

**quetiapine, 25mg, 100mg, 200mg, 300mg tablets (Seroquel®)**  
**No. (549/09)**

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**AstraZeneca**

09 April 2009 (*Issued 04 September 2009*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**quetiapine (Seroquel®)** is not recommended for use within NHS Scotland for the treatment of major depressive episodes associated with bipolar disorder.

In monotherapy studies quetiapine was superior to placebo and compared favourably with two active comparators. Efficacy relative to current practice for the management of depression in the framework of bipolar disorder in NHS Scotland involving combination therapy with a mood stabiliser or an atypical antipsychotic plus an antidepressant, was not demonstrated

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman**  
**Scottish Medicines Consortium**

**Indication**

For the treatment of major depressive episodes associated with bipolar disorder.

**Dosing information**

Quetiapine should be administered once daily at bedtime, starting with 50mg on day one and increasing to the recommended daily dose of 300mg by day four. Individual patients may benefit from a 600mg daily dose. In the event of tolerance concerns, dose reduction to a minimum of 200mg daily could be considered

Treatment should be initiated by physicians experienced in treating bipolar disorder.

**Product availability date**

August 2009.

**Summary of evidence on comparative efficacy**

Bipolar disorder is a long-term psychiatric illness characterised by episodes of mania/hypomania and depression. Quetiapine is an atypical antipsychotic drug with affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub> and D<sub>2</sub> receptors. The use of antidepressants to treat major depressive episodes in patients with bipolar disorder is associated with a potential risk of triggering a switch to a manic state. Evidence is now emerging to support the efficacy of atypical antipsychotic drugs in this setting.

The evidence presented in this submission is from four similarly designed studies. All were double-blind, randomised, placebo-controlled, 8-week, monotherapy studies that recruited patients between 18 and 65 years with bipolar I or II disorder who were experiencing a major depressive episode (Diagnostic and Statistical Manual of Mental Disorders IV [DSM-IV]), and had a Hamilton Depression Rating Scale (HAM D) 17-item score  $\geq 20$ , HAM D item 1 score  $\geq 2$ , and a Young Mania Rating Scale (YMRS) score  $\leq 12$ . All studies included an initial washout period.

The primary outcome in all four studies was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to week 8, assessed in all randomised patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment. The MADRS is a validated rating scale composed of 10 items (rated 0 to 6) and is conducted as a semi-structured clinician-rated interview. All studies used last observation carried forward to impute missing data for patients who withdrew early. Definitions of response, ( $\geq 50\%$  reduction from baseline score in MADRS total score), and remission, (MADRS total score  $\leq 12$ ), were the same for all studies.

One study included a lithium treatment group, although the primary endpoint was for the comparison between quetiapine and placebo. It randomised 802 patients (499 bipolar I, 303 bipolar II) in a 2:2:1:1 ratio to receive 8 weeks treatment with a single night-time oral dose of quetiapine 300mg daily (titrated from 50mg over 4 days), 600mg daily (titrated from 50mg over 8 days), or lithium 300mg to 900mg twice daily, or placebo.

The change from baseline in the MADRS total score at 8 weeks was -15.4, -16.1, -13.6 and -11.8 for quetiapine 300mg, quetiapine 600mg, lithium and placebo, respectively. Comparisons versus placebo were significant for the quetiapine groups only.

Significantly more patients met response and remission criteria in the quetiapine groups than in the placebo group. Response: quetiapine 300mg (69%), quetiapine 600mg (70%), lithium (63%) and placebo (56%); Remission: quetiapine 300mg (70%) and 600mg (70%), lithium (63%) and placebo (55%). Both quetiapine doses were significantly superior to lithium in improving the HAM-D total score.

Patients in remission at the end of the acute phase were eligible for a 26 to 52 week continuation phase. In patients previously treated with quetiapine, further treatment with quetiapine, compared with placebo, significantly increased the time to recurrence of a mood event (hazard ratio (HR): 0.56; 95% Confidence Interval [CI]: 0.39 to 0.82;) and a depression event (HR: 0.48; 95% CI: 0.29 to 0.77).

One study included a paroxetine treatment arm, although the primary endpoint was for the comparison between quetiapine and placebo. It randomised 740 patients (478 bipolar I, 262 bipolar II) in a 2:2:1:1 ratio to receive 8 weeks treatment with quetiapine 300mg daily, quetiapine 600mg daily (dose titrations as before), paroxetine 20mg daily or placebo.

The change from baseline in the MADRS score at 8 weeks was: -16.19, -16.31, -13.76 and -12.60 for quetiapine 300mg, quetiapine 600mg, paroxetine and placebo respectively. Comparisons versus placebo were significant for the quetiapine groups only. Both quetiapine doses, but not paroxetine, produced significant improvements in most MADRS individual items. The percentage of responders was significantly higher for the quetiapine groups than placebo: quetiapine 300mg (67%) and 600mg (67%), paroxetine (55%) and placebo (53%). Significantly more patients in the quetiapine 600mg group achieved remission than patients in the placebo group: quetiapine 300mg (65%), quetiapine 600mg (69%), paroxetine (57%) and placebo (55%).

