All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Aripiprazole (Abilify®) tablets for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment

Bristol-Myers Squibb Pharmaceuticals Ltd and Otsuka Pharmaceuticals (UK)

Advice No: 1209 – June 2009

Recommendation of AWMSG

Aripiprazole (Abilify®) is recommended as an option for use within NHS Wales for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole (Abilify®) may be suitable for shared care when used for long term treatment (i.e. prevention of manic episode) after hospital initiation.

This report should be cited as:

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, 24th June 2009

The recommendation of AWMSG is:

Aripiprazole (Abilify®) is recommended as an option for use within NHS Wales for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole (Abilify®) may be suitable for shared care when used for long term treatment (i.e. prevention of manic episode) after hospital initiation.

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
df	Degrees of freedom
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	Electrocardiogram
EMEA	The European Medicines Agency
EPS	Extrapyramidal symptoms
HAM-D	Hamilton Depression Rating Scale
HR	Hazard ratio
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
NS	Not significant
OR	Odds ratio
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
UKPDS	UK Prospective Diabetes Study
WHO	World Health Organisation
WMP	Welsh Medicines Partnership
YMRS	Young Mania Rating Scale

2.0 PRODUCT DETAILS

2.1 Licensed indication

Aripiprazole (Abilify®) is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment[1].

The original licence was granted for schizophrenia in June 2004 but that indication does not form part of this submission.

2.2 Dosing

For manic episodes, the recommended starting dose for aripiprazole is 15mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy. Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30mg[1].

For preventing recurrence of manic episodes in patients who have been receiving aripiprazole, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction, should be considered on the basis of clinical status[1].

There is no experience of aripiprazole use in children and adolescents under 18 years of age and a lower starting dose should be considered in the elderly when clinical factors warrant. Comprehensive information on potential drug interactions and special precautions for use can be found in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date

The European Medicines Agency (EMEA) was granted marketing authorisation for bipolar I disorder on 31st March 2008[2].

2.4 UK Launch date

Aripiprazole was launched in the UK for bipolar 1 disorder in April 2008[3].

3.0 DECISION CONTEXT

Bipolar disorder is an illness that causes two distinct mood disturbances (poles): mania and depression. It is a chronic relapsing-remitting disorder and recurrent episodes may be in the same pole or fluctuate between poles. Bipolar I disorder is characterised by predominantly manic episodes with occasional depressive episodes; whereas in bipolar II disorder, episodes fluctuate between hypomania (similar to mania, but less severe) and depression[4]. For many people, however, the predominant experience is of low mood[5]. Currently there is no cure, but treatment can substantially decrease the morbidity and mortality (due to suicide and cardiovascular events) associated with bipolar disorder. Only 20% of people who experience a bipolar episode will recover fully[6]. The World Health Organisation (WHO) estimates the disorder to be the seventh leading cause of "non-fatal burden of disease"[7]. This condition affects around one to two percent of the UK population[4]. The peak age of onset is in late adolescence or early adult life, with a further small increase in incidence in mid to late life. The estimated annual societal cost of bipolar disorder in the UK is estimated to be around £2 billion[5].

Treatment aims include maximising the patient's level of personal and social functioning by ameliorating the severity of symptoms, reducing the frequency of recurrent instability in mood, and minimising the adverse effects associated with treatment. Treatment has also been shown to reduce the risk of suicide[8]. The National Institute for Health and Clinical Excellence (NICE) guidance on bipolar disorder highlights that only the following drugs were licensed in the UK at the date of publication (2006):

- For mania: lithium, olanzapine, quetiapine, risperidone and valproic acid (as valproate semisodium)
- For prophylaxis: lithium and olanzapine
- For prophylaxis when unresponsive to lithium: carbamazepine[5].

The NICE guidelines also state that lithium, olanzapine or valproate should be considered for long-term management[5]. Since the guidelines were published, aripiprazole has been licensed for the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole is a novel atypical antipsychotic that is distinct from other agents in this class due to its pharmacodynamic profile. It is a partial dopamine agonist at D_2 and D_3 receptors, a partial agonist at 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors. Generally, atypical antipsychotics have a lower risk of neurological side effects and may be less likely to exacerbate depressive symptoms compared to typical antipsychotics. However, currently available atypical antipsychotics are associated with weight gain[9], hyperprolactinaemia[10], QTc prolongation[11], hyperglycaemia[12,13] and dyslipidaemia[14]. The company propose that a partial dopaminergic agonist will reduce the risk of side effects associated with dopamine receptor blockade, such as extrapyramidal symptoms (EPS)[15]. The company propose that when an atypical anti-psychotic is required, aripiprazole should be recommended as a second-line option for patients with bipolar I disorder for both acute mania and long term relapse prevention.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission provides details of six double-blind, randomised trials comparing aripiprazole to placebo. Four of these studies investigated treatment in acute mania (duration 3 to 12 weeks) and one study focussed on recurrence prevention (duration 26 to 100 weeks). The remaining trial investigated adjunctive aripiprazole in patients with manic or mixed episodes who had a partial non-response to either lithium or valproate therapy (duration six weeks). In all the acute studies, the primary outcome was mean change in Young Mania Rating Scale (YMRS) total score at three weeks, and aripiprazole was shown to be superior to placebo in reducing manic episodes. In addition, improvements from baseline in YMRS total score for aripiprazole at 12 weeks were similar to those for haloperidol and lithium demonstrating a comparable maintenance of treatment effect. In the relapse prevention study, when compared to placebo, results demonstrated that aripiprazole was superior in the prevention of relapse and time to manic relapse, but not depressive relapse. Mean improvement from baseline in YMRS total score at week six (primary outcome) was significantly greater for adjunctive aripiprazole compared to adjunctive placebo in the combination study.

In the absence of head to head data, the company have undertaken indirect meta-analyses to assess the relative efficacy of aripiprazole as compared to other atypical antipsychotics. In the acute phase, no statistically significant differences between treatments have been demonstrated in either the relative likelihood of YMRS response or drop-out. The company report that in the prevention of relapse phase, aripiprazole was shown to have a smaller probability of experiencing a weekly event? and a higher likelihood of continuing on treatment compared to lithium. It would appear, however, that this is not statistically significant.

The results of an indirect meta-analysis showed that the probability of weight gain in the first year of initiation of treatment was lower for aripiprazole than olanzapine, risperidone, quetiapine and lithium. This was supported by monotherapy studies and one combination therapy study included in the submission (duration 3-12 weeks). Data from the monotherapy study in relapse prevention was, however, in contrast to this.

In the acute studies, the incidence of EPS-related adverse events was higher for aripiprazole compared to both placebo and lithium, but lower compared to haloperidol. The incidence of somnolence in the aripiprazole arms was generally low.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a cost utility analysis of aripiprazole used as a first- or second-line treatment in patients with acute mania in bipolar I disorder. A Markov model has been developed to represent a hospitalised acute manic phase and a longer-term relapse prevention phase. Aripiprazole treatment strategies are compared against treatment strategies involving the sequential use of the atypical antipsychotics olanzapine, risperidone and quetiapine for one to three weeks each. Patients who respond to olanzapine or aripiprazole continue on these agents in the relapse prevention phase, whereas patients who receive and respond to risperidone and quetiapine in the acute manic phase are assumed to switch to lithium therapy in the relapse prevention phase due to their licensed indications.

