Clinical Study Report Synopsis

Drug Substance	SEROQUEL®/XR
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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)

Study dates: Start of data collection: 24 April 2012
End of data collection: 20 March 2014

Phase of development: Therapeutic use (IV)

Study centre(s)

This report includes patients recruited from 75 sites across Sweden (n=10), Germany (n=15), Italy (n=14), Romania (n=20), and Spain (n=16). The majority of sites were located in urban settings (n=66, 86.8%) and were distributed across various regions within their respective countries. The majority of practices included in this final report were located in university hospitals (n=24, 31.6%), private offices (n=18, 23.7%), or mental health centres (n=13, 17.1%).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study objectives were to: document characteristics of patients under specialist (psychiatric) care who were prescribed SEROQUEL XR as treatment for MDD in each of the selected countries over a 9 month period, starting 3 months following the launch of the product for its approved indication; and describe the differences between countries concerning treatment practices involving use of SEROQUEL XR, through the use of a drug utilisation questionnaire of psychiatrists in five European countries.

Study design

This was a multinational, multicenter, retrospective, observational study of antidepressant drug utilisation among an inception cohort of patients under specialist (psychiatrist) care who were prescribed SEROQUEL XR for treatment of major depressive episodes associated with MDD following launch of the indication in each country. The study was conducted in five European countries: Sweden, Germany, Italy, Romania, and Spain, in order to include geographic representation across different regions of the European Union.

A drug utilisation questionnaire (DUQ) was designed to collect key variables on characteristics of physicians, patients, and the drugs utilised in the medical management of depressive episodes in MDD where the treatment regimen included SEROQUEL XR. The study was performed through centre-based medical record abstractions. The DUQ was tested in a pilot study and modified on the basis of pilot study findings and recommendations of a Scientific Advisory Board (SAB). Specifically trained independent medical record abstractors were provided to the sites to complete the study. The data were collected as a single medical record review. The data to be abstracted was determined a priori and incorporated into an electronic case report form (eCRF) to ensure systematic collection.

Target subject population and sample

Data were abstracted from patients under specialist (psychiatric) care who were prescribed SEROQUEL XR as treatment for MDD in each of the selected countries over a 9 month period, starting 3 months following the launch of the product for its approved indication.

There was lower than expected patient enrolment in all countries except for Romania. Based on estimates included in the Site Qualification Questionnaires used to select sites for

participation, it was anticipated that a total of 1903 patients would be enrolled in the study overall: Germany (434), Sweden (103), Spain (430), Romania (394), and Italy (542). Sites significantly overestimated their recruitment potential, mainly due to a lack of clear understanding of the eligibility criteria and uncertainty over patient diagnosis and treatment. In some instances, this was due to difficulties in directly accessing patient records, which were often paper based, or to lack of clear documentation in the records.

In total, 811 patients were included in the final analysis population. This corresponds to 31 patients from Sweden, 152 from Germany, 105 from Italy, 327 from Romania, and 196 from Spain.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

This was a non-interventional study.

Duration of treatment

This was a non-interventional study.

Statistical methods

Data obtained from the DUQ are reported descriptively by individual country and overall. Individual country results are appended to the final study report. Data are presented by all patients, and by monotherapy treatment and add-on treatment. General demographics and characteristics of participating psychiatrists are summarised. Summary statistics are provided for patient demographic and clinical characteristics. The number and percentage of patients taking MDD medication during the 12 months prior to initiation of SEROQUEL XR treatment as well as during the study are presented by drug subclass and the generic name of the drugs within these subclasses taken by 5% or more of the study population.

SEROQUEL XR utilisation characterization included the following parameters: initial and modal dosing, proportion of patients with modal doses outside (high, low) the recommended daily dose and the number of patients receiving SEROQUEL as monotherapy or add-on therapy during the observation period.

For continuous variables, the number of responses, mean, median, minimum (min), maximum (max) and standard deviation (SD) are provided. For discrete variables, the number and percent of observed responses and proportion of each category represented as well as 95% confidence intervals (CIs) are summarised.

Associations between four response variables (initial dose of Seroquel XR, modal dose of Seroquel XR, Seroquel XR as monotherapy at initiation, and Seroquel XR dose higher than recommended) and exploratory factors were explored via linear regression for continuous variables (initial daily dose and modal daily dose) and logistic regression for categorical variables (Seroquel XR as monotherapy and Seroquel XR higher than recommended). Each exploratory variable was evaluated individually through univariate analysis. A multivariate analysis was performed including only those variables which were found significant in the

univariate analysis. A backward elimination technique was employed to determine which variables should remain in the model based on their relative contribution in association with the dependent variable. Additional exploratory multivariate logistic regression models were considered in the evaluation of factors predictive of use of monotherapy taking into account the univariate and full models above, while minimizing the amount of missing data among explanatory variables. The intent was to provide a parsimonious and stable model which would aid in understanding the factors affecting the use of monotherapy.

Subject population

Data were abstracted from patients under specialist (psychiatric) care who were prescribed SEROQUEL XR as treatment for MDD in each of the selected countries over a 9 month period, starting 3 months following the launch of the product for its approved indication.

