Scottish Medicines Consortium

paliperidone 3, 6 and 9mg prolonged release tablets (Invega®) No. (453/08)

Janssen-Cilag

07 March 2008

The Scottish Medicines Consortium 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

paliperidone (Invega®) is not recommended for use within NHS Scotland for the treatment of schizophrenia.

Paliperidone has been shown to be superior to placebo in reducing symptoms of schizophrenia. However, there are limited statistical comparative data versus other atypical antipsychotics.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of schizophrenia.

Dosing information

Paliperidone 6 mg once daily, administered in the morning. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg/day. Dosage adjustment, if indicated, should occur only after clinical reassessment. Administration should be standardised in relation to food intake.

Product availability date

2 July, 2007

Summary of evidence on comparative efficacy

Paliperidone, the active metabolite of risperidone, is an atypical antipsychotic that is available as a once daily prolonged-release oral preparation.

Three double-blind placebo-controlled, fixed dose trials of similar design have been conducted in a total of 1692 adult patients with schizophrenia, according to DSM-IV criteria for greater than one year before screening, experiencing an acute episode, and with a Positive and Negative Syndrome Scale (PANSS) score between 70 and 120. The PANSS is a 30-item, 7-point severity scale with scores ranging from 30 to 210. Each trial evaluated a different fixed dose combination and all included olanzapine 10 mg/day as an active control arm to confirm that the studies were appropriately designed to detect a drug effect. Following screening, patients were randomised to a double-blind phase (6 weeks), and initially hospitalised for a minimum of 14 days. The primary outcome measure was the change from baseline in the PANSS score at the end of week-6. Secondary endpoints included: change from baseline to endpoint in PANSS factor scores (depression / anxiety, uncontrolled hostility / excitement, disorganised thoughts, positive symptoms and negative symptoms), treatment responders (subjects with at least a 30% reduction in PANSS total score from baseline to endpoint), change in baseline to endpoint for the personal and social performance (PSP) scale, clinical global impression scale-severity (CGI-S), the symptoms and quality of life in schizophrenia scale and day-time drowsiness.

The first trial in 630 patients evaluated paliperidone 6, 9 and 12 mg/day, the second in 444 patients evaluated paliperidone 6 and 12 mg/day and the third in 618 patients evaluated paliperidone 3, 9 and 15 mg/day. For the primary endpoint, change from baseline in the PANSS score at the end of week-6, paliperidone was significantly superior to placebo for all studies. The table below details the baseline and change in PANSS total scores.

Table: Change in scores from baseline to week-6 for the primary endpoint (PANSS) in three phase III placebo-controlled trials with active controls.

	placebo	paliperidone dose/day					olanzapine 10 mg/day
		3 mg	6 mg	9 mg	12 mg	15 mg	
Trial 1	n=126		n=123	n=122	n=129		n=128
baseline	94.1		94.3	93.2	94.6		93.0
change	-4.1		-17.9	-17.2	-23.3		-19.9
Trial 2	n=105		n=111		n=111		n=105
baseline	93.6		92.3		94.1		94.9
change	-8.0		-15.7		-17.5		-18.4
Trial 3	n=120	n=123		N=123		n=113	n=126
baseline	93.9	91.6		93.9		92.4	93.3
change	-2.8	-15.0		-16.3		-19.9	-18.1

P<0.006; for all comparisons of paliperidone versus placebo.
PANSS: Positive and Negative Syndrome Scale.

Results of the secondary endpoints were similar across all studies with paliperidone significantly superior to placebo for treatment responders, PSP (with the exception of paliperidone 12 mg), CGI-S and PANSS factor scores (positive and negative symptoms, hostility / excitement).

Pooled results from 1083 patients who entered open label extensions of the 3 trials have been reported. The population was divided into 3 groups according to prior double-blind treatment. Improvements in PANSS total score from double-blind endpoint in all treatment groups were observed over the first 12 weeks of the open-label phase and were maintained throughout the remainder of the 52-week period.

Preliminary results from another trial have been reported as a poster. In this double-blind placebo-controlled study, 394 adult patients with schizophrenia were included and, at baseline, had a mean PANSS score of between 102 and 104. Patients were randomised to paliperidone (up to 12 mg/day), quetiapine (up to 800 mg/day) or placebo for 6 weeks, comprising a 2-week monotherapy and a 4-week additive phase. Paliperidone was superior to quetiapine and placebo for the primary endpoint, change in PANSS total score at the end of the monotherapy phase and continued to be significantly superior to quetiapine and placebo at the end of the additive phase.