There are no direct, head to head studies that compare aripiprazole against other atypical antipsychotic agents. Indirect, pair-wise meta-analyses were therefore undertaken to estimate the relative efficacy of aripiprazole against atypical antipsychotics and lithium. The data included in the meta-analyses for the comparators were identified via literature searches and are limited. There are over-simplified assumptions made in relation to drug costs, and discrepancies in the estimates of other costs.

The base case analysis indicates that aripiprazole would not be cost effective as an alternative first-line treatment to olanzapine, as it is both more expensive and less effective. This finding is supported by probabilistic sensitivity analysis (PSA), which indicates the probability of aripiprazole being cost effective at a willingness to pay threshold of £20,000/quality adjusted life year (QALY) is 8%.

When compared against risperidone as a second-line agent, the incremental cost per QALY gained is estimated to be £12,745, although this would appear to be subject to some uncertainty as reflected by the PSA; the probability of aripiprazole being cost effective at a willingness to pay threshold of £20,000/QALY is 47%.

5.0 LIMITATIONS OF DECISION CONTEXT

- The company submission is for aripiprazole tablets and therefore the scope of this appraisal does not include other licensed oral preparations, which are included within the SPC.
- There is no evidence presented in the submission for the use of aripiprazole in children and adolescents under 18 years of age.
- There is a lack of robust evidence to demonstrate the efficacy of aripiprazole monotherapy in patients who have failed first-line treatment options. The company provides limited information in relation to augmentation of antipsychotics with lithium or valproate. NICE guidance states that such augmentation should be considered when antipsychotics are ineffective. Furthermore, clinical opinion sought by the Welsh Medicines Partnership (WMP) suggests that in practice it is more common for patients to receive both an antipsychotic and a mood stabiliser such as lithium or valproate.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy

The company submission[15] provides details of six double-blind, randomised trials comparing aripiprazole to placebo. Four of these studies investigated monotherapy in acute mania (duration 3 to 12 weeks), namely CN138009[16], CN138074[17], CN138135[18], CN138162[19,20], with study CN138010 focussing on monotherapy in relapse prevention (duration 26 to 100 weeks)[21,22]. The remaining trial, CN138134, compared aripiprazole adjunctive to either lithium or valproate therapy with adjunctive placebo in acute mania (duration six weeks)[23].

In the absence of head to head data, the company have undertaken indirect meta-analyses to assess the relative efficacy of aripiprazole compared to other atypical antipsychotics. All of the above mentioned aripiprazole trials were included in the indirect analyses of aripiprazole in either acute mania or relapse prevention as appropriate. A further five placebo-controlled, double-blind, randomised trials were used in the acute phase analysis. These were monotherapy studies comparing placebo to olanzapine[24], risperidone[25,26], risperidone and haloperidol[27], and quetiapine and haloperidol[28]. The indirect comparison for the prevention of relapses used one aforementioned aripiprazole trial[21] plus additional studies with olanzapine[29] and lithium[30] and/or divalproex (semisodium valproate)[31].

Details and results from the studies included in this section can be found in Tables 1A and 1B, in Appendix 1. Further secondary outcome data can be found in the corresponding references.

6.1.1 Aripiprazole trials

6.1.1.1 Monotherapy in acute mania

Studies CN138009[16], CN138074[17], CN138135[18] and CN138162[19,20] (n= 245, 268, 472 and 479 respectively for efficacy analysis) included adults (≥18years) with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) bipolar disorder, experiencing a manic or mixed episode requiring hospitalisation, with a YMRS score ≥20 and no serious risk of suicide. All four studies had a primary outcome of mean change from baseline in the YMRS total score at three weeks. Two of the studies were conducted over three weeks (CN138009[16] and CN138074[17]) and investigated acute response. Participants were randomised to received aripiprazole 30mg daily (reduced to 15mg if necessary), or placebo.

Although the primary outcome was assessed at three weeks, studies CN138135[18] and CN138162[19,20] were conducted over 12 weeks and also investigated maintenance of effect. These patients were randomised to receive aripiprazole 15mg (increased to 30mg if necessary), placebo, or an active control (in study CN138135[18] this was lithium and in study CN138162 this was haloperidol[19,20]). Patients receiving placebo were switched to double-blind aripiprazole at the end of week three and were not included in subsequent analyses.

Aripiprazole treated patients demonstrated significantly greater improvements from baseline in mean change in YMRS total score at three weeks compared to placebo in studies CN138009 ($p=0.002$)[16] and CN138074 ($p<0.001$)[17]. Significantly greater improvement in mean change in YMRS total score at three weeks was also observed for all treatments as compared to placebo in the maintenance studies CN138135 (aripiprazole versus placebo; lithium versus placebo)[15,18] and CN138162 (aripiprazole versus placebo, $p=0.039$; haloperidol versus placebo, $p=0.005$)[19,20]. Improvements from baseline in the YMRS total score were maintained to week 12 (last observation carried forward [LOCF]) and were similar for aripiprazole, lithium and haloperidol (see Table 1A, Appendix 1 for secondary outcome data).

In the main, secondary outcomes supported the efficacy of aripiprazole compared to placebo[16-20]. However, response and remission rates at three weeks were not significantly greater with aripiprazole or haloperidol compared to placebo in CN138162[19,20].

6.1.1.2 Monotherapy in relapse prevention

Study CN138010 comprised of three phases and included adults (≥18years) with DSM-IV bipolar disorder, experiencing a manic or mixed episode who initially received open-label aripiprazole for 6 to 18 weeks (phase one). A total of 161 patients achieving stabilisation were then randomised to aripiprazole or placebo for 26 weeks in the double-blind maintenance phase (phase two). Completers of phase two then continued to the double-blind extension phase for an additional 74 weeks (phase three). The primary outcome, time to relapse (any mood episode, i.e. manic, depressive or mixed), was defined as discontinuation due to lack of efficacy; measured at 26 weeks (end of phase two). This was significantly superior for aripiprazole compared to placebo (hazard ratio [HR] 0.523, $p=0.02$). Time to manic relapse, but not time to depressive relapse, proved to be significantly longer for aripiprazole compared to placebo (HR 0.31, $p=0.01$; HR 0.83, $p=0.68$ respectively). Twelve patients completed the extension phase. At 100 weeks, time to relapse was significantly longer with aripiprazole than placebo (HR 0.53, $p=0.01$); with the proportion of patients experiencing relapse by week 100 being significantly lower for the aripiprazole group compared to placebo (33% versus 52%, respectively; $p=0.02$)[21,22].

6.1.1.3 Combination therapy in acute mania

Combination therapy in acute mania was addressed using study CN138134[23]. This randomised, placebo-controlled, double-blind study consisted of four phases. Adults (≥18years) with DSM-IV bipolar disorder, experiencing a manic or mixed episode requiring hospitalisation, with a YMRS score ≥20 and no serious risk of suicide entered a wash-out stabilisation phase of 3 to 30 days (phase one). During the two-week mood stabiliser baseline period (phase two), patients received open-label lithium or valproate monotherapy. At week two, patients with a partial non-response (YMRS ≥16 during phase one and end of phase two, with ≤25% decrease between phases) were randomised to adjunctive aripiprazole or adjunctive placebo for phase three (n=384; stratified by mood stabiliser). This was subsequently followed by an open-label phase of 46 weeks (phase four).

The primary outcome of mean change in YMRS total score at the end of phase three was significantly ($p<0.01$) different for adjunctive aripiprazole compared to adjunctive placebo. Secondary outcomes largely supported the efficacy of adjunctive aripiprazole compared to adjunctive placebo[23].

