All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Quetiapine prolonged-release tablets (Seroquel XL®▼) for the treatment of schizophrenia in adults

AstraZeneca UK Ltd

Advice No: 1509 – August 2009

Recommendation of AWMSG

Quetiapine prolonged-release tablets (Seroquel XL®▼) are recommended as an option for use within NHS Wales for the treatment of schizophrenia in adults.

In order to limit errors, prolonged-release quetiapine should be prescribed by brand name.

AWMSG is of the opinion that quetiapine prolonged-release tablets (Seroquel XL®▼) may be suitable for shared care within NHS Wales.

Quetiapine prolonged-release tablets (Seroquel XL®▼) are not endorsed for the treatment of manic episodes associated with bipolar disorder within NHS Wales. AstraZeneca UK Ltd is not in a position to progress a submission to AWMSG for its appraisal in this indication. As a result, AWMSG cannot provide advice to the Minister for Health and Social Services

This report should be cited as:

ABBREVIATIONS

AE	Adverse events
AUC	Area under the concentration versus time curve
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CI	Confidence interval
Cmax	Maximum plasma concentration at steady state
Cmin	Concentration at the end of the 24 hour dosing interval
EPS	Extrapyramidal symptoms
IR	Immediate release
mITT	Modified intention to treat
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
PANSS	Positive and Negative Syndrome Scale
PR	Prolonged release
SAEs	Serious adverse events
SPC	Summary of Product Characteristics
Tmax	Time to reach Cmax
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 12th August 2009

The recommendation of AWMSG is:

Quetiapine prolonged-release tablets (Seroquel XL®▼) are recommended as an option for use within NHS Wales for the treatment of schizophrenia in adults.

In order to limit errors, prolonged-release quetiapine should be prescribed by brand name, as Seroquel XL®▼.

AWMSG is of the opinion that quetiapine prolonged-release tablets (Seroquel XL®▼) may be suitable for shared care within NHS Wales.

Quetiapine prolonged-release tablets (Seroquel XL®▼) are not endorsed for the treatment of manic episodes associated with bipolar disorder within NHS Wales. AstraZeneca UK Ltd is not in a position to progress a submission to AWMSG for its appraisal in this indication. As a result, AWMSG cannot provide advice to the Minister for Health and Social Services

2.0 PRODUCT DETAILS

2.1 Licensed indication

Prolonged release (PR) quetiapine (Seroquel XL®▼) is indicated for:

- treatment of schizophrenia
- treatment of manic episodes associated with bipolar disorder[1].

It is effective in preventing relapse in stable schizophrenic patients who have been maintained on quetiapine PR[1].

The submission made by the company relates only to the treatment of schizophrenia as no published data is currently available that compares the efficacy and safety of IR and XL for the bipolar disorder mania indication.

As quetiapine PR is a new PR formulation of a product already recommended within the National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of schizophrenia[2], it was considered by the All Wales Medicines Strategy Group (AWMSG) Steering Committee to be suitable for a limited submission and subsequent appraisal.

2.2 Dosing

Quetiapine PR tablets should be administered once daily, without food (at least one hour before a meal). The tablets should be swallowed whole and not split, chewed or crushed[1].

For the treatment of schizophrenia in adults, the daily dose at the start of therapy is 300mg on day one and 600mg on day two. The recommended daily dose is 600mg. Enhanced efficacy at doses higher than 600mg has not been demonstrated, although individual patients may benefit from a dose up to 800mg daily. Doses greater than 600mg should be initiated by a specialist. The dose should be adjusted within the effective dose range of 400mg to 800mg/day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia, no dosage adjustment is necessary[1].

Patients who are currently being treated with divided doses of the immediate release (IR) formulation may be switched to the PR preparation at the equivalent total daily dose taken once daily. To ensure the maintenance of clinical response, a period of dose titration may be required[1].

Elderly patients should be started on 50mg/day. The dose can be increased in increments of 50mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient[1].

The safety and efficacy of quetiapine PR have not been evaluated in children and adolescents[1].

2.3 Marketing authorisation date

10th September 2008[1].

2.4 UK Launch date

22nd September 2008[3] .

3.0 DECISION CONTEXT

Following discussions with the Welsh Medicines Partnership (WMP) and agreement by the AWMSG steering committee, the company has made a limited submission to AWMSG in relation to the use of quetiapine PR for the treatment of schizophrenia in adults[1].