Summary of evidence on comparative safety

In the three placebo-controlled trials the rate of adverse events for the pooled population of paliperidone (3 to 12 mg), olanzapine and placebo was 71% (602/850), 69% (252/364) and 66% (235/355) respectively. The only clinically relevant difference in reporting rates for common adverse events between the paliperidone and olanzapine groups was for somnolence, which was more frequent with olanzapine. Mean changes in body weight and BMI in the paliperidone 3 to 12 mg groups (0.6 to 1.1 kg and 0.2 to 0.4 kg/m^2) were around half of those seen in the olanzapine group (2.0 kg and 0.7 kg/m^2). Similarly, weight increases from baseline of ≥7% were more common among subjects in the olanzapine (18%) compared to the placebo group (5%) or paliperidone 3 to 12 mg dose groups (6 to 9%).

In the comparative study with quetiapine only adverse events with an incidence of ≥10% were reported. Adverse events which were more common for paliperidone than quetiapine included akathiesia, hypertonia and tremor. Conversely, dizziness, sedation and somnolence were more common for the quetiapine group.

Paliperidone is not significantly metabolised by cytochrome P450 (CYP450) isoenzymes (including 1A2, 2D6, or 3A4). Therefore, patients who take concomitant medications that are metabolised by these pathways are unlikely to experience any clinically important pharmacokinetic interactions.

Summary of clinical effectiveness issues

In a post-hoc pooled analysis of three pivotal studies 24% (285/1193) of patients in the paliperidone (3-12 mg/day) or placebo groups had prior treatment with risperidone within 2 weeks of study entry. Therefore, the populations of the 3 trials may be considered responder-rich and not representative of patients being considered for paliperidone in the submission under review. In patients previously treated with risperidone, paliperidone was significantly more effective than placebo for improving acute symptoms of schizophrenia and personal and social performance, with no unexpected AEs. Patients with a documented history of treatment resistance to risperidone were excluded from the trials, therefore efficacy in these patients is unknown.

There are few direct comparative data and none of duration beyond 6 weeks, making it difficult to assess the benefit of paliperidone compared with current treatments. In particular there are no studies currently available that directly compare oral risperidone with paliperidone. An indirect comparative cohort analysis has been conducted that included 982 patients from 6 studies (the 3 pivotal paliperidone studies and 3 risperidone studies). The analysis suggests that paliperidone 6 to 12 mg/day is more effective than risperidone 2 to 4 mg/day and as effective as risperidone 4 to 6 mg/day.

In the comparative study with quetiapine, patients were experiencing more severe symptoms than the population of the placebo-controlled studies and the doses of paliperidone and quetiapine were high. Therefore, this study is likely to reflect a sub-population of severe acute patients on the schizophrenia spectrum. Furthermore the study duration was of 2 weeks for the monotherapy endpoint, which may be considered too short to observe the full treatment effect.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of paliperidone compared to olanzapine (the primary comparator), with aripiprazole and quetiapine as secondary comparators for the second-line treatment of schizophrenia, after risperidone as first-line treatment. No comparison with risperidone was performed. Olanzapine appears an appropriate comparator as it represents the most used atypical antipsychotic in Scotland for the treatment of schizophrenia and the other two antipsychotics considered are also used in Scotland.

The economic analysis used a previously published discrete event simulation model of schizophrenia costs and events and despite being complex appears a robust and valid model. However, it is likely that a simpler analysis could have been performed

as in the comparison between paliperidone and the comparator antipsychotics the only differences evaluated in the base case were in drug acquisition costs, side effect incidence and disutilities. Efficacy was assumed to be the same.

While paliperidone had a higher estimated annual drug cost than olanzapine and quetiapine (but lower than aripiprazole) it was estimated to generate additional QALYs due to a better side effect profile. There was a lack of evidence on side effects from direct comparator trials; therefore, an indirect comparison was also performed for this key variable. The cost per QALY gained in the base case was £10,900 versus olanzapine (based on an estimated incremental cost of £320 per patient, and 0.03 QALY gain over a 5-year time horizon) £8,300 versus quetiapine and dominant (less costly and better outcomes) versus aripiprazole. In sensitivity analysis an assumption of 5% greater compliance, due to a better side effect profile, improved cost-effectiveness of paliperidone further.

