this rule.

### 3.2.2 Exclusion Criteria

Healthcare providers or their immediate family members who have been employed by AstraZeneca or for a European Regulatory Agency are not eligible to participate.

## 3.3 Sample Size

A sample size of 100 completed questionnaires from healthcare providers in each of eight selected countries representing the geographic diversity of the EU is proposed. The size of the sample was determined based on both practical and statistical considerations. There is no presumed target rate for success in risk minimization measures based upon either a process measure (e.g., receiving educational materials) nor is there a rate specified *a priori* for success in outcome measures (e.g., metabolic monitoring). A sample of 100 completed questionnaires will allow estimation of the rate for process and outcome measures with a moderate degree of precision (within 6-10 percentage points regardless of the actual level of the process or outcome measure). The table below shows the precision of the estimates for level process and outcome measure using two-sided 95% confidence intervals (CIs) obtained with the sample size of 100 completed surveys. The noted CIs are used to indicate that for any survey-estimated level of effectiveness of risk minimization, the true population level of effectiveness is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

**Table 1: Precision of estimated Rates of effectiveness of risk minimization including: 1) Receiving information (as Process measure) or 2) performance of metabolic monitoring (as Outcome measure) with a Sample Size of 100 (Two-sided 95% Confidence Interval)**

| Estimated Rate | 95% Confidence Interval Lower Limit | 95% Confidence Interval Upper Limit |
|---|---|---|
| 1% | 0.0% | 3% |
| 6% | 1.3% | 10.7% |
| 11% | 4.9% | 17.1% |
| 16% | 8.8% | 23.2% |
| 21% | 13% | 29% |
| 26% | 17.4% | 34.6% |

| Estimated Rate | 95% Confidence Interval Lower Limit | 95% Confidence Interval Upper Limit |
|---|---|---|
| 31% | 21.9% | 40.1% |
| 36% | 26.6% | 45.4% |
| 41% | 31.4% | 50.6% |
| 46% | 36.2% | 55.8% |
| 51% | 41.2% | 60.8% |
| 56% | 46.3% | 65.7% |
| 61% | 51.4% | 70.6% |
| 66% | 56.7% | 75.3% |
| 71% | 62.1% | 79.9% |
| 76% | 67.6% | 84.4% |
| 81% | 73.3 % | 88.7% |

## 3.4 Healthcare Provider Recruitment

A random sample of healthcare providers who were targeted to receive SEROQUEL® / SEROQUEL® XR educational materials and who are considered likely to prescribe SEROQUEL® / SEROQUEL® XR will be invited to participate. An invitation will be sent to the healthcare providers.

If the required number of completed surveys is not achieved within the expected timeframe of approximately two weeks after the first invitation, a second one will be sent to non-respondents from the original sample with subsequent follow-up to maximize participation. If these efforts do not result in the required number of surveys within three to four weeks, then a new sample of prescribers will be randomly selected.

All participating healthcare providers will be offered a nominal fee consistent with approved market value for the physician's time for a completed survey. The survey is estimated to take less than 10 minutes to complete.

# 4. STUDY PROCEDURES

## 4.1 Study Validation Plan

In order to effectively evaluate the questionnaire prior to implementation, questionnaire validation will be implemented with a sample of healthcare providers to permit pilot testing of the questionnaire to be performed. Face validity assessment and pilot testing will be done in a single language.

### 4.1.1 Face Validity

Prior to administering the questionnaire, an evaluation by two practicing healthcare providers will be performed. The purpose of this evaluation will be to determine whether there are any items that are not readily understood or where the response requested may be misinterpreted. Face validity will be assumed if any items on the questionnaire are not flagged as problematic by both healthcare providers.

### 4.1.2 Translation of the survey

Translation will be done after the validation of the questionnaire. All translations to the respective languages will be done using forward and backward translations.

## 4.2 Survey Administration

Healthcare providers who select to participate in the survey will be directed to a secure website where they will be instructed to enter a unique code to access the survey. The questionnaire will begin with a screening module that includes questions to verify that the respondent has met all of the inclusion criteria and none of the exclusion criteria for the survey. Respondents will provide their consent to participate in a study that is designed for market research purposes and not intended to be promotional in any way. Respondents are asked not to share the content of the survey.

Depending on the answers to the screening questions, survey participation could either be terminated or continued. If deemed ineligible, respondents will be immediately notified with a "thank you" message that the survey participation has ended and they will not receive compensation. If deemed eligible, respondents will be allowed to continue survey participation.