Patients in remission at the end of the acute phase were eligible for a 26 to 52 week continuation phase. In patients previously treated with quetiapine, further treatment with quetiapine, compared with placebo, significantly increased the time to recurrence of a mood event (HR: 0.43; 95% CI: 0.27 to 0.69;) and a depression event (HR: 0.36; 95% CI: 0.21 to 0.63).

Two further studies randomised 542 and 509 patients equally, with stratification for bipolar type, to quetiapine 300mg daily, quetiapine 600mg daily (dose titrations as before) or placebo for 8 weeks. Completion rates were 64% and 59%, respectively.

In both studies quetiapine 300mg and 600mg doses produced significant improvements compared with placebo in MADRS total scores: quetiapine 300mg (-16.39 and -16.94), quetiapine 600mg (-16.73 and -16.0) and placebo (-10.26 and -11.93).

In both studies the proportions of patients who met response and remission criteria were significantly higher for the quetiapine groups than placebo. Response: quetiapine 300mg (58% and 60%), quetiapine 600mg (58% in both studies) and placebo (36% and 45%); Remission: quetiapine 300mg (53% and 52%), quetiapine 600mg (53% and 52%) and placebo (28% and 37%).

**Table 1: Primary endpoint (mean change in MADRS total score from baseline) in the four studies.**

Study	Intervention	N	Mean MADRS total score		p value versus placebo
			Baseline	Reduction at week 8	
1	quetiapine 300mg	255	28.1	15.4	p<0.05
	quetiapine 600mg	263	28.3	16.10	p<0.05
	lithium	136	28.3	13.6	NS
	placebo	129	28.5	11.81	-
2	quetiapine 300mg	229	27.1	16.19	p<0.001
	quetiapine 600mg	232	26.5	16.31	p<0.001
	paroxetine	118	27.3	13.76	NS
	placebo	121	27.2	12.60	-
3	quetiapine 300mg	172	30.3	16.39	p<0.001
	quetiapine 600mg	170	30.3	16.73	p<0.001
	placebo	169	30.6	10.26	-
4	quetiapine 300mg	155	31.1	16.94	p<0.001
	quetiapine 600mg	151	29.9	16.00	p<0.001
	placebo	161	29.6	11.93	-

MADRS= Montgomery-Asberg Depression Rating Scale, NS= not significant

### Summary of evidence on comparative safety

Neither of the active-controlled studies described previously reported statistical significance for adverse event comparisons. Compared with lithium, quetiapine-treated patients experienced more weight gain, somnolence, dry mouth, dizziness, sedation and constipation and less nausea, diarrhoea and insomnia.

Compared with paroxetine, quetiapine-treated patients experienced more weight gain, somnolence, dry mouth, sedation and dizziness and less headache, nausea, insomnia and treatment emergent mania/hypomania (quetiapine 300mg [2.1%], quetiapine 600mg [4.1%], paroxetine [11%] and placebo [8.9%]).

### Summary of clinical effectiveness issues

The reversible, episodic nature of bipolar disorder poses difficulties for clinical research into the condition. The long term prevention of relapse is an important aim of treatment. A limitation of treating bipolar depression with an antidepressant is the risk of triggering a manic or hypomanic episode.

Quetiapine compared favourably with lithium and paroxetine in two monotherapy studies, however these studies were designed only for the comparison between quetiapine and placebo. The use of these drugs in the management of patients with bipolar disorder is complex. Quetiapine is already licensed for the treatment of manic episodes associated with bipolar disorder. Lithium is licensed for the prophylaxis of bipolar affective disorders, and in the management of acute manic or hypomanic episodes, and episodes of recurrent depressive disorders where treatment with other antidepressants has been unsuccessful. Paroxetine is licensed for major depressive disorder and, as with all antidepressants, should be used with caution in patients with a history of mania and discontinued in patients entering a manic phase.

Clinical experts have advised that the predominant treatment strategy in NHS Scotland involves the use of a mood stabilising agent (such as lithium or valproic acid) or an atypical antipsychotic in combination with a selective serotonin reuptake inhibitor (SSRI) antidepressant. There are no comparative data for quetiapine versus current Scottish practice.

Current treatment guidelines do not make any recommendation on the use of atypical antipsychotic drugs as monotherapy for the treatment of bipolar depression. but these guidelines predate publication of the studies described and the licensing of quetiapine for the treatment of bipolar depression.

## **Summary of comparative health economic evidence**

The economic evaluation was a cost-utility analysis using a Markov model comparing daily doses of quetiapine 300mg and 600mg with two other atypical antipsychotics, olanzapine 10mg/day and aripiprazole 15mg/day, in the treatment of bipolar depression. The manufacturer indicated that quetiapine should be considered for a niche of patients for whom monotherapy with an atypical antipsychotic is appropriate. Hence, the comparators were considered in monotherapy use, whereas clinical experts have indicated that when used to treat depression, atypical antipsychotics are added to prophylactic drugs or alternatively antidepressants are used alone or in combination with prophylactic drugs. As the comparators in the economic analysis do not reflect clinical practice in Scotland they do not appear to be appropriate.