There were a number of weaknesses in the evaluation. While the evidence of similar efficacy between paliperidone and olanzapine seemed potentially plausible based on evidence from 3 similarly designed trials, there were concerns over the ability to compare outcomes across the treatment arms. The assumption of equal efficacy compared to the secondary comparators was not sufficiently justified. A further limitation was that the paliperidone daily dose used in the base case economic analysis was 6mg, the recommended starting dose, whereas due to titration it is possible that higher doses are also used in practice. Additional sensitivity analysis was provided to estimate cost-effectiveness where upward titration of palperidone occurred. This increased the ICER versus olanzapine to £12209 per QALY. The QALY gain associated with a difference in side effect profile was small and the cost-effectiveness results sensitive to this especially if combined with any increase in paliperidone drug cost.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) issued Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia in June 2002. NICE recommend the use of the oral atypical antipsychotic drugs; amisulpride, olanzapine, quetiapine, risperidone and zotepine as choices for the first-line treatment of individuals with newly diagnosed schizophrenia. For individuals currently receiving typical 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 typical antipsychotic drugs, the oral atypical antipsychotic drugs should be considered as treatment options. Where more than one atypical antipsychotic drug is considered appropriate, the drug with the lowest purchase cost should be prescribed.

Additional information: previous SMC advice

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice on 10 September 2007 that risperidone 3mg, 4mg orodispersible tablets (Risperdal Quicklet) are accepted for restricted use within NHS Scotland for treatment of acute and chronic schizophrenia and similar psychosis and treatment of mania in bipolar disorder. These new strengths of risperidone orodispersible tablets should be used in patients for whom risperidone is an appropriate choice of antipsychotic and an orodispersible tablet is an appropriate formulation.

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice on 11 July 2005 that aripiprazole tablets 5mg (Abilify) are accepted for restricted use in NHS Scotland for the treatment of schizophrenia. Where aripiprazole is an appropriate antipsychotic, this new dosage is restricted to patients who may benefit from a dose reduction to 5mg daily, taking account of SMC advice issued in August 2004. This 5mg tablet is the same price as the 10mg and 15mg tablets.

After review of a full the Scottish Medicines Consortium (SMC) issued advice on 9 August 2004 that aripiprazole (Abilify) is accepted for use within NHS Scotland for the treatment of schizophrenia. It is one of several atypical antipsychotic medicines that improve symptoms of an acute relapse and reduce the risk of relapse comparable to a typical antipsychotic. The evidence of comparable efficacy to other atypical antipsychotics is limited. It is associated with a lower incidence of extra-pyramidal side effects than typical antipsychotics, and comparable to other atypicals. It is associated with less elevation of serum prolactin, less lipid abnormalities and less clinically significant weight gain over the short-term compared with other atypical antipsychotics. It does not adversely effect blood glucose nor have a clinically significant advantage compared to other antipsychotics with respect to this.

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 9 May 2003 that risperidone orodispersible tablets (Risperdal Quicklet) is recommended for restricted use within NHS Scotland. Risperdal Quicklet, for the treatment of acute and chronic schizophrenia and other similar psychotic conditions, should be reserved for those patients in whom rapid oral absorption is indicated.

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 6 December 2002 that risperidone prolonged-release injection is recommended for restricted use within NHS Scotland. Risperdal Consta may be considered as a treatment option for patients who require an atypical antipsychotic and for whom depot injection is the preferred route of administration. Its use should be under the overall supervision of a consultant psychiatrist.

Additional information: comparators

The atypical antipsychotic agents recommended in the NICE guidance (2002) are amisulpiride, olanzapine, quetiapine, risperidone, and zotepine. The Scottish Medicines Consortium accepted aripiprazole for use in 2004.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
paliperidone	**3 - 12 mg/day**	**1,265 - 2,530**
amisulpride	400 - 800 mg/day	745 -1,489
olanzapine	5 - 20 mg/day	634 - 2,066
quetiapine	300 - 450 mg/day	1,031-1717
risperidone	4 - 6 mg/day	809 - 1,226
zotepine	75 - 300 mg/day	406 - 1,147
aripiprazole	10 - 15 mg/day	1,321

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 12/12/07.

Additional information: budget impact

The manufacturer estimated that the direct budget impact of paliperidone 6 mg dose was £225k in 2008 rising to £991k in 2012, based on an estimated 6% and 24% of patients who discontinue existing atypical antipsychotics and commence paliperidone in 2008 and 2012 respectively. The net budget impact after displacement of other antipsychotics was estimated at £2k and £10k in 2008 and 2012 respectively.

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 15 February 2008.

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.

Kane J, Canas F, G, Kramer M et al. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo controlled trial. Schizophr. Res. 2007;90:147-161.

Marder R, Kramer M, Ford L et al. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. Biol Psychiatry [Epub ahead of print], (2007).

Davidson M, Emsley R, Kramer M et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): Results of a 6-week, randomized, placebo-controlled study. Schizophr. Res. 2007;93:117-130.

Canuso C., Dirks B., Carothers J., Zhu Y., & Kosik-Gonalez C. A double-blind, placebo-controlled trial of paliperidone ER and quetiapine in patients with a recent acute exacerbation of schizophrenia. 20th Annual US Psychiatric and Mental Health Congress. 2007. 11-10-2007.