The company submission highlights the benefits of a reduction in complexities of a prolonged titration period with the use of quetiapine PR compared to the IR formulation. This includes a reduction in the requirement for multiple tablet strengths, thus simplifying treatment initiation for prescribers, patients and their carers and reducing the potential for medicines wastage, together with fact that once daily dosing also has the potential to improve treatment adherence in patients for whom compliance is an issue[3].

The prevalence for schizophrenia in Wales is 0.2%[4]. Based on an >18yrs population of 2,343,014 in Wales this equates to 4686 people suffering from schizophrenia in Wales[3]. The company submission states that out of these patients, 675 patients are projected to receive treatment with quetiapine in 2009[3]. It must be noted that as at January 2009 there are currently 478 items prescribed per month for quetiapine PR within primary care across Wales of which 106 items appear to be hospital initiated[5].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical and cost effectiveness

The company has made a limited submission to AWMSG in relation to the use of quetiapine PR for the treatment of schizophrenia in adults.

The company submission is based on one pharmacokinetic study, which is considered to demonstrate bioequivalence of the PR and the IR formulation, and four additional randomised controlled trials. Three out of the four randomised controlled trials compared the efficacy and tolerability of quetiapine PR versus placebo and the remaining study evaluated the efficacy and safety of switching patients from quetiapine IR to the same dose of once daily quetiapine PR. These studies were not pre-specified to compare the PR and IR formulations, as the IR arm was only included for sensitivity testing. Primary results of these placebo controlled trials were mixed, one study demonstrated a significant improvement in the efficacy of quetiapine PR (400mg, 600mg and 800mg) versus placebo; one showed an improvement with quetiapine PR at 600mg only, and one showed no significant differences between quetiapine PR and placebo. The study designed to demonstrate equivalence by switching from the IR to the PR preparation failed to meet the primary endpoint of non-inferiority of the PR formulation compared with the IR formulation in the modified intention to treat (mITT) population, but non-inferiority was shown in the per protocol analysis.

The assumption of therapeutic equivalence is based on the meta-analysis of the four randomised controlled trials, the results of which are referenced to data on file and have not been verified. There are no details provided in relation to any literature search to identify relevant studies to include within such an analysis, only headline results of the analysis are provided. The meta-analysis results presented within the company submission indicate that there are no statistically significant differences between the PR and IR formulation in terms of efficacy (as measured by Positive and Negative Syndrome Scale [PANSS] total scores) or adverse events (AEs). The company submission considers that the lack of statistically significant differences suggests that the PR and IR formulations are therapeutically equivalent. No

consideration is given to, or assumptions made around, any potential benefits of the once daily PR formulation compared with the twice daily IR formulation in terms of convenience, adherence or quality of life.

Drug acquisition costs are presented, which demonstrate that within the dose range 50-750mg/day, quetiapine PR is no more expensive than the IR formulation, and at a daily dose of 200mg or 300mg, the acquisition costs for the PR formulation are lower than those for the IR formulation.

5.0 LIMITATIONS OF DECISION CONTEXT

- The company submission is only for the indication of schizophrenia; not for the treatment of manic episodes associated with bipolar disorder[3] for which it is also licensed and for which the IR formulation is currently used**.** The company have agreed to submit data for manic episodes associated with bipolar disorder at a later date[6].
- No consideration is given to, or assumptions made around, any potential benefits of the once daily PR formulation compared with the twice daily IR formulation in terms of convenience, adherence or quality of life
- Three[7,8,9] of the four trials were not originally designed to compare the quetiapine PR formulation against the IR formulation; they were designed to compare the PR formulation against placebo over a six-week treatment period and the IR formulation arms were included for internal validation[3].
- The assumption of therapeutic equivalence is based on the meta-analysis of the four randomised controlled trials, the results of which are referenced to data on file and have not been verified.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy

The company submission includes one open label study which compares the pharmacokinetic profile and tolerability of quetiapine PR and quetiapine IR[10]. In addition, there are four randomised controlled trials from which it is possible to compare the efficacy and tolerability of once daily quetiapine PR with twice daily quetiapine IR on a dose-for-dose basis [7,8,9,11].