6.1.2 Points to note from aripiprazole trials

- Direct comparisons of primary outcomes were only made to placebo.
- Discontinuation rates were high in the two three-week studies in acute mania and incidence of discontinuation due to lack of efficacy did include participants in the aripiprazole groups.
- Sample size was not pre-planned and power was not considered for phase three of study CN138010[21,22]. The study was therefore not powered to detect differences in rates of depressive relapse.
- Study CN138010 provided data on treatment effect on relapse prevention up to 100 weeks, however very few patients in either the aripiprazole or placebo groups completed this extension phase of the study (n=7 and n=5 respectively). Nearly 40% (24 out of 66 patients) participating in the extension study discontinued due to study closure once the pre-defined number of patients (n=45) had relapsed; determined by the study protocol[22].
- Primary outcomes used the LOCF approach (see Table 1A, Appendix 1).
- High placebo response and remission rates are described as not uncommon in bipolar disorder trials[20,27,32].
- Study CN138162[19,20] did not have a placebo comparator arm beyond the first three weeks. The authors of this paper state that this is an accepted methodology that has been used previously; identifying that there are a number of ethical issues associated with the use of placebo beyond acute treatment of bipolar disorder.

6.1.3 Non-aripiprazole trials included in the indirect comparisons

Five non-aripiprazole, randomised, placebo-controlled, double-blind studies were used in the company's indirect comparison in acute mania. With the exception of Hirschfield and colleagues[25] who recruited patients with pure mania, all studies recruited adults (≥18years) with DSM-IV bipolar disorder, experiencing a manic or mixed episode, with a YMRS score ≥20 and no serious risk of suicide. One three-week study compared olanzapine to placebo[24], two three-week studies were included comparing risperidone to placebo[25,26] and a further three-week parallel study compared risperidone and haloperidol to placebo, with a nine-week double-blind follow up[27]. A final parallel 12-week study compared quetiapine and haloperidol to placebo[28].

The indirect comparison for the prevention of relapses used two non-aripiprazole randomised, placebo-controlled, double-blind studies with olanzapine (48 week)[29] and lithium and divalproex (semisodium valproate) (52 week)[31]. A further study was included comparing olanzapine and lithium without a placebo control (52 week)[30]. Both studies were carried out following up to a 12-week open-label phase.

6.1.3.1 Results

The company have carried out an indirect meta-analysis using the trials highlighted under section 6.1 and have reported the relative likelihood of YMRS response and the relative risk of drop-out for each treatment comparison in the acute phase (see Table 1). The likelihood of YMRS response was defined by ≥50% decrease from baseline YMRS total score. The results of the indirect meta-analysis for the prevention of relapse phase are presented in Table 2.

Table 1. Relative likelihood of achieving YMRS response and drop-out in the acute phase[15]

Direct Comparisons (study references)	Relative likelihood of response Mean (95% CI)*	Indirect Comparisons	Relative likelihood of response Mean*†
YMRS Response at Week 3			
ARI vs. placebo[16-20]	1.59 (1.39 to 1.80)	**ARI vs. OLA**	0.75
OLA vs. placebo[24]	2.00 (1.22 to 3.27)	**ARI vs. RIS**	0.92
RIS vs. placebo[25-27]	1.76 (1.49 to 2.08)	**ARI vs. QTP**	1.07
QTP vs. placebo[28]	1.22 (0.86 to 1.73)		
Drop-Out at Week 3			
ARI vs. placebo[16-20]	0.85 (0.75 to 0.96)	**ARI vs. OLA**	1.47
OLA vs. placebo[24]	0.59 (0.42 to 0.83)	**ARI vs. RIS**	1.24
RIS vs. placebo[25-27]	0.55 (0.36 to 0.83)	**ARI vs. QTP**	1
QTP vs. placebo[28]	0.65 (0.34 to 1.22)		

ARI= Aripiprazole; CI= Confidence interval ;; OLA= Olanzapine; QTP= Quetiapine; RIS= Risperidone; *= A value >1 indicated better response with active agent than with placebo; †= A value >1 indicated better response with aripiprazole than with comparator.

Table 2. Results of indirect comparison of long-term relapse prevention[15]

Treatment	Relative HR* vs. Placebo†	Probability of experiencing an event§ per week	Probability of continuing on treatment per week¶
Placebo	–	0.03895 (0.037 to 0.041)	0.96105 (0.959 to 0.963)
Lithium[30,31]	0.945 (0.784 to 1.140)	0.03684 (0.032 to 0.043)	0.96316 (0.957 to 0.968)
Olanzapine [29,30]	0.596 (0.505 to 0.703)	0.02338 (0.021 to 0.026)	0.97662 (0.974 to 0.979)
Aripiprazole[21]	0.638 (0.532 to 0.882)	0.02503 (0.021 to 0.034)	0.97497 (0.966 to 0.979)

HR= Hazard ratio; *= Conditional probability of an event given that a patient has not already had an event; †= Hazard rate of treatment arm/Hazard rate of placebo arm; §= mania/depression/drop-out; ¶= 1- probability of event. Calculated using relative HRs of having an event versus placebo.

6.1.3.2 Points to note

- The indirect analyses consider the management of mania with only monotherapy and provided limited information in relation to augmentation of antipsychotics with lithium or valproate. NICE guidance states that such augmentation should be considered when antipsychotics are ineffective. Furthermore, WMP sought clinical opinion, which identified that in practice it is more common for patients to receive both an antipsychotic and a mood stabiliser such as lithium or valproate[33].
- No statistically significant differences between treatments have been demonstrated in both the relative likelihood of YMRS response and drop-out rate in the acute phase.

- Acute mania studies of 4 to 12 weeks were not included in the indirect comparison, as some of them did not report sustained efficacy of response at week 12. The company therefore considers that there were insufficient data available.
- Figures in Table 1 have been calculated by WMP using economic data provided in the company submission.
- Risperidone[34] and quetiapine[35] are not licensed for long-term relapse prevention and were therefore not included in the indirect analyses for this phase[15].
- The company report that aripiprazole was shown to have a smaller probability of experiencing an event per week (which was statistically significant) and consequently a higher likelihood of continuing on treatment per week compared to lithium.
- As the study reported by Tohen and colleagues[30] was not placebo-controlled, an artificial placebo arm was created based on the HRs of lithium versus placebo[31] and olanzapine versus placebo[29] for the indirect comparison of long-term relapse prevention.
- HRs from two studies for olanzapine were combined for the indirect comparison of long-term relapse prevention using the inverse variance method. The same approach was used for the lithium studies.

6.2 Safety

Safety data was extracted from all of the aripiprazole trials included in the company's efficacy analyses (see section 6.1.1)[15].

6.2.1 Monotherapy in acute mania

Table 3 shows the incidence of treatment related adverse events at weeks three and 12. The most common treatment-related adverse events in the aripiprazole arm of the acute studies included headache, akathisia, somnolence, nausea, anxiety and insomnia.