Across all countries, 1119 patients were screened, 247 patients were ineligible, 58 patients refused to participate, and three patients were excluded from the analysis due to missing data on SEROQUEL XR, leaving 811 patients included in the final analysis: 31 in Sweden, 152 in Germany, 105 in Italy, 327 in Romania, and 196 in Spain.

Summary of efficacy results

Substantial difficulties were encountered with recruitment both of study sites and of patients within the sites in several of the countries included in the study, and as a result patient numbers were lower than the original estimates.

Participating psychiatrists had been in practice for approximately 25 years on average and were in their current specialty for more than 20 years. The majority of practice settings that enroled patients were located in university hospitals, private offices, or mental health centers (MHCs). The distribution of practice settings differed by country and differed from the expected distribution in Germany, Italy and Romania. The study sites were from different geographical regions within each country, with the majority of sites located in urban settings.

Across the five countries there were similarities in basic demographic characteristics of patients receiving SEROQUEL XR as treatment for MDD with regard to gender and race. One noteworthy difference in patient characteristics was finding the mean age of patients' first treatment with SEROQUEL XR for MDD in Sweden to be on average 8 years younger than patients from the other countries studied. A possible reason for Swedish patients tending to be younger than those from other countries may be the guidance from the National Board for Health and Welfare (Socialstyrelsen 2010), which specifically states 'do not do' for the addition of antipsychotic agents to antidepressants for severe/treatment resistant depression in elderly patients.

Many important aspects of patients' psychiatric and medical history were similar across the populations studied and indicated that the majority of the study population had experienced the burden of severe MDD. The majority of the study population were candidates for additional treatment as their physician's rated the therapeutic effect of prior treatment regimens in categories of "minimal or slight improvement" or "unchanged or worse". Where

documentation in the medical record was available, patients receiving SEROQUEL XR had a history of three or more lifetime depressive episodes among the majority of patients (57.9% of patients from Spain, 70.3% of patients from Romania, 70.7% of patients from Germany, 78.8% of patients from Italy, and 83.3% from Sweden).

Differences in patients' psychiatric history were in evidence as well. For example, a higher proportion of patients with a past history of hospitalization for MDD was observed among patients in Germany (89.3%) and Romania (76.2%) compared to Sweden (33.3%), Italy (44.2%), and Spain (8.3%).

There were similarities across countries in drug utilisation measures that were in accordance with the recommendations in the SmPC. During the study observation period, the vast majority of patients received SEROQUEL XR added-on to another antidepressant.

On average, patients initiated SEROQUEL XR treatment 4.7 years following the confirmation of MDD diagnosis with an average initial dose of 160.5 mg. Both the mean (193.1 mg) and median (200 mg) for the most frequently prescribed (modal) dose in Sweden approximated the measures for all countries combined and were within the SmPC-recommended range.

There were differences in drug utilization for some of the outcome measures observed across the countries including the comparison of Sweden with the other EU countries in this final report. The initial dose of SEROQUEL XR administered was different than the recommended level of 50 mg on the first day of treatment for a majority of patients with MDD in four of the five countries (the exception being Spain).

The mean initial dose of SEROQUEL XR that was prescribed in Sweden fell within the range defined by Spain, on the low end, and Romania on the high end; however it was recognized that these exceeded the recommendation for the start dose for the MDD indication in the SmPC.

A total of 127 patients (15.7%) used SEROQUEL XR treatment as monotherapy at initiation and 102 patients (12.6%) remained on SEROQUEL XR as monotherapy over the course of the study observation period. More patients received SEROQUEL XR as monotherapy in Sweden and Italy than in the other three countries. Although the magnitude of use of SEROQUEL XR as monotherapy decreased during the course of treatment; in these two countries the proportion of patients prescribed SEROQUEL XR as monotherapy remained higher than recorded for patients from the other countries studied. Exploratory modelling of factors that were predictive of use of monotherapy included i) patients' age <40 years, ii) either no prior antidepressant therapy or prior medication with tricyclic antidepressants, iii) patients from Italy and Sweden, iv) the interaction of prior medication and country, with a greater number of patients receiving no therapy or prior medication with tricyclics or other psychoactive medications in Italy and Sweden who initiated monotherapy than patients in those countries receiving prior medication with SSRIs and SNRIs and v) patients from general and university hospitals. The vast majority of patients (n=684, 84.3%) received SEROQUEL XR as an add-on at initiation to regimens that included other antidepressants. Among the patients who initiated SEROQUEL XR as add-on therapy, concomitant MDD treatment across the study

period included: selective serotonin reuptake inhibitors [SSRIs] (49.3%), anxiolytics (47.1%), serotonin-norepinephrine reuptake inhibitors [SNRIs] (42.4%), other atypical antidepressants (30.1%), mood stabilizers (18.1%), sedatives/hypnotics (16.4%), atypical antipsychotic drugs (12.9%), tricyclics (8.2%), conventional antipsychotics (5.3%), antidepressants in combination with psycholeptics (0.9%), and MAO A inhibitors (0.4%). On the basis of a sensitivity analysis that corrected calculation of daily doses when prescribed regimens had one day of overlap, the proportion of patients who received doses of SEROQUEL XR above the recommended limit were quite similar (ranging between 11.8% - 16.5%) in all countries except Spain (7.1%).