Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

Resubmission:

quetiapine, 25mg, 100mg, 150mg, 200mg, 300mg tablets (Seroquel), quetiapine, 50mg, 150mg, 200mg, 300mg, 400mg sustained release tablets (Seroquel XL) SMC No. (549/09)

AstraZeneca

08 April 2011

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 re-submission

quetiapine (Seroquel/Seroquel XL) is not recommended for use within NHS Scotland.

Indication under review: Treatment of major depressive episodes in 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 manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Quetiapine (Seroquel/Seroquel XL) is also licensed for preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment. The manufacturer's submission related only to use in the treatment of major depressive episodes in bipolar disorder. Therefore, SMC cannot recommend its use for preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of major depressive episodes in bipolar disorder.

Dosing Information

50mg on day 1, 100mg on day 2, 200mg on day 3 then 300mg thereafter with doses taken at night. In clinical trials no additional benefit was seen with 600mg daily compared to 300mg daily. Individual patients may benefit from a 600mg daily dose. In individual patients, in the event of tolerance concerns a 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

22 May 2009 for quetiapine immediate release (Seroquel) and 25 August 2009 for quetiapine sustained release (Seroquel XL).

Summary of evidence on comparative efficacy

Quetiapine is an atypical antipsychotic that antagonises serotonin (5-HT2) and dopamine (D1 and D2) receptors. This submission is a resubmission for the immediate release (IR) preparation in the treatment of depressive episodes in bipolar disorder and is the first submission for the sustained release (Seroquel XL) preparation which has recently received marketing authorisation in this indication.

Five double-blind studies recruited patients aged between 18 and 65 years with bipolar I or II disorder who were experiencing a major depressive episode and had a Hamilton Depression Rating Scale (HAM-D) 17-item score ≥20, HAM-D item 1 score ≥2 and a Young Mania Rating Scale (YMRS) score ≤12. In four of the studies, after a wash-out of psychotropic drugs, patients were randomised to placebo, quetiapine 300mg or 600mg IR at night for eight weeks. One study also included a paroxetine 20mg daily group and another study included a lithium 300mg to 900mg twice daily group as active comparators. In the fifth study, patients were randomised to quetiapine 300mg SR or placebo at night for eight weeks. The primary outcome, mean change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to week 8, was assessed in intention to treat (ITT) populations which comprised all randomised patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment, with last observations carried forward to impute missing data for patients who withdrew early. The MADRS score, which has a range of 0 to 60, was significantly reduced with quetiapine 600mg IR and quetiapine 300mg IR and SR compared to placebo in all studies. The differences between the active comparators and placebo were not significant.

The proportion of patients achieving a response, defined as a reduction of at least 50% in MADRS score from baseline at week eight, was significantly greater with quetiapine compared to placebo in all studies. The proportion of patients achieving remission, defined as MADRS total score less than or equal to 12 at week eight, was significantly greater with quetiapine compared to placebo in all studies, except for quetiapine 300mg IR in study A. The mean reduction in HAM-D total score was significantly greater with quetiapine IR compared to placebo. This outcome was not reported in the quetiapine 300mg SR study. For all of these endpoints the differences between active comparators and placebo were not significant.

Table: Results at week eight for primary and secondary outcomes

Study	Treatment group	N	Reduction in MADRS	Responders (%)	Remission (%)	Reduction in HAM-D	Reduction in CGI-S
A	quetiapine 300mg IR	255	15.36	68.6	69.8*	13.98	1.51
	quetiapine 600mg IR	263	16.10	69.6	70.3	14.17	1.57
	lithium	136	13.60	62.5	62.5	12.36	1.40
	placebo	129	11.81	55.8	55.0	10.72	1.14
B	quetiapine 300mg IR	229	16.19	66.8	64.6	14.68	1.67
	quetiapine 600mg IR	232	16.31	67.2	68.5	15.09	1.65
	paroxetine	118	13.76	55.1	56.8	12.53	1.44
	placebo	121	12.60	52.9	55.4	11.42	1.33
C	quetiapine 300mg IR	172	16.39	58	52.9	13.38	1.63
	quetiapine 600mg IR	170	16.73	58	52.9	13.84	1.66
	placebo	169	10.26	36.1	28.4	8.54	0.95
D	quetiapine 300mg IR	155	16.94	60.0	51.6	13.81	1.68
	quetiapine 600mg IR	151	16.00	58.3	52.3	12.97	1.59
	placebo	161	11.93	44.7	37.3	9.92	1.12
E	quetiapine 300mg SR	133	17.4	65.4	54.1	NR	1.8
	placebo	137	11.9	43.1	39.4	NR	1.2

MADRS = Montgomery-Asberg Depression Rating Scale. HAM-D = Hamilton Depression Rating Scale. CGI-S = Clinical Global Impressions-Bipolar-Severity of Illness. NR = not reported. All outcomes for quetiapine significant versus placebo, except for * = proportion of patients in remission with quetiapine 300mg IR in study A. All outcomes for paroxetine and lithium not significant versus placebo.