Table 3. Incidence of treatment-related adverse events in acute studies

	Incidence of treatment-related adverse events (%)			
Study	**Aripiprazole**	**Placebo**	**Lithium**	**Haloperidol**
3 week				
CN138009[16] CN138074[17] CN138135[18] CN138162[19,20]	63-93	44-83	-	-
CN138135[18]	88	75	77	-
CN138162[19,20]	63	44	-	65
12 week				
CN138135[18]	91	-	82	-
CN138162[19,20]	68	-	-	73

No statistically significant difference in clinically significant weight gain (≥7% increase from baseline) was detected between aripiprazole and placebo in studies CN138009[16] and CN138074[17]. Likewise, no clinically significant weight gain was observed between aripiprazole, placebo and lithium or haloperidol in CN138135[18] and CN138162[19,20]. The overall incidence of EPS-related adverse events was higher for aripiprazole (20%-27%) than placebo (6%-12%) in the acute studies at three weeks. The incidence of EPS-related adverse events was lower for aripiprazole compared to haloperidol[19,20], but higher when compared to lithium[18]. The incidence of serious adverse events was low in both groups at three weeks; however, rates were higher in the aripiprazole arms at 12 weeks in CN138135[18] and CN138162[19,20]. The rates of discontinuation due to an adverse event were similar between treatment groups (≤ 4% difference between groups; range 8% to 20%) at both three and 12 weeks. The incidence of death was low and similar across the study arms in these acute studies[20]).

6.2.2 Monotherapy in relapse prevention

The incidence of treatment-related adverse events during the maintenance phase (phase two) of CN138010 was similar for the aripiprazole (74%) and placebo (70%) arms[21,22]. The most common treatment-related adverse events in the aripiprazole arm included nausea, anxiety, insomnia, depression and nervousness. In contrast to the studies discussed in section 6.2.1, in study CN138010, clinically significant weight gain (≥7% increase from randomisation) was observed in 13% of patients receiving aripiprazole compared to none of the patients receiving placebo (p value not available) at the end of the 26 week maintenance phase (phase two); and 20% of patients receiving aripiprazole compared to 5% of patients receiving placebo (p=0.01) at the end of the 74 week extension phase (phase three). The incidence of EPS-related adverse events was similar between treatment groups in phase two. The incidence of serious adverse events in phase two was lower in the aripiprazole arm compared to the placebo arm (8% versus 13.3%). In addition, the rate of discontinuation was lower in the aripiprazole arm (10% versus placebo 19%).

6.2.3 Combination therapy in acute mania

The overall incidence of treatment-related adverse events in CN138134 was 62% for adjunctive aripiprazole and 54% for placebo. The only adverse event reported at a rate of ≥10% for the aripiprazole arm was akathisia and the incidence of EPS-related adverse events was higher in the aripiprazole arm. There was no significant difference in weight gain between treatment groups and there were no deaths in the six week placebo-controlled phase (phase 3). The discontinuation rate was higher for the aripiprazole arm compared to the placebo arm (12% versus 6%). With regards to laboratory analyses, vital signs and ECGs, abnormalities were low in incidence in both the aripiprazole and placebo arms[23].

6.2.4 Points to note

- The company have used results from a meta-analysis on weight gain from the NICE schizophrenia clinical guideline published in 2006 which states that the probability of weight gain in the first year of initiation of treatment was reportedly lower for aripiprazole than for olanzapine, risperidone, quetiapine and lithium (0.1311 versus 0.4419, 0.2269, 0.2970 and 0.1450 respectively)[15]. The recently updated guidance[36] states the probability of weight gain in the first year of initiation of treatment was reportedly lower for aripiprazole than for olanzapine, amisulpiride, risperidone and haloperidol (0.1516 versus 0.4172, 0.3175, 0.2141 and 0.2000 respectively). This was supported by the monotherapy studies in acute mania (see section 6.2.1) and the combination therapy study (see section 6.2.3), but not the monotherapy study in relapse prevention (see section 6.2.2).

- The company report that robust data on weight gain in bipolar disorder is scarce and highlight that a study by Correll and colleagues[37] concluded that patients with bipolar disorder and schizophrenia who are treated with atypical antispsychotic agents have similarly high rates of metabolic syndrome and shared susceptibility to antipsychotic-related metabolic dysregulations. The meta-analysis presented in the NICE guidelines does not include data on lithium and quetiapine and the company have calculated the incidence of weight gain using two studies[30,38]. No attempt has been made to use data from the studies used in the company's indirect analysis, and the studies were not powered to assess this.
- The company have used results from a meta-analysis on diabetes from the NICE schizophrenia clinical guideline update[15]. The probability of diabetes in the first year of initiation of treatment was reportedly lower for aripiprazole than olanzapine, risperidone, quetiapine and lithium (0.0145 versus 0.0490, 0.0252, 0.0329 and 0.0161 respectively).
- As the meta-analysis presented in the NICE guidelines did not consider lithium and quetiapine, the probabilities of diabetes with these agents have been estimated by the company, based on the relative risks of events in single trials of olanzapine versus lithium and quetiapine versus placebo. No attempt has been made to use data from the studies used in the company's indirect analysis, and the studies were not powered to assess this. The recently updated NICE guidance[36] only states that the ranking of antipsychotics in terms of risk for diabetes is consistent with evidence suggesting that olanzapine is strongly associated with diabetic events, while aripiprazole, risperidone and haloperidol are poorly associated with such events.
- The incidence of EPS-related adverse events was higher for aripiprazole compared to both placebo and lithium, but lower when compared to haloperidol.
- The incidence of somnolence in the aripiprazole arms was generally low, although higher than for placebo arms. At 12 weeks, the incidence was marginally higher for patients receiving aripiprazole compared to those receiving lithium or haloperidol[15].
- The occurrence of suicidal behaviour is inherent in psychotic illnesses and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Lithium, haloperidol, carbamazepine and valproate are all used for the treatment of bipolar I disorder. Olanzapine, risperidone and quetiapine are atypical antipsychotics and are licensed to treat manic episodes; hence they are appropriate comparators for aripiprazole.

7.2 Comparative effectiveness

- NICE recommends lithium, olanzapine or valproate for the treatment of bipolar I disorder[5]. However, olanzapine is the only atypical antipsychotic other than aripiprazole that is licensed for preventing recurrent manic episodes[5].
- The NICE clinical guideline for bipolar disorder recommends treatment with an antipsychotic, valproate or lithium when a patient develops an acute manic episode when not taking anti-manic medication. Valproate and lithium are options if symptoms have responded to these drugs previously and NICE

further recommends that, due to its slower onset of action compared with antipsychotics and valproate, lithium is used only if symptoms are not severe[5].

- NICE guidance states that augmentation with lithium or valproate should be considered when antipsychotics are ineffective[5]. Clinical opinion sought by WMP suggests that in practice it is common for patients to receive an antipsychotic augmented with such mood stabilisers[33].
- The company have stated in their submission that when an atypical antipsychotic is required, aripiprazole should be recommended as a second-line option for patients with bipolar I disorder for both acute mania and long-term relapse prevention. However, there is a lack of evidence provided in the company submission to support the efficacy of aripiprazole monotherapy in patients who have failed first-line treatment options in accordance with NICE guidelines.
- The company report that robust data on weight gain in bipolar disorder is scarce. The results of an indirect meta-analysis showed that the probability of weight gain in the first year of initiation of treatment was lower for aripiprazole than for olanzapine, risperidone, quetiapine and lithium. This was supported by monotherapy studies and one combination therapy study included in the submission (duration 3-12 weeks). Data from the monotherapy study in relapse prevention was, however, in contrast to this.
- In the acute studies, the incidence of EPS-related adverse events was higher for aripiprazole compared to both placebo and lithium, but lower compared to haloperidol. The incidence of somnolence in the aripiprazole arms was generally low.
- Patients receiving antipsychotics require weight / body mass index (BMI), blood glucose and lipids to be measured. In addition to weight / BMI, patients receiving valproate treatment require liver function and full blood count to be measured. Lithium requires therapeutic drug monitoring to be undertaken five to seven days after treatment initiation (or after change in dose, brand or other medication) and once stabilised, patients should be tested at least every three months.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by aripiprazole over the relevant comparator(s) justify any associated increase in costs and, if so, whether the total budgetary impact of supporting the use of aripiprazole is acceptable.