The data entry system used for the survey will be secure for receiving and storing survey data. Prescriber-identifying information will be stored separately from survey data.

# 5. MEASURES TO MINIMIZE BIAS IN THE SAMPLE AND QUESTIONNAIRE ADMINISTRATION

Several measures will be used to minimize bias in the sample. Every effort will be made to ensure diversity in the distribution of healthcare providers invited to participate with regard to geography and physician specialty; however, the choice to ultimately participate in the survey is voluntary.

All participants who might have access to confidential information about this survey will be excluded. Also, Healthcare providers or their immediate family members employed by AstraZeneca or a European Regulatory Agency will not be eligible to participate.

An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location. Healthcare providers will be provided

with a unique code during the recruitment process and will then be asked to provide the unique code in order to gain access to the online survey. All respondents who are eligible to participate will answer the same questions outlined in Appendix B. The code will be inactivated after use to minimize fraud and reduce the chance of a respondent participating in the survey more than once. In order to minimize self-selection bias, a reminder notice will be sent to invited participants who have not responded within two weeks of the initial invitation.

## 6. ANALYSIS

The survey questionnaire contains questions about the specialty of the physician sample completing the survey, questions specific to whether referrals are made to other healthcare providers for metabolic monitoring, whether the healthcare provider conducts monitoring of patients, general questions regarding receipt of the educational materials, and behavior about reading the materials. Information obtained from responses to each question of the survey will be reported as descriptive statistics. A frequency distribution of responses to each question (the number of respondents who give answers to each response option) will be presented.

Each risk minimization behavior will be evaluated individually.

Related behaviors, such as:

- Monitoring for weight
- Monitoring for signs and symptoms of hyperglycaemia and monitoring blood glucose changes in patients with diabetes mellitus will be combined to report the number of survey respondents who answered each risk minimization activity individually, any one activity and both activities. This will be expressed as a percent of the total number of respondents who answered the questions on these risk minimization activities.

Frequency distributions of the responses to having received SEROQUEL® / SEROQUEL® XR educational materials and behaviors about reading the educational materials, will also be calculated and displayed. The analysis of frequencies will include exact binomial 95% confidence intervals.

The following will be reported, as appropriate, as part of this analysis:

- The number of invitations issued to healthcare providers
- The number of healthcare providers screened for participation
- The number of healthcare providers eligible for participation
- The number of healthcare providers who completed the survey

- Description of healthcare provider survey participants, including:
  - Specialty of respondent
  - Country of practice
- Frequency distribution of responses to each survey question (the number of respondents who give each answer to each question)
- Percent of respondents selecting desired response to each question relating to each risk minimization activity and 95% confidence interval
- Percent of respondents demonstrating success of composite risk minimization activities and 95% confidence interval

Additional analyses may be performed as needed.

**Risk Minimization Physician Survey Protocol**

| | |
|---|---|
| Drug Substance | Quetiapine fumarate |
| Study Code | D1443C000127 |
| Edition Number | 1 |
| Date | 19 December 2012 |
| Protocol Dated | 19 December 2012 |

# Appendix A
# Signatures

## ASTRAZENECA SIGNATURE(S)

Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended Release Tablets in selected countries in the European Union (EU)

This Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

Robert S. Brody

Robert S. Brody, MPH
Director, Global Epidemiology
Payer & Real World Evidence
Global Medicines Development
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437 USA

20 December 2012
Date
(Day Month Year)

## ASTRAZENECA SIGNATURE(S)

Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended Release Tablets in selected countries in the European Union (EU)

This Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

Matt Wilhelm
Business Insight Director
Global Commercial
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437 USA

21 December 2012
Date
(Day Month Year)

## ASTRAZENECA SIGNATURE(S)

Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended Release Tablets in selected countries in the European Union (EU)

This Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

Dhaval Desai, MD
Medical Science Director
Global Clinical Development
Global Medicines Development
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437 USA

12-2012
Date
(Day Month Year)

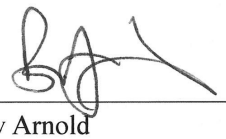
## ASTRAZENECA SIGNATURE(S)

Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended Release Tablets in selected countries in the European Union (EU)

This Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development representative**



21ST December 2012

Barry Arnold
EU Qualified Person for Pharmacovigilance
AstraZeneca Pharmaceuticals
Global Medicines Development
Chief Medical Office
Alderly Park, England

Date
(Day Month Year)

# Appendix B
# Questionnaire

# QUESTIONNAIRE

**The questionnaire is designed to be administered as an on-line survey via Internet. The following are mock-up version of what the successive screens that would be displayed**

**Screen 1**

Thank you for agreeing to participate in this survey. You have been recruited on behalf of X, an independent research agency. They are conducting research for a pharmaceutical company. The company who is commissioning this research does not hold or see any information regarding respondents.