The Quality of Life Enjoyment and Satisfaction Short Form (Q-LES-SF) scores were reported for studies B, C and D. Mean Q-LES-SF improved from baseline to week eight with quetiapine and this was significant compared with placebo in study C (both doses) and study D (300mg dose).

Summary of evidence on comparative safety

In the studies that included an active comparator, the most common adverse effects were somnolence, dry mouth, dizziness with quetiapine; nausea with lithium; and dry mouth, sedation, headache, nausea and insomnia with paroxetine. In the comparison to lithium, the incidence of treatment-emergent mania was low, but higher in the quetiapine 300mg and 600mg and lithium groups compared with placebo: 4.2%, 2.2%, 2.2% and 0.8%, respectively. Adverse events potentially related to extrapyramidal side effects were reported by 5.0%, 7.5%, 8.1% and 3.8% of patients in the respective groups. In the comparison to paroxetine, the incidence of treatment-emergent mania was 2.1%, 4.1%, 10.7% and 8.9% in the quetiapine 300mg, 600mg, paroxetine 20mg and placebo groups, respectively.

Adverse events potentially related to extrapyramidal side effects were reported by 8.2%, 9.8%, 4.1% and 2.4% of patients in the respective groups.

Summary of clinical effectiveness issues

Quetiapine is the first atypical antipsychotic to be licensed for the treatment of bipolar depression. The main issue is the lack of data on efficacy relative to current practice within NHS Scotland, which comprises treatment with an antidepressant in combination with a mood stabiliser or an antipsychotic. An indirect comparison was presented comparing quetiapine monotherapy with olanzapine monotherapy and aripiprazole monotherapy in a mixed treatment comparison. These were considered to be inappropriate comparators as they do not represent current practice in Scotland. The submitting company asserts that this indirect comparison is appropriate because guidelines issued by the British Association for Psychopharmacology (BAP) in 2009 and the World Federation of Societies of Biological Psychiatry (WFSBP) in 2010 better reflect current practice than guidelines from the National Institute of Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) issued in 2006 and 2005, respectively. The BAP and WFSBP guidelines both recognise that quetiapine monotherapy is a treatment option and that the current treatment within Scotland, an antidepressant in combination with a mood stabilising agent, is also a treatment option. The key issue is that neither of these guidelines recommend aripiprazole monotherapy or olanzapine monotherapy as a treatment choice. Therefore, they fail to support the relevance to current practice of the comparators used in the indirect comparison. The WFSBP guidelines note that for aripiprazole monotherapy, two negative controlled studies have been reported and although aripiprazole enhanced improvement from weeks 1 to 6, it was not better than placebo at the 8-week study endpoint (these studies were used in the indirect comparison). The WFSBP guidelines also note that both olanzapine monotherapy and olanzapine in combination with fluoxetine showed efficacy in a double-blind study. However, olanzapine in combination with fluoxetine was superior to olanzapine monotherapy (the olanzapine monotherapy group from this study was used in the indirect comparison). The WFSBP guidelines note that if a choice has to be made between olanzapine monotherapy and olanzapine in combination with fluoxetine, the latter clearly appears to be more effective.

Other clinical effectiveness issues include the lack of data in patients with prolonged depression or depression resistant to other drugs, as these were excluded from the studies. In addition, the studies which included an active comparator (lithium or paroxetine) were not designed or powered to assess efficacy of these relative to placebo or quetiapine.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing quetiapine 300mg and 600mg to aripiprazole and olanzapine for the treatment of major depressive episodes in bipolar disorder. A Markov model was used to estimate the costs and benefits of quetiapine treatment over a three year time horizon. A mixed treatment comparison was conducted because of the lack of direct trial data available comparing quetiapine with the other atypical antipsychotics used in the analysis.

The mixed treatment comparison showed that across some of the outcome measures there was a numerical difference in favour of quetiapine. However, the results did not achieve statistical significance against the other active treatments.

The utility values used in the model relating to depression, mania, remission and adverse events were selected from two studies identified through a literature search. Resource use assumptions outlined in the NICE Clinical Guideline 38 for the management of bipolar disorder were applied in the model. The structure of the model allowed patients to enter an initial phase of depression, mania or remission where resource use was intensive, followed by a second phase where resource use and monitoring were less intense.

For the quetiapine 300mg analysis, the manufacturer estimated quetiapine would dominate both olanzapine and aripiprazole i.e. would be more effective and also cost saving. In the comparison with olanzapine, quetiapine 300mg was estimated to result in a saving of £625 and a quality-adjusted life year (QALY) gain of 0.0093. In the aripiprazole comparison, quetiapine 300mg was estimated to result in a saving of £1,625 and a QALY gain of 0.034.

In the quetiapine 600mg analysis compared to olanzapine, the manufacturer estimated a cost per QALY of £3,739 (incremental cost of £42 and QALY gain of 0.011). For the comparison with aripiprazole, quetiapine 600mg was estimated to be dominant (savings of £957 and a QALY gain of 0.036).

The key weakness with the economic analysis is the choice of comparators. Atypical antipsychotics as monotherapy are not widely used for the treatment of major depressive episodes in Scotland. SMC clinical experts have indicated that current treatment for these patients is a mood stabilising agent or an atypical antipsychotic plus an antidepressant. As such, the economic analysis does not reflect current practice.