8.2. Description and critique of the company's submission

The company submission[15] describes a cost utility analysis of treatment strategies in which aripiprazole is used as a first- or second-line treatment in patients with acute mania in bipolar I disorder. A Markov model has been developed to represent an acute manic phase and a longer-term relapse prevention phase. Patients enter the model following hospitalisation for acute mania, during which aripiprazole treatment strategies are compared against treatment strategies involving the sequential use (where necessary) of the atypical antipsychotics olanzapine, risperidone and quetiapine for one to three weeks each. Patients who respond to olanzapine or aripiprazole, (defined as 50% reduction in their YMRS score) continue on these agents in the relapse prevention phase in the outpatient setting. As risperidone[34] and quetiapine[35] are not licensed for relapse prevention, patients who receive and respond to these agents in

the acute manic phase are assumed to switch to lithium therapy in the relapse prevention phase.

Patients may move from the relapse prevention phase into the acute manic phase, drop-out or become depressed. There are also several post-acute, not treated states into which patients may move if they stop taking their medication[15].
There are no direct, head to head studies that compare aripiprazole against other atypical antipsychotic agents. Indirect meta-analyses were undertaken, using data from studies identified in a literature search, to estimate the relative efficacy of aripiprazole against atypical antipsychotics in the acute manic phase and against olanzapine and lithium in the relapse prevention phase. The data included in the meta-analyses for the comparators are limited, which would result in some uncertainty in the parameter values that are generated. This is reflected in the results of the PSAs that have been conducted.

The indirect comparison in the acute manic phase erroneously contained duplicate aripiprazole studies, and the company subsequently provided new analyses with the duplicate studies removed.

The economic model only considers the management of mania with monotherapy. It does not provide information in relation to the augmentation of antipsychotics with lithium or valproate, which may be options when antipsychotics are ineffective[5]. The model has not been provided to WMP and the model inputs and outputs have not been verified; this also applies to the new analyses that have been provided by the company.

8.3 Population
The model reflects a hypothetical cohort of 1,000 adult patients who meet the DSM-IV criteria for bipolar I disorder, either manic or mixed, who are hospitalised with acute mania[15].

8.4 Perspective and time horizon
The analysis is conducted from the perspective of NHS Wales. A five year time horizon is used in the base case analysis[15], as the company has interpreted the 2006 NICE clinical guideline on bipolar disorder[5] to suggest that treatment should normally continue for up to five years if the person has risk factors for relapse. The NICE guideline states that treatment should continue for at least two years; and up to five years if the person has risk factors for relapse[5]. A three-year time horizon has been considered in sensitivity analyses[15]. It appears that a cycle length of one week is used throughout the model.

8.5 Comparator
Aripiprazole is compared against other atypical antipsychotics in the treatment and prevention of mania in bipolar I disorder[15]. The NICE clinical guideline for bipolar disorder indicates that atypical antipsychotics are options in the management of acute episodes of mania, and that valproate and lithium are options if symptoms have responded to these drugs previously. It further recommends that lithium is used only if symptoms are not severe due to its slower onset of action compared with antipsychotics and valproate[5]. Other atypical antipsychotics would appear to be appropriate comparators for aripiprazole.

Treatment strategies involving sequential use of agents are compared. In the base case analysis, usual care in the acute manic phase is considered to consist of first-line use of olanzapine, followed by second-line risperidone and then third-line quetiapine where necessary. This is reportedly based the expert opinion of two Scottish psychiatrists. In the model, aripiprazole is compared against olanzapine as a first-line agent, and also against risperidone as a second-line agent following first-line treatment with olanzapine. Alternative scenarios are also considered in which quetiapine is the second-line agent and risperidone the third-line agent in the usual care pathway[15]. In all cases, as risperidone[34] and quetiapine[35] are not licensed for relapse prevention, patients who receive and respond to these agents in the acute manic phase are assumed to switch to lithium therapy in the relapse prevention phase.

8.6 Clinical inputs

8.6.1 Efficacy data

There are no direct, head to head studies that compare aripiprazole against other atypical antipsychotic agents. Indirect meta-analyses were undertaken, using data from studies identified in a literature search, to estimate the relative efficacy of aripiprazole against atypical antipsychotics in the acute manic phase and against olanzapine and lithium in the relapse prevention phase. Pair wise comparisons via placebo were possible for each comparator of interest for the model, and meta-regression was used to derive an indirect relative estimate. The company submission states that a Bayesian network analysis involving direct and indirect mixed treatment comparisons was not undertaken as the results of such an analysis are highly dependent on assumptions of data linkage across chains of evidence[15]. However, pair wise comparisons also require similar assumptions to be made across the pairs of treatments that are compared[39].

The main efficacy measure used in the model is YMRS response, defined as $\geq$50% reduction from baseline in YMRS score, taken from randomised controlled trials of aripiprazole and the other agents. Drop-out rates were also extracted and compared across the trials.

8.6.1.1 Acute manic phase

For the acute manic phase, the company submission reported that four aripiprazole studies, three risperidone studies, one olanzapine study, and one quetiapine study were included in the indirect analyses[15]. However, the forest plots and statistical outputs of the meta-analyses and indirect meta-regression, presented as a separate appendix to the original submission, indicated that six studies had been used to provide an estimate of the effect of aripiprazole on YMRS response. It appeared that two of the aripiprazole studies had been duplicated in the estimation of the overall relative risk of response (studies CN138009 and CN138074 were also included as separate studies by Keck et al 2003[16] and Sachs et al 2006[17], respectively, when in fact they are the same studies). These two studies produced the greatest estimates of response out of the four studies that were actually considered. Their duplication in the meta-analysis would increase the overall estimate of response to aripiprazole and bias the model in favour of aripiprazole. The company has subsequently provided new analyses with the duplicate studies removed, which as expected reportedly results in marginally lower estimates of likelihood of response with aripiprazole, and marginally lower estimates of drop-outs for the comparators when compared with the estimates in the original submission.

The meta-analyses show that, in the acute phase of treatment, olanzapine and risperidone have a numerically higher likelihood of achieving YMRS response at three weeks (as defined by ≥50% decrease from baseline on the YMRS total score) and a numerically lower likelihood of leading to treatment drop-out than aripiprazole, although the 95% CIs that are generated around the estimates are reportedly wide and indicate no statistically significant differences[15]. The ability to extract data from the studies of other atypical antipsychotics has limited the number of studies included for olanzapine and quetiapine to one each[15]. The estimates of response rates used in the indirect meta-analyses for these comparators would therefore appear to be subject to some uncertainty, as reflected by the wide CIs. One-way sensitivity analyses, conducted using the upper and lower limit of the 95% CIs of early phase response rates, indicate that the deterministic model outputs are relatively insensitive to this parameter.,

8.6.1.2 Relapse prevention phase

The relapse prevention phase is considered to be composed of two stages to reflect that fact that company-sought clinical expert opinion (no further details provided) is that patients do not achieve full euthymia until some weeks after discharge from hospital; a maintenance of effect phase is modelled followed by a euthymic phase.