6.1.1 Pharmacokinetic profile comparison of quetiapine PR and quetiapine IR[10]

This ten day, single centre, open label, randomised, crossover study compared pharmacokinetic profiles and tolerability of the two formulations. Twenty eight patients entered the study and were randomised to one of two treatment sequences: (i) quetiapine IR (150mg twice daily for four days [days three to six]) followed by quetiapine PR (300mg once daily for four days [days seven to ten]) or (ii) quetiapine PR (300mg once daily for four days [days three to six]) followed by quetiapine IR (150mg twice daily for four days [days seven to ten]). The primary objective of this study was to compare the steady state area under the concentration versus time curve for the PR and IR formulations across a 24-hour dosing interval ($AUC_{[0\text{-}24hrs]}$). Maximum plasma concentration at steady state (Cmax) was approximately 13% lower for quetiapine PR than for quetiapine IR (495.3 versus 568.1 nanogram/ml), time to reach Cmax (tmax) was five hours versus two hours and mean concentration at the end of the 24 hour dosing interval (Cmin) was 95.3 versus 96.5 nanogram/ml, for quetiapine PR and quetiapine IR respectively. The 90% confidence interval (CI) of the

ratio for $AUC_{[0-24hrs]}$ for quetiapine PR/IR was 1.04 (0.92 - 1.19); within the pre-defined range set for equivalence (0.80 – 1.25)[10].

6.1.2 Comparison of the efficacy and safety of quetiapine PR versus placebo[8]

The efficacy of quetiapine PR in patients with schizophrenia was demonstrated in a six-week, randomised, double-blind, placebo-controlled study. A total of 588 in- or outpatients were randomised to one of five treatment arms: quetiapine PR 400mg/day, 600mg/day, 800mg/day; quetiapine IR 200mg twice daily or placebo. The IR group was included for assay sensitivity. The study was not designed or powered to compare the efficacy of the two different formulations. Improvement in the primary endpoint of change in PANSS total score at week six was significant versus placebo (-18.8) in all groups: -24.8 (p=0.03), -30.9 (p<0.001) and –31.3 (p<0.001) for quetiapine PR 400mg, 600mg, and 800mg respectively, and –26.6 (p=0.004) for quetiapine IR. A post hoc analysis of the PANSS total score data showed that increasing doses of quetiapine PR was statistically significant (p=0.013) for a dose response for quetiapine PR across the 400mg to 800mg dosage range.

6.1.3 Comparison of the efficacy and safety of quetiapine PR versus placebo Study D1444C00133[9]

A six week, multicentre, randomised, double blind, placebo-controlled study was conducted at 40 centres in the United States. This study was designed to demonstrate the efficacy of quetiapine PR versus placebo. A total of 565 patients were randomised to one of five treatment arms: quetiapine PR 400mg/day, 600mg/day, 800mg/day; quetiapine IR 400mg twice daily or placebo. The IR group was included for assay sensitivity and the study was not designed or powered to compare the efficacy of the two different formulations. Improvement in the primary endpoint of change from baseline in PANSS total score at week six was seen in all groups, with a greater improvement in the quetiapine dose groups (quetiapine PR: 400mg: -13.8; 600mg: -16.8; 800mg: -14.8; quetiapine IR 800mg: -15.0) than in the placebo group (-12.1). However, quetiapine PR at each of the three doses and quetiapine IR was not statistically superior to placebo at the end of treatment.

6.1.4 Efficacy and tolerability of quetiapine PR in acute schizophrenia[7]

In this six week, randomised, double-blind study patients (n=532) were randomised to receive quetiapine PR (300mg, 600mg or 800mg), quetiapine IR (300mg or 600mg daily) or placebo. The primary endpoint of change in PANSS total score showed improvement in PANSS total scores from baseline to week six of: quetiapine PR 300mg/day: -5.01;, 600mg/day: -13.01; and 800mg/day: -11.17; for quetiapine IR 300mg/day: -9.42 and 600mg/day: -6.97; for placebo: – 5.19. The difference in change was only statistically significant for quetiapine PR 600mg/day (p=0.033)[7].

6.1.5 Switching from IR to PR quetiapine in stable outpatients with schizophrenia[11]

This study was a switch programme that compared the PR formulation against the IR formulation in 497 patients already stabilised on the IR formulation (400mg to 800mg daily). The primary objective was to demonstrate that the efficacy of quetiapine PR was non-inferior to quetiapine IR. The primary outcome variable was the proportion of patients who discontinued the study treatment owing to lack of efficacy or whose PANSS total score increased by 20% or more from randomization to any visit. This trial failed to meet the primary endpoint of non-inferiority of the PR formulation compared with the IR formulation in the mITT population, (quetiapine PR: 9.1%; quetiapine IR: 7.2%; difference 1.86%; 95% confidence interval [CI]: -3.78, 6.57; p=0.0431) but non-inferiority was shown in the per protocol analysis (quetiapine PR: 5.3%; quetiapine IR: 6.2%; difference -0.83%; 95% CI: -6.75, 3.71; p=0.0017)[11].

Points to note:

- Primary results for all these trials were mixed, with only one of the trials[8] showing consistent superiority of quetiapine PR compared with placebo over the range of quetiapine PR doses considered (400mg to 800mg daily).
- The company submission details results of a meta-analysis, which was not provided with the submission[12]. It states that analysis of the seven possible dose-for-dose comparisons of quetiapine PR to IR using a fixed effects model shows that changes in PANSS total score from baseline, and the relative risk of both AE and serious AEs (SAEs) were not statistically significant between the two formulations [3].
- The four randomised controlled studies[7,8,9,11] were not pre-specified to compare the PR and IR formulations, as the IR arm was only included for sensitivity testing[3].
- The quetiapine IR formulation is not licensed at a dosage of 800mg daily[3].

6.2 Safety

NICE has highlighted extrapyramidal symptoms (EPS), sexual dysfunction, sedation, and weight gain, as the outcomes considered by patients taking atypical antipsychotics to be the most troublesome[2]. The most frequent adverse drug reactions detailed in the SPC as being very common at ≥10% are dizziness, somnolence, headache and dry mouth[1].

Based on the four trials with the quetiapine IR and PR formulations, the relative risk of AEs (1.01; 95% CI 0.93 to 1.09; p=0.90) and SAEs (1.05; 95% CI 0.60 to 1.84; p=0.87) are also reported not to be significantly different, and neither are the relative risks for specific AEs of EPS, orthostatic hypotension, sedation and weight gain (see Table 1). However, it should be noted that the 95% CIs are wide for some of these estimates[3,12]. The incidence rates of the individual EPS AEs (eg. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3% in any treatment group[3]. From the pharmacokinetic profile study of the two different formulations no patients withdrew from the study due to AEs and there were no SAEs or deaths related to study medication. No unexpected AEs, changes in vital signs or laboratory values were observed[10].

Table 1. Results of relative risks for specific adverse events from the meta-analysis of the seven possible dose-for-dose comparisons of quetiapine PR and quetiapine IR

Adverse Event	Relative Risk	95% Confidence Interval	P value
Extrapyramidal symptoms (EPS)	1.067	0.69 to 1.64	p=0.77
Orthostatic hypotension	1.089	0.74 to 1.60	p=0.66
Sedation	0.781	0.57 to 1.07	p=0.13
Weight gain	0.784	0.52 to 1.18	p=0.24

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

There is no comparative data with other antipsychotic medication included within the company submission, as this is a limited submission for the purposes of comparing the quetiapine PR to the IR preparation, which has already been recommended within previous NICE guidance from 2002[2].

7.2 Comparative effectiveness

The British National Formulary (BNF)[13] states that " the atypical antipsychotic drugs; amisulpiride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and zotepine may be better tolerated than other antipsychotic drugs; EPS may be less frequent than with older antipsychotic drugs". Previous NICE guidance does not make any distinction as to efficacy between the atypical antipsychotics and states that choice of medication should be made following consideration of the AE profile with service user[2].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by quetiapine over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of quetiapine is acceptable (see section 9.0).

8.2. Description and critique of the company's submission

Following discussions with WMP and agreement by the AWMSG steering committee, the company has made a limited submission to AWMSG in relation to the treatment of schizophrenia in adults[3]. The basis of the limited submission is that there are no clinical differences between quetiapine PR and the IR formulation, and quetiapine PR is not more expensive in terms of drug acquisition cost than the IR formulation. The assumption of therapeutic equivalence is a meta-analysis of four randomised controlled trials, the results of which are referenced to data on file and have not been verified. No consideration is given to, or assumptions made around, any potential differences between the once daily PR formulation compared with the twice daily IR formulation in terms of convenience, adherence or quality of life.

8.3 Clinical and cost data

8.3.1 Clinical efficacy

The limited submission[3] provides brief details of a pharmacokinetic study[10], which is considered to demonstrate bioequivalence of the PR and the IR formulation, and a meta-analysis of four randomised controlled trials that are reported to permit comparison of the efficacy and tolerability of quetiapine PR and the IR formulation (company data on file, not provided). There are no details provided in relation to any literature search to identify relevant studies to include within such an analysis and only headline results of the meta-analysis are provided and have not been verified.

It is reported in the submission that a fixed effects model has been used to provide an estimate of the change in PANSS total score from baseline with the PR and the IR formulations. A weighted mean difference of 0.31 (95% CI -1.29 to 1.91; p=0.71) is reported, indicating no statistically significant difference between the PR and IR formulation[3].

Based on these four trials, the relative risk of AEs (1.01; 95% CI 0.93 to 1.09; p=0.90) and SAEs (1.05; 95% CI 0.60 to 1.84; p=0.87) are also reported not to be significantly different, and neither are the relative risks for specific AEs of EPS, orthostatic hypertension, sedation and weight gain; however, it should be noted that the 95% CIs are wide for some of these estimates (see Table 1). The company submission states that there was no evidence of heterogeneity and considers that the lack of statistically significant differences between the PR and IR formulations suggests that they are therapeutically equivalent[3].

8.3.2 Healthcare resource utilisation and cost

Drug acquisition costs are presented, which demonstrate that within the dose range 50 to 750mg/day, quetiapine PR is no more expensive than the IR formulation, and at a daily dose of 200mg or 300mg, the acquisition costs for the PR formulation are lower than for the IR formulation[13]. Although the SPC for quetiapine IR formulation states that the usual effective dose range is 300 to 450mg/day (adjusted within the range 150 to 750mg/day, depending on clinical response and tolerability of the individual patient)[14], the SPC for the PR formulation states that the recommended daily dose is 600mg (adjusted within the effective dose range of 400 to 800mg/day)[1]. The drug acquisition costs for delivering daily doses above 400mg are the same for the PR and IR formulations[3].

8.4 Conclusions

The company submission concludes that these data indicate that the quetiapine PR formulation is therapeutically equivalent to the IR formulation and has the same acquisition costs[3].

8.5 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of quetiapine PR tablets.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

As the PR and IR formulations have practically the same drug acquisition costs[13] and are assumed to be therapeutically equivalent[3], the limited submission concludes that the PR formulation will not result in any additional costs to NHS Wales compared with the IR formulation[3]. Based on market research data and a Government cited prevalence estimate[4], the company predicts that 20% of patients with schizophrenia (675 patients) will receive quetiapine, 30% of which (203 patients) are predicted will receive the PR formulation in 2009[3]. Uptake over a longer time frame of five years, or any potential changes in uptake, is not considered.

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- The British National Formulary[13] states that 'atypical' antipsychotic drugs; amisulpiride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and zotepine may be better tolerated than other antipsychotic drugs; EPS may be less frequent than with older antipsychotic drugs.
- If accepted for use, quetiapine PR may be suitable for shared care.

10.2 Related advice
The most recent NICE guidance[15] states that for people with newly diagnosed schizophrenia, oral antipsychotic medication should be offered and the benefits and side-effect profile of each drug discussed with the service user. The choice of drug should be made by the service user and healthcare professional together; considering:

- relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects (including weight gain) and other side effects (including unpleasant subjective experiences)
- views of the carer if the service user agrees.

Specific guidance as to the place in therapy of quetiapine for schizophrenia is not given within the new guidance[15].

Previous NICE guidance[2] stated that the oral atypical antipsychotic drugs (amisulpiride, olanzapine, quetiapine, risperidone, zotepine) should be considered as treatment options for individuals currently receiving conventional antipsychotic drugs who, despite adequate symptom control, are experiencing unacceptable side effects, and for those in relapse who have previously experienced unsatisfactory management or unacceptable side effects with conventional antipsychotic drugs. The decision as to what are unacceptable side effects should be taken following discussion between the patient and the clinician responsible for treatment.

10.4 Ongoing studies
The company submission indicated that no new relevant data is likely to become available with the next six to twelve months[3].

10.5 Patient organisation information
A patient organisation submission was not received.

10.6 Medical expert / Clinical expert summary
A summary of medical / clinical expert views was provided to AWMSG members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[17].

Positive and Negative Syndrome Scale (PANSS)[16]
A testing device for schizophrenic patients. A range of scores; 30–210; is used to evaluate the clinical state of a patient with schizophrenia. The higher the score, the worse the clinical patient status.

Prevalence:
The proportion of a population that are cases at a point in time[17].

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