In addition to the inappropriate comparator, the following weaknesses were noted:

- The economic model included the numerical differences in the probabilities of each outcome measure, but the results of the indirect comparison showed no significant difference between the active treatments. The one-way sensitivity analysis highlighted that there is considerable uncertainty around the assumption that quetiapine is more effective than olanzapine or aripiprazole due to the small numerical differences in the effect between treatments.
- The utility value for remission was relatively high and may therefore bias the analysis slightly in favour of quetiapine as more patients in the quetiapine arm experienced remission. In addition, there may be some double counting of adverse event disutilities which again may introduce some bias.

Due to the inappropriate comparators and the uncertainty around the assumption that quetiapine is the more effective treatment, the economic case has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Support in Mind Scotland (operating name of National Schizophrenia Fellowship (Scotland))
- Bipolar Scotland

Additional information: guidelines and protocols

In July 2006 NICE published Clinical Guideline number 38 on Bipolar Disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. For the treatment of depressive symptoms in patients not taking anti-manic medication it is recommended that a patient who is prescribed antidepressant medication should also be prescribed an anti-manic drug. The choice of anti-manic drug should be compatible with decisions about future prophylactic treatment. In patients taking anti-manic medication it is recommended that if a person has an acute depressive episode when taking anti-manic medication, prescribers should first check that they are taking the anti-manic agent at the appropriate dose and adjust the dose if necessary. For those with mild depressive symptoms, a further assessment should be arranged, normally within two weeks ('watchful waiting') if previous episodes of mild depression have not developed into chronic or more severe depression in this patient, or the patient is judged not to be at significant risk of developing a more severe depression. If the patient is judged to be at significant risk of worsening or on review continues to be unwell, they should be managed as for moderate or severe depression, particularly if functional impairment is evident. For patients with moderate or severe depressive symptoms, prescribers should normally consider prescribing an SSRI antidepressant (but not paroxetine in pregnant women) because these are less likely than tricyclic antidepressants to be associated with switching, or consider adding quetiapine, if the patient is already taking anti-manic medication that is not an antipsychotic. The review decision date for this guideline is July 2011.

In May 2005 SIGN published guideline number 82 on Bipolar Affective Disorder. It recommends an antidepressant in combination with an anti-manic drug (lithium, semisodium valproate or an antipsychotic drug) or lamotrigine for the treatment of acute bipolar depression in patients with a history of mania. The good practice points are made that, patients maintained on mood stabilizers who suffer a depressive episode should be started on an antidepressant after optimizing their mood stabiliser and interactions between serotonergic antidepressants, antipsychotic drugs and lithium and the risk of triggering mania or rapid cycling should be considered when selecting an antidepressant.

These guidelines predate the availability of quetiapine for use in bipolar disorder.

Additional information: comparators

Bipolar depression is usually treated with a selective serotonin inhibitor (SSRI) antidepressant in combination with a mood stabiliser (e.g. lithium or valproate) or antipsychotic (e.g. olanzapine, aripiprazole, quetiapine or risperidone) to protect against a switch to hypomania or mania. Most of these drugs are not specifically licensed for treatment of bipolar depression. There is a great variety of possible combinations of these and some examples are included in the cost table.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Quetiapine (Seroquel and Seroquel XL)	**300mg to 600mg at night**	**1,031 to 2,058**
Valproate semisodium, plus quetiapine	1g to 2g daily 300mg to 600mg daily	1,228 to 2,451
Olanzapine, plus fluoxetine	10mg to 20mg daily 20mg to 60mg daily	1,157 to 2,128
Lithium, plus quetiapine	400mg to 1600mg daily 300mg to 600mg daily	1,044 to 2,107
Olanzapine, plus paroxetine	10mg to 20mg daily 20mg daily	1,164 to 2,093
Valproate semisodium plus paroxetine	1g to 2g daily 20mg daily	225 to 421
Carbamazepine plus paroxetine	400mg to 600mg daily 20mg daily	62 to 78
Lithium, plus paroxetine	400mg to 1600mg daily 20mg daily	40 to 77

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 January 2011, 1 February 2011 and 6 April 2011.

Additional information: budget impact

The manufacturer estimated a net drug budget impact for quetiapine 300mg and 600mg of £6k in year one rising to £36k in year five. This assumed a 3% increase in quetiapine use and some displacement of aripiprazole and olanzapine. The patient numbers were estimated to be 1,158 in year one and 1,829 in year five. Assuming a 5% increase, the net drug budget impact was estimated to be £10k in year one and £62k in year five based on 1,218 patients in year one and 2,189 patients in year five.

References

The undernoted references were supplied with the submission.

Calabrese JR, Keck PE Jr, Macfadden W et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005; 162: 1351-60.

Thase ME, Macfadden W, Weisler RH 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.

Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 2010; 71:150-62.

McElroy SLW, Weisler RH, Chang W et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 2010; 71: 163-74.

Suppes T, Datto C, Minkwitz M et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. Journal of Affective Disorders 2010; 121: 106-15.

This assessment is based on data submitted by the applicant company up to and including 11 March 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.