Four studies were included in the indirect meta-analysis for the longer-term relapse prevention phase. These compared lithium versus placebo, lithium versus olanzapine, olanzapine versus placebo and aripiprazole versus placebo. The placebo data from these studies were combined to determine the hazard rate for having an event of mania, depression or drop-out (an artificial placebo arm was created for the study that compared lithium versus olanzapine, using placebo data from the studies of lithium and olanzapine versus placebo). HRs for an event with lithium, olanzapine or aripiprazole were then generated and compared with the placebo event HRs. Aripiprazole treatment was estimated to result in a smaller probability of experiencing an event per week and a higher likelihood of continuing on treatment per week compared to lithium, but not compared with olanzapine.

8.6.2 Adverse events

The model considers the adverse effects of weight gain and diabetes, along with its associated complications of cardiovascular events and amputation[15]. It should be noted that the probabilities of weight gain and development of diabetes (which is based in part on the probability of weight gain) apply only in the first year of the model[15] and are based on studies of up to 12 weeks duration[36]. As treatment is for up to five years in the base case analysis, the risks of these adverse events may be underestimated., which the company considers to favour the comparators over aripirazole.

The probability of clinically relevant weight gain (≥7% increase in BMI from baseline) and the probability of developing diabetes in the first year of treatment with olanzapine, aripiprazole and risperidone were derived from meta-analyses of atypical antipsychotics that were conducted for the now published update to the NICE clinical guideline on schizophrenia[36]. As these meta-analyses did not consider lithium and quetiapine, the probabilities of weight gain and diabetes with these agents have been estimated by the company, based on the relative risks of events in single trials of olanzapine versus lithium and quetiapine versus placebo. The probabilities of weight gain and development of diabetes in the first year of treatment are lower for aripiprazole than for olanzapine and risperidone as estimated in the NICE guideline meta-analyses[36], and are lower for aripiprazole than for both quetiapine and lithium in the company estimated probabilities[15].

The probabilities of cardiovascular and microvascular complications of diabetes are also based on those used in the model developed for the NICE schizophrenia guideline update[36], which are derived from the UK Prospective Diabetes Study (UKPDS)[40]. EPS are not considered in the current model[15], in contrast to the model developed for the NICE schizophrenia guideline update[36], which the company considers to favour the comparators over aripiprazole..

8.6.3 Utility weights

The utility values assumed in the model appear to be those used in a recent Health Technology Assessment (HTA) of interventions for preventing relapse in bipolar disorder[41], and are based on a study of US adult patients with bipolar disorder who were asked to rate hypothetical bipolar disorder health states[42]. For diabetes complications, the values assumed in the model developed for the NICE schizophrenia clinical guideline update are used (although disutility associated with myocardial infarction is greater than that reported in the NICE update)[36].

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

The drug costs assumed in the model for olanzapine, risperidone, quetiapine and aripiprazole are stated to be simply based on an average of the highest and lowest daily drug costs as listed for the treatment of mania in the British National Formulary (BNF)[43]. The range of doses considered for these drugs is the usual dose range as listed in the BNF, with the exception of the range of doses used to cost olanzapine in the model (10-20mg, crude average daily cost £4.26). This range is not the usual dose range listed in the BNF (5-20mg, crude average daily cost £3.71)[43], which would result in a higher cost being assumed for olanzapine in the model. The company has provided a supplementary analysis which indicates this has little impact on the model outputs.

For lithium, the dose range considered is 400mg to1,200mg per day, based on company-sought expert opinion[15].

8.7.2 Other resource use and costs

Monitoring and laboratory costs, healthcare professional visits, inpatient costs and weight management costs are reported to be taken from the NICE clinical guideline on bipolar disorder[5]. There appear to be some variations in the costs and assumed frequencies of use of these resources between those reported in the company submission[15] and those in the NICE bipolar clinical guideline[5]. The company has provided additional analyses, reportedly using the actiual costs used in the NICE bipolar disorder guideline, which reportedly results in little impact on the model outputs.

The annual costs of managing diabetes complications are based on the model developed for the NICE schizophrenia guideline update[36].

8.8 Discounting

Costs and outcomes have been discounted at 3.5% per annum[15], which is the preferred discount rate. Rates of 0% and 6% were explored in sensitivity analyses[15].

8.9 Results

8.9.1 Base case analysis

8.9.1.1 Aripiprazole versus olanzapine as first-line treatment

When used first-line, aripiprazole is not cost effective compared with first-line olanzapine. Based on 1,000 hypothetical patients modelled over a five-year time frame, aripiprazole was estimated to be associated with additional costs of £721,325 (£20.9m versus £20.2m) and 19.9 fewer QALYs compared with olanzapine (2,788 QALYs versus 2,808)[15].

8.9.1.2 Aripiprazole versus risperidone as second-line treatment following first-line olanzapine

The incremental cost per QALY gained for aripiprazole compared against risperidone as a second-line treatment following first-line olanzapine treatment was estimated to be £12,745. This is based on additional costs of £203,355 (£20.4m versus £20.2m) and a gain of 15.96 QALYs (2,824 QALYs versus 2,808) across 1,000 hypothetical patients modelled over a five-year time frame.

The greatest costs in the model are associated with treatment during the acute mania phase, which occurs in the hospital setting. There are only marginal differences in the costs of the acute mania phase across all treatments.

8.9.2 Scenario analyses

Three scenario analyses have been conducted in the hypothetical cohort of 1,000 patients.

8.9.2.1 Three-year time horizon

When a time horizon of three years is used, instead of five years, the overall model outputs are similar to the base case analysis. First-line use of aripiprazole is still dominated by first-line use of olanzapine. The incremental cost per QALY gained for aripiprazole compared against risperidone as a second-line treatment following first-line olanzapine treatment was reduced to £3,803, based on additional costs of around £35,500 and a gain of around 9 QALYs with aripiprazole compared with risperidone[15].

8.9.2.2 Quetiapine as second-line treatment instead of risperidone

When quetiapine is considered as the second-line treatment in the usual care pathway, the model outputs remain relatively unchanged compared with the base case analysis. First-line use of aripiprazole is still dominated by first-line use of olanzapine. The incremental cost per QALY gained for aripiprazole compared against quetiapine as a second-line treatment following first-line olanzapine treatment was £8,124, based on additional costs of around £183,000 and a gain of around 22.5 QALYs[15].

8.9.2.3 Exclusion of adverse events from the analyses

When adverse events of weight gain and diabetes complications are excluded from the analyses, the model outputs remain relatively unchanged. Olanzapine still dominates aripiprazole as a first-line treatment, and the incremental cost per QALY gained with the use of aripiprazole as a second-line treatment following olanzapine treatment, instead of risperidone, is £13,310[15].

8.9.3 Sensitivity analyses

8.9.3.1 One-way sensitivity analyses

Thirty seven one-way sensitivity analyses are presented in which parameter values have been varied between their 95% CIs, or where not available between +/-25% of their base case values. Only at the upper limit of the 95% CI for the week three response of aripiprazole versus olanzapine or at the lower limit of the 95% CI for the utility value associated with stable, euthymic state was first-line use of aripiprazole not dominated by first-line use of olanzapine. In isolation, these two analyses are of limited value and would not counter the main conclusion that aripiprazole is dominated by olanzapine when used first-line.