This study is for research purposes only and not intended to be promotional in any way. It is being conducted to measure your recall of information you might have received about their product(s).

The questionnaire will be an online survey and should take no more than 10 minutes to complete. Your responses will automatically save as you proceed, therefore you may close and rejoin the questionnaire at any point.

Please click here to view our statement regarding data protection, privacy, invisible processing and ways to contact us. [INSERT PRIVACY STATEMENT] To print the privacy statement, please click here.

I consent to participate in this survey based on the information above.

- ⊙ Yes CONTINUE
- ○ No THANK AND TERMINATE

**Screen 2**

You are about to enter a research interview. We are now required to pass on to our client details of adverse events that are raised during the course of research interviews. Although this is an on-line research interview and how you respond will, of course, be treated in confidence, should you raise an adverse event in a specific patient or group of patients, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities. In such a situation you will be contacted to ask whether or not you are willing to waive the confidentiality given to you under the Research Codes of conduct specifically in relation to that adverse event. Everything else you contribute during the course of the interview will continue to remain confidential.

Are you happy to proceed with the interview on this basis?

- ⊙ Yes CONTINUE
- ○ No THANK AND TERMINATE

**Screen 3** Question 1:

What is your medical specialty*? Please select one from the drop-down list below.

- ○ General Medicine/General Practice
- ○ Neurology
- ○ Psychiatry
- ○ Other SPECIFY:_____

* NOTE – OTHER SPECIALTIES TO BE INCLUDED BASED ON AUDIENCES TO WHOM MATERIAL WAS SENT

**Screen 4** Question 2:

Instructions: Please think about your patients with schizophrenia, bipolar disorder, and/or major depressive disorder who are treated with Seroquel® or Seroquel® XR. Describe the "monitoring" of metabolic factors* potentially related to treatment with Seroquel® or Seroquel® XR.

A. What proportions of your patients are being monitored by you, someone else in your practice or are referred to other healthcare providers? ____ %

B. What proportion of your patients is referred to other healthcare providers for monitoring? ____%

*Monitoring of metabolic factors includes: weight at initiation and during continuing treatment, ordering or reviewing lipid panel tests, observing patients for signs or symptoms associated with hyperglycaemia, ordering or reviewing tests for blood glucose measurement for patients with diabetes mellitus or in patients with risk factors for diabetes mellitus for worsening of glycaemic control, and counseling on nutrition, exercise and maintaining a healthy lifestyle

**Screen 5** Question 3:

Instructions: Thinking now of the patients that you yourself monitor for metabolic issues potentially related to treatment with Seroquel® or Seroquel® XR, which of the following activities do you perform? Please check all that apply.

- ▫ I counsel patients taking Seroquel® or Seroquel® XR on healthy eating, exercise, and healthy lifestyle improvements
- ▫ I monitor patients' weight at the initiation of treatment with Seroquel® or Seroquel® XR
- ▫ I monitor patients' weight on a regular basis after initiating treatment with Seroquel® or Seroquel® XR
- ▫ I monitor tests for hyperlipidemia in patients who are taking Seroquel or Seroquel® XR
- ▫ I observe for signs and symptoms of hyperglycaemia in patients who are taking Seroquel® or Seroquel® XR
- ▫ I monitor patients with diabetes mellitus or with risk factors for diabetes mellitus for worsening of glucose control if they are taking Seroquel® or Seroquel® XR

**Screen 6** Question 4:

Instructions: The following question has two parts; please respond to both parts of the question

A. Did you receive educational information relevant to the issues in this survey from AstraZeneca, either as a mailing or from a company representative, in (INSERT LOCAL MARKET REFERENCE MONTH) 2012 regarding the Product Label for Seroquel® or Seroquel® XR?

- ○ Yes
- ○ No
- ○ Do not know/not sure

B. Did you read the educational information?

- ○ Yes
- ○ No
- ○ Do not know/not sure