There were no head-to-head data for quetiapine versus the comparators, hence an indirect comparison of the drugs used in monotherapy, using placebo as the reference comparator was performed to assess relative treatment effectiveness. Using a three-year time horizon, this demonstrated that both quetiapine 300mg/day and 600mg/day were superior to olanzapine and aripiprazole in reducing risks of treatment emergent mania (although none of the drugs were significantly better than placebo), improving remission rates, reduced weight gain (versus olanzapine) and reduced withdrawals due to lack of efficacy. Resource use estimates associated with depression, mania, remission and related health states were based on service provision recommended within NICE Clinical Guideline 38 and 2005 SIGN guidelines for the management of bipolar disorder. Utility estimates for the health states and key adverse events were literature based and were largely consistent with utilities used in previous submissions to SMC and in an earlier NICE Technology appraisal of bipolar treatments.

The main result was that although quetiapine 300mg and 600mg/day were associated with a slightly higher annual drug cost than the comparator antipsychotics used in monotherapy (e.g. £1,147 for quetiapine 300mg/day and £1,190 for quetiapine 600mg/day versus £1,133 for olanzapine 10mg/day and £1,139 for aripiprazole), the greater estimated effectiveness of quetiapine resulted in lower comparative healthcare resource costs and additional QALYs. The main result versus olanzapine was a net cost saving of £264 and QALY gain of 0.010 per patient over 3 years for quetiapine 300mg and respective estimates of a £177 saving and 0.014 QALY gain for quetiapine 600mg/day. The net cost savings and QALY gains were relatively larger for the comparisons with aripiprazole.

Overall, the estimated net savings/QALY gains were very small in particular for the comparison with olanzapine. Although well conducted, there were limitations in the indirect comparison, in particular the strength of the evidence for quetiapine having an impact on recurrence of treatment emergent mania. In addition, one way sensitivity analysis indicated that the base-case results for the comparison with olanzapine were very sensitive to

variations in key efficacy estimates, resulting in uncertainty over the cost-effectiveness results. Another weakness was that the mania health state is likely to involve treatment switches and the economic analysis has not explored the utility and cost implications of that possibility. In addition, the utility of the two remission health states, despite differing in resource intensity, were both estimated to be 0.87 which may be optimistic and therefore slightly favour quetiapine.

Primarily due to concerns over the relevance of the comparators to clinical practice, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the Scottish Medicines Consortium.

### **Summary of patient and public involvement**

A Patient Interest Group Submission was not made.

### **Additional information: guidelines and protocols**

In July 2006, the National Institute of Health and Clinical Excellence (NICE) published Clinical Guideline 38: Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. It does not provide advice on the use of quetiapine as monotherapy in patients with bipolar depression.

In May 2005, the Scottish Intercollegiate Guidelines Network (SIGN) published national clinical guideline 82: Bipolar Affective Disorder. All references to quetiapine relate to the treatment of mania.

In 2003, the British Association for Psychopharmacology published evidence-based guidelines for treating bipolar disorder. All references to quetiapine relate to the treatment of mania.

All guidelines predate the licensing of quetiapine for bipolar depression.

### **Additional information: comparators**

No other atypical antipsychotic drugs are licensed for this indication although aripiprazole, olanzapine and risperidone have been used outwith licence in combination with a mood stabiliser or antidepressant drug.

## Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
<b>quetiapine</b>	<b>300 to 600mg daily</b>	<b>1,031 to 2,063</b>
valproate semisodium plus quetiapine	1 to 2g daily  300 to 600mg daily	1,227 to 2,456
lithium plus quetiapine	400 to 1600mg daily  300 to 600mg daily	1,047 to 2,126
olanzapine plus paroxetine	10 to 20mg daily  20mg daily	1,068 to 2,101
lithium plus paroxetine	400 to 1600mg daily  20mg daily	51 to 98

Doses are for general comparison and do not imply therapeutic equivalence. Paroxetine is the SSRI drug included as it has been used in a quetiapine study. Costs of quetiapine, olanzapine and paroxetine accessed from eVadis on 20 January 2009. Costs of valproate semisodium and lithium were taken from the British National Formulary 2008: 56 on 25.02.09

## Additional information: budget impact

The manufacturer estimated a net direct drug budget impact of quetiapine 300mg/day and 600mg/day of £11k in year 1 rising to £68k in year 5. This assumed a 3% increase in total quetiapine use and some displacement of olanzapine and aripiprazole (estimated to be 83 patients switched to quetiapine in year 1 rising to 521 patients in year 5). If a 5% increase in use was assumed, the net direct drug budget impact was estimated at £18k in year 1 rising to £115k in year 5 (estimated to be 139 patients switched to quetiapine in year 1 rising to 868 patients in year 5). The relatively low uptake rates are based on the assumption that there is currently some use of quetiapine in this indication.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 12 March 2009.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The undernoted references were supplied with the submission.*

Calabrese J, Keck P, MacFadden W et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *American Journal of Psychiatry*. 2005;162:1351-360.

Thase M, MacFadden W, Weisler R et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26:600-9