In relation to the second-line use of aripiprazole instead of risperidone, several of the one-way sensitivity analyses increased the incremental cost effectiveness ratio (ICER) estimate from the base case estimate of £12,745 to values in excess of £20,000/QALY. These included the lower limit of the 95% CI for the proportion of patients not relapsing with aripiprazole (ICER increased to £53,479 per QALY gained), which demonstrates a degree of sensitivity in the model outputs based on the point estimate of some parameters. This is reflected in the probabilistic sensitivity analyses (see section 8.9.3.2).

8.9.3.2 Probabilistic sensitivity analyses (PSA)

PSA were conducted using appropriate distributions for parameters. The probability that first-line use of aripiprazole would be cost effective compared with first-line use of olanzapine at a willingness to pay of threshold of £20,000/QALY was estimated to be 8%, and at £30,000/QALY was 11%. The probability that second-line use of aripiprazole following first-line use of olanzapine would be cost effective compared with second-line use of risperidone at a willingness to pay threshold of £20,000/QALY was estimated to be 47%, and at £30,000/QALY was 62%.

In the scenario analysis in which quetiapine was considered the second-line agent in the usual care pathway, the probability that first-line use of aripiprazole would be cost effective compared with first-line use of olanzapine at a willingness to pay of threshold of £20,000/QALY was estimated to be 9%, and at £30,000/QALY was 12%. The probability that second-line use of aripiprazole would be cost effective compared with second-line use of quetiapine at a willingness to pay threshold of £20,000/QALY was estimated to be 76%, and at £30,000/QALY was 89%.

8.10 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of aripiprazole in the treatment or prevention of mania in bipolar I disorder.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The budget impact analysis relates to the use of aripiprazole only as a second-line agent following the use of olanzapine. NICE costing report estimates of the prevalence of bipolar I disorder are applied to projected population estimates. Market research data, which is not verifiable, is then used to estimate the proportions of patients eligible for treatment with aripiprazole. A number of assumptions are made, including the implicit assumption that risperidone and quetiapine are currently only used for second-line treatment following failure of olanzapine. This would appear subject to some uncertainty. Three scenarios of aripiprazole uptake are considered, which provide substantially different estimates of the net budget impact of the introduction of aripiprazole.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[15].

9.3 Data sources

9.3.1 Incident and prevalent cases

The national cost impact report for the NICE clinical guideline on bipolar disorder assumes a prevalence of 0.9% for bipolar I disorder (in people aged 17+ years)[44]. Based on population projections for Wales from the Office of National Statistics[45], the company estimates that there would be 27,145 patients with bipolar I disorder in 2009, rising to 27,986 in 2013. However, these estimates are based on the whole population of Wales, and not just those aged 17 years or older. Company market research is reported to show a diagnosis rate of 61% (data on file – not verified)[15]. Therefore, the number of diagnosed patients is estimated to be 16,432 in 2009, rising to 17,072 in 2013[15]. The cost impact report for the NICE clinical guideline on bipolar disorder assumes that 9% of patients do not receive treatment[44]. Therefore, of the diagnosed patients, the company submission estimates that 91% will receive treatment, equivalent to 14,953 patients in 2009, rising to 15,535 in 2013[15] (minor variations exist in reported figures).

9.3.2 Projected rate of adoption and market share

Company market research is reported to show that 63.6% of patients are treated with atypical antipsychotics and that this is expected to increase by 2% each year to 70.2% in 2013 (data on file – not verified)[15]. Therefore, the number of patients estimated to receive atypical antipsychotics in 2009 is assumed to be 9,510, rising to 10,909 in 2013[15].

Company-obtained market research is reported to show that olanzapine accounts for 24.3% of the atypicals market, quetiapine accounts for 18.3% and risperidone accounts for 11.7% for the quarter December 2007-March 2008 (data on file – not verified)[15]. It is then assumed that these three agents comprise 100% of the market share of atypical in the treatment of bipolar I disorder. The respective market shares are therefore scaled to 44.8%, for olanzapine, 33.7% for quetiapine and 21.5% for risperidone[15] (in the absence of aripiprazole). Using data from the quarter December 2006-March 2007 and combining this with the above data for the quarter December 2007-March 2008, a logarithmic increase in market share has reportedly been estimated.

The analysis assumes that aripiprazole will be used only as a second-line agent following first-line use of olanzapine. However, the analyses do not consider first-line treatment failure rates, which implicitly assume that the estimates of use of risperidone and quetiapine are related to their use as second-line agents. This would seem subject to some uncertainty. It is assumed that aripiprazole will account for 2% of the market for atypical antipsychotics in the treatment of bipolar I disorder in 2009, rising to 10% by 2013. Different scenarios are considered: aripiprazole replaces risperidone only, aripiprazole replaces quetiapine only, or aripiprazole replaces risperidone and quetiapine in equal proportions.

9.3.3 Costs and resource use

As in the economic evaluation, the drug costs assumed for olanzapine, risperidone, quetiapine and aripiprazole in the budget impact analysis are stated to be simply based on an average of the highest and lowest daily drug costs as listed for the treatment of mania in the BNF[43]. The range of doses considered for these drugs is the usual dose range as listed in the BNF, with the exception of the range of doses used to cost olanzapine in the model (10-20mg, crude average daily cost £4.26). This range is not the usual dose range listed in the BNF (5-20mg, crude average daily cost £3.71)[43], which would result in a marginally higher cost being assumed for olanzapine in the analysis.

The company submission highlights that cost savings may be possible with the use of aripiprazole in relation to lower rates of weight gain and the development of diabetes complications. However, these have not been quantified[15].

9.4 Results

Without aripiprazole being available, the cost of treating bipolar I disorder patients with the atypical antipsychotics olanzapine, risperidone and quetiapine is estimated to be £15.02m in 2009, rising to £16.51m in 2013[15]. Table 4 summarises the net budgetary impact of the three scenarios of aripiprazole uptake. If aripiprazole is assumed to replace only quetiapine, this is estimated to result in small cost savings over each of the five years. If aripiprazole is assumed to replace only risperidone, this is estimated to result in more substantial cost increases.

Table 4. Estimated net budgetary impact of aripiprazole uptake

	2009	2010	2011	2012	2013
Aripiprazole replaces only quetiapine	-£15,698	-£32,271	-£49,754	-£68,183	-£87,597
Aripiprazole replaces only risperidone	£247,608	£509,003	£784,763	£1.08 million	£1.38 million
Aripiprazole replaces only quetiapine and risperidone equally	£115,955	£238,366	£367,504	£503,627	£647,020

9.5 Sensitivity analysis

No further analyses have been conducted for the budget impact estimate.

9.6 Relevant comparator costs

Agents used for the treatment of acute mania include atypical and typical antipsychotics, lithium, carbamazepine and valproate semisodium. Not all are licensed for prevention of mania. Table 5 summarises comparative costs, based on BNF list prices[43].

Table 5. Example of comparator costs

Drug	Example daily doses	Daily cost[43]
Atypical antipsychotics		
Aripiprazole (Abilify®)	15-30mg	£3.63 - £7.26
Olanzapine (Zyprexa®)	5-20mg	£1.74 - £5.68
Risperidone (Risperdal®)	1-6mg	£0.58 - £3.37
Quetiapine (Seroquel®)	400-800mg	£3.77 - £7.55
Typical antipsychotics		
Haloperidol*	3-5mg 2-3 times a day	£0.41 - £0.83
Other agents		
Lithium carbonate (Priadel®)	400-1,200mg	£0.04 - £0.11
Carbamazepine*	400-600mg	£0.24 - £0.35
Valproate semisodium (Depakote®)	1,000-2,000mg	£0.54 - £1.08
This table does not imply therapeutic equivalence between drugs or doses *Non-proprietary		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- The Scottish Intercollegiate Guidelines Network (SIGN) issued guidance on bipolar affective disorder in 2005[46].
- As with other atypical antipsychotics, the SPC for aripiprazole states that a patient's clinical condition may take several days to some weeks to improve and they should be closely monitored throughout this period. Adjustment of daily doses should also be considered on the basis of clinical status in the prevention of relapse[1]. Aripiprazole may be suitable for shared care when used for long term treatment (i.e. prevention of manic episode) after hospital initiation.

10.2 Related advice

- The Consensus Group of the British Association for Psychopharmacology published evidence-based guidelines for treating bipolar disorder in 2003[47].

10.3 Previous AWMSG/NICE advice

- NICE issued guidance on the management of bipolar disorder in adults, children and adolescents, in primary and secondary care in 2006[5].
- NICE have updated guidelines on core interventions in the treatment and management of schizophrenia in adults in primary and secondary care.[36].

10.4 Patient organisation submission

A patient organisation submission was not received.

10.5 Ongoing studies

Two of the aripiprazole trials included in the company submission are currently ongoing:

- Forty-six week open-label extension phase of study CN138134 with lithium or valproate in combination with aripiprazole. The company have not provided an estimate of when the anticipated 52-week data will become available[15].
- Forty week blinded extension phase of study CN138135 with aripiprazole or lithium. The company have not provided an estimate of when the anticipated 52 week data will become available[15].

GLOSSARY

Euthymia:
The neutral mood (absence of a depressive or manic cycle) that some people with bipolar disorder experience with varying frequency[55].

Incidence:
The rate at which new cases occur in a population during a specified period[48].

Prevalence:
The proportion of a population that are cases at a point in time[48].

Young Mania Rating Scale (YMRS):
An 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar I disorder. Mean change in YMRS score from baseline is routinely used in clinical trials as the primary end point to assess treatment response. The YMRS score is also used to evaluate rate of response (number of patients with YMRS decrease of ≥50% from baseline), time to onset of effect, as well as rate of remission (number of patients with YMRS ≤12)[15].

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Appendix 1. Additional Clinical Information
Table 1A. Placebo-controlled aripiprazole studies

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (aripiprazole versus placebo)
Monotherapy in acute mania						
CN138009 15, 16	Randomised, placebo-controlled, double-blind, 3wk study. Conducted in 38 centres in USA.	Randomised, n=262 Efficacy analysis: aripiprazole n=123, placebo n=122. Completed: aripiprazole 42%, placebo 21%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode requiring hospitalisation, YMRS score ≥20, no serious risk of suicide.	Male: 44% Mean age: 40.5yr (18-74yr) History not rapid cycling versus rapid cycling: 77% versus 23% Current episode manic versus mixed: 67% versus 33%	aripiprazole 30mg/day (reduced to 15mg/day if required) versus placebo	**Primary outcome:** **Mean change in YMRS total score†:** -8.2 (95% CI -10.6 to -5.7) versus -3.4 (-5.8 to -0.9); Treatment difference -4.80, p=0.002.
CN138074 15, 17	Randomised, placebo-controlled, double-blind, 3wk study. Conducted in 29 centres in USA.	Randomised, n=272 Efficacy analysis: aripiprazole n=136, placebo n=132. Completed: aripiprazole 55%, placebo 52%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode requiring hospitalisation, YMRS score ≥20, no serious risk of suicide.	Male: 49% White: 72% Mean age: 38.8yr (18-72yr) History not rapid cycling versus rapid cycling: 82% versus 18% Current episode manic versus mixed: 58% versus 42%	aripiprazole 30mg/day (reduced to 15mg/day if required) versus placebo	**Primary outcome:** **Mean change in YMRS total score†:** -12.5 versus -7.2; Treatment difference -5.33, p<0.01.
CN138135 15, 18	Randomised, placebo- and lithium-controlled, double-blind, 3wk (3 arms) / 12wk (2 arms) study. Conducted in 46 centres in USA.	Randomised, n=480 Efficacy analysis: Aripiprazole n=154, placebo n=163, lithium n=155. Completed 3wks: aripiprazole 47%, lithium 49%, placebo 47%. Completed 12wks: aripiprazole 27%, lithium 34%, placebo 29%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode requiring hospitalisation, YMRS score ≥20, MADRS total score ≤17.	Male: 51-52% White: 62-72% Mean age: 39.7yr (18-69yr) Current episode manic versus mixed: 61% versus 39%	aripiprazole 15mg/day (increased to 30mg/day if required) versus lithium 900-1,500mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score at 3wks†:** aripiprazole versus placebo: -12.64 versus -9.01; Treatment difference -3.63. Lithium versus placebo: -12.03 vs -9.01; Treatment difference -3.03. **Secondary outcome*:** **Mean change in YMRS total score at 12wks†:** aripiprazole versus lithium: -14.48 versus -12.71; Treatment difference -1.78, no p value provided.

Table 1A. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (aripiprazole versus placebo)
CN138162 15, 19, 20	Randomised, placebo- and haloperidol-controlled, double-blind, parallel, 3wk (3 arms) / 12wk (2 arms) study. Conducted in 59 centres in Bulgaria, Croatia, Mexico, Peru, Russia, South Africa and USA.	Randomised, n=485 Efficacy analysis: Aripiprazole n=166, placebo n=152, haloperidol n=161. Completed 3wks: aripiprazole 75%, haloperidol 73%, placebo 71%. Completed 12wks: aripiprazole 57%, haloperidol 58%, placebo 54.9% (received aripiprazole weeks 3-12).	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode requiring hospitalisation, YMRS score ≥20, MADRS total score ≤17, no serious risk of suicide.	Male: 43-46% White: 77-80% Mean age: 40.8yr (18-76yr) Current episode manic versus mixed: 81% versus 19%	aripiprazole 15mg/day (increased to 30mg/day if required) versus haloperidol 5mg/day (increased to max 15mg/day if required) versus placebo	**Primary endpoint:** **Mean change in YMRS total score at 3wks†:** aripiprazole versus placebo: -11.98 versus -9.7; Treatment difference -2.28, p=0.039. Haloperidol versus placebo: -12.83 versus -9.7; Treatment difference -3.13, p=0.005. **Secondary outcome*:** **Mean change in YMRS total score at 12wks†:** aripiprazole vs haloperidol: -17.16 versus -17.84; Treatment difference 0.68, p=0.564.
Monotherapy in relapse prevention						
CN138010 15, 21, 22	Randomised, placebo-controlled, double-blind, 3 phase study; 1: Open label stabilisation phase (6-18wks), 2: Double-blind maintenance phase (26wks), 3: Double-blind extension phase (74wks). Conducted in 76 centres in Agentina, Mexico and USA.	Recruited, n=633 Entered phase 1, n=567 Entered phase 2, n=161 (Randomised to: aripiprazole: n=78; placebo: n=83) Entered phase 3, aripiprazole n=39, n=27 Completed phase 2: aripiprazole 50%, placebo 34% (to week 26). Completed phase 3: aripiprazole 18%, placebo 19%.	Age ≥18yr DSM-IV bipolar disorder, recent manic or mixed episode.	Male: 33% White: 65% Mean age: 39.6yr History not rapid cycling versus rapid cycling: 83% versus 17% Current episode manic vs mixed: