**Clinical Study Report Synopsis**

Drug Substance quetiapine fumarate

Study Code D1444C00006

# Epidemiologic study to assess the safety of the extended-release form of Seroquel® (quetiapine) in the post-marketing phase in the UK. CPRD/GPRD Study

**Study dates:** First subject enrolled: 10 September 2008

Last subject last visit: 30 December 2012

**Phase of development:** Therapeutic use (IV)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centre(s)

This observational study was conducted using data from the Clinical Practice Research Datalink (CPRD) which is a United Kingdom (UK) primary care, longitudinal, electronic medical record database.

## Publications

None at the time of writing this report

## Objectives and criteria for evaluation

**Table S1 Research question and objectives**

| Objectives | Outcome |
|---|---|
| To characterize new users of quetiapine XR as well as new users of comparison drugs with regard to the indication for which they received the study drug, diagnosed co-morbidities and drug utilization patterns prior to receiving a study drug, as well as the duration of treatment prior to discontinuation. | Description of patients and drug use patterns |
| To quantify the risk of developing incident outcomes of interest in new users of quetiapine XR and comparison subjects, namely death of all causes, suicide or suicidal attempt/ideation, acute myocardial infarction (AMI), thrombotic or haemorrhagic stroke, diabetes mellitus, hypothyroidism, neuroleptic malignant syndrome (NMS), fractures, syncope, extrapyramidal symptoms (EPS) associated with new use of parasympathicolytic drugs, seizures, and cataract. | Crude Incidence Rates, Odds Ratio (OR) |

## Study design

This was an observational study to characterize new users of quetiapine XR as well as new users of other study drugs (i.e. the comparison group) and to quantify the risk of developing newly diagnosed outcomes of interest in new users of quetiapine XR as well as in other study drugs. This was a population-based cohort and nested case-control study using data from CPRD. The cohort analysis allowed calculating incidence rates (IRs) of the various outcomes of interest in quetiapine XR users and users of comparison drugs, while the nested case-control analyses were useful to assess in more detail the relative risks of these outcomes in association with previous exposure to quetiapine XR or comparison drugs. In addition, the nested case-control approach – as compared for instance to a cohort analysis – does allow to better take into account largely varying exposures with frequent switching or add-on of the various study drugs over short-term periods. The nested case-control also allows better control of temporary trends of exposures since the index date for cases and controls is the same date. Each case and control can be classified into mutually exclusive exposure groups, taking exposure duration, timing, and switching of study drugs or concomitant drug use into account. It further allows assessing many explanatory variables/risk factors of interest at the same time; this would be much more complex in a cohort study. In addition, it also avoids the computational burden associated with multiple time-dependent explanatory variables.

### Target subject population and sample size

Based on published background incidence rates in schizophrenic patients or, if not available, in the general population, with the assumption of a steady enrolment rate we could have expected an average follow-up time of some 2 years per patient. If were possible to enrol some 1300 quetiapine XR users and 8 times as many subjects in the comparison group, we would expect to have 1300 plus 10,400 = 11,700 subjects in the study population and therefore with 11,700 times 2 person-years = approx. 23'400 person-years.

### Investigational product and comparator(s): dosage, mode of administration and product reference

| Investigational product | Dosage form, strength, and route of administration | Manufacturer | Product Reference |
|---|---|---|---|
| quetiapine XR | Tablet, 50 mg, oral | AstraZeneca | PL 17901/0249 |
| quetiapine XR | Tablet, 150 mg, oral | AstraZeneca | PL 17901/0259 |
| quetiapine XR | Tablet, 200 mg, oral | AstraZeneca | PL 17901/0250 |
| quetiapine XR | Tablet, 300 mg, oral | AstraZeneca | PL 17901/0251 |
| quetiapine XR | Tablet, 400 mg, oral | AstraZeneca | PL 17901/0252 |
| Non-quetiapine XR comparison group | | | |

### Duration of treatment

The study was to last approximately 4 years from enrolment of the first patients until the end of the project.

### Statistical methods

Using data from the CPRD, crude incidence rates (IRs) per 100 person-years (py) with 95% confidence intervals (CIs) of each outcome of interest for quetiapine XR users and users of comparison group, overall and by indication (schizophrenia, bipolar disorder, or major depressive disorder), stratified by age, sex and timing of drug exposure (i.e. current, recent, or past use) and calculated corresponding incidence rate ratios (IRRs) with 95% CIs by comparing IRs from quetiapine XR users with IRs from patients in the comparison group were assessed.

In the nested case-control analysis, conditional logistic regression analyses to compare the exposure to quetiapine XR or comparison drugs, in detail between cases and controls were used. Crude and adjusted (for various confounders) relative risks estimates as odds ratios (ORs) with 95% CIs, stratified by timing of drug exposure were calculated. In addition,

absolute numbers and percentage of current use, stratified by number of previous prescriptions, and the daily dose (displayed as defined daily dose equivalents) were provided.

**Subject population**

The study population consisted of 37,372 patients who were treated for schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) (5,564 patients receiving quetiapine XR and 31,808 patients receiving non-quetiapine comparison drugs). Non-quetiapine comparison group consisted of patients with a first time prescription for an antipsychotic drug (other than quetiapine), a mood stabilizer, an antidepressant drug or any combined therapy (including combined preparations of antidepressants/antipsychotic drugs). Amongst quetiapine XR users, 628 (11.3%) were prescribed the drug for schizophrenia, 1,113 (20%) for BD, and 2,758 (49.6%) for MDD; for the remaining 1,065 (19.1%) quetiapine XR users the indication was unknown or not determinable. Among the 31,808 users of comparison drugs, 853 users (2.7%) were prescribed the drugs for schizophrenia, 376 (1.2%) for BD, 22,059 (69.3%) for MDD, and for 8520 users (26.8%) the indication was unknown or not determinable.

**Summary of results**

In the cohort analysis, overall study population encompassed more women (approx. 59%) than men. Current smoking status was more frequent among quetiapine XR users (44.0%) than among users of comparison drugs (27.5%), whereas 33.1% of quetiapine XR users were never smokers as compared to 43.1% of users of comparison drugs. Alcohol consumption was more common for comparison drug users than quetiapine XR users (46.7% of comparison drug users reported alcohol use versus 39.9% of quetiapine XR users). Whilst alcohol consumption was assessed for the cohort population, information on substance abuse was not collected in this study. A large part of the study population was overweight with BMI >30 $kg/m^2$ among quetiapine XR users than among users of comparison drugs (schizophrenia: 33.5% vs. 19%, BD: 31.9% vs. 16.2%, and MDD: 30.2% vs. 22.7%, respectively).

There were a number of comorbidities and history of outcome diagnoses that were recorded in different proportions of patients in the quetiapine XR and comparison groups. Of all assessed comorbidities, insomnia was by far the most frequently recorded diagnosis with higher numbers among quetiapine XR users (36.0%) as compared to 10.4% among users of a comparison drug. These numbers were approximately consistent across all three subgroups of drug indication. Other frequently recorded comorbidities were hypertension (15.3% of quetiapine XR users, 15.5% of users of comparison drugs), dyslipidaemia (8.8% of quetiapine XR users, 6.7% of users of comparison drugs). One other noteworthy finding included the prevalence of dementia (4.4% of quetiapine XR users, 0.8% of users of comparison drugs).

The percentage of recorded previous suicide attempts / suicidal ideations were increased in quetiapine XR users in all three subgroups of indication with the largest difference between

study groups in patients with MDD (26.2% of quetiapine XR users, 3.5% of users of comparison drugs). Furthermore, many patients had a history for diabetes mellitus (8.8% of quetiapine XR users, 6.3% of users of comparison drugs), hypothyroidism (8.1% of quetiapine XR users, 4.6% of users of comparison drugs), as well as of at least one previous syncope (8.9% of quetiapine XR users, 5.4% of users of comparison drugs). Of note, patients with a history of outcomes diagnoses included among the primary objectives of the study (e.g. suicidal attempt/ideation) were excluded from the corresponding subsequent nested case-control analyses (e.g. suicide or suicidal attempt/ideation).

There were notable differences in prior and concomitant medication use between quetiapine XR users and comparison drug users. Concomitant drugs that were used at a higher rate by quetiapine XR users versus comparison drug users included antidepressants (62.8% vs. 0.4%), benzodiazepines (37.9% vs. 8.4%), mood stabilizers (18.2% vs. 0.7%), anticonvulsants (18.1% vs. 1.8%), atypical antipsychotics (16.8% vs. 0.1%), typical antipsychotics (8.2% vs. 1.1%), and thyroid hormones (7.4% vs. 4.2%). The differences in the use of psychiatric medications between quetiapine XR users and comparison drug users may be reflective of more severe or complex underlying psychiatric disease in the quetiapine XR patients.

The overall median duration of quetiapine XR use was 5.3 months, with similar numbers in the subgroups of patients with schizophrenia and MDD. Patients with BD revealed a somewhat longer median duration of quetiapine XR use with 6.3 months.

During the study period 615 patients died, 257 committed suicide or attempted/thought of committing suicide, 25 developed an incident acute myocardial infarction (AMI), 109 developed an incident thrombotic or haemorrhagic stroke, 46 were diagnosed with diabetes mellitus, 20 were diagnosed with hypothyroidism, 3 were diagnosed with neuroleptic malignant syndrome (NMS), 215 had a fracture, 241 a syncope, 3 had extrapyramidal symptoms (EPS) associated with new use of parasympathicolytic drugs, 75 had a seizure, and 120 had a cataract diagnosis.

In the cohort analysis, the IR of suicide or suicidal attempt/ideation was 1.11 (0.87–1.36) for quetiapine XR users and 0.33 (0.29–0.38) for users of comparison drugs, resulting in an IRR of 3.33 (2.56–4.33). Analogously, in the nested case-control analyses the OR of suicide or suicidal attempt/ideation was 2.3 (1.6–3.4) for patients over all indications, 2.0 (0.2–22.5) for patients with schizophrenia, 2.1 (0.7–6.1) for patients with BD, and 2.9 (1.8–4.8) for patients with MDD.

The IR of AMI was 0.05 (0.01–0.10) for quetiapine XR users and 0.04 (0.02–0.05) for users of comparison drugs, resulting in an IRR of 1.42 (0.53–3.78). The IR of thrombotic or haemorrhagic stroke was 0.19 (0.10–0.28) for quetiapine XR users and 0.17 (0.14–0.21) for users of comparison drugs, resulting in an IRR of 1.13 (0.68–1.88). The IR of diabetes mellitus was 0.09 (0.03–0.16) for quetiapine XR users and 0.08 (0.05–0.10) for users of comparison drugs, resulting in an IRR of 1.25 (0.58–2.67). The IR of hypothyroidism was 0.07 (0.01–0.13) for quetiapine XR users and 0.03 (0.01–0.04) for users of comparison drugs, resulting in an IRR of 2.56 (0.99–6.67). The IR of fractures was 0.34 (0.20–0.48) for quetiapine XR users and 0.47 (0.41–0.54) for users of comparison drugs, resulting in an IRR of 0.72 (0.47–1.11). The IR of syncope was 0.50 (0.35–0.65) for quetiapine XR users and 0.39 (0.33–0.44) for users of comparison drugs, resulting in an IRR of 1.29 (0.93–1.79). The IR of

seizures was 0.17 (0.08–0.25) for quetiapine XR users and 0.11 (0.08–0.14) for users of comparison drugs, resulting in an IRR of 1.47 (0.84–2.59). The IR of cataract was 0.09 (0.03–0.15) for quetiapine XR users and 0.21 (0.18–0.25) for users of comparison drugs, resulting in an IRR of 0.40 (0.20–0.82). Regarding the IRs of NMS and EPS associated with new use of parasympathicolytic drugs, the number of cases was too small for a meaningful assessment.

Comparing quetiapine XR users to users of comparison drugs in the nested case-control analysis, the odds ratio (with 95% CI) of death of all causes over all indications was 1.3 (1.0–1.7), 0.6 (0.2–2.3) for patients with schizophrenia, 0.9 (0.2–0.3) for patients with BD, and 1.8 (1.8–2.9) for patients with MDD. Analogously, the odds ratio (OR) of suicide or suicidal attempt/ideation was 2.3 (1.6–3.4) for patients over all indications, 2.0 (0.2–22.5) for patients with schizophrenia, 2.1 (0.7–6.1) for patients with BD, and 2.9 (1.8–4.8) for patients with MDD. The OR of AMI over all indications was 1.8 (0.4–7.9), of thrombotic or haemorrhagic stroke 1.2 (0.6–2.5), of diabetes mellitus 0.7 (0.2–2.4), of hypothyroidism 0.9 (0.2–3.3), of fractures 0.8 (0.5–1.4), of syncope 1.3 (0.8–1.9), of seizures 1.5 (0.7–3.3), and of cataract 0.4 (0.2–1.0). For the outcomes NMS and EPS associated with new use of parasympathicolytic drugs, the number of cases was too small for a meaningful analysis.

In the cohort analysis, the incidence rate (IR) of death from all causes per 100 py (with 95% CI) was 1.14 (0.93–1.36) for quetiapine XR users and 0.93 (0.85–1.01) for users of comparison drugs, resulting in an IRR of 1.23 (1.00–1.51). In the nested-case control analysis, the OR (with 95% CI) for death from all causes over all indications was 1.3 (1.0–1.7); 0.6 (0.2–2.3) for patients with schizophrenia, 0.9 (0.2–0.3) for patients with BD, and 1.8 (1.2–2.9) for patients with MDD. When stratification of the patient population according to prior history of dementia was considered in both the cohort and nested-case control analyses the association between quetiapine XR use and death from all causes was no longer statistically significant; i.e., in the cohort analysis, the risk of death from all causes in patients with dementia using quetiapine XR compared to patients with dementia using a comparison drug was 1.0 (0.6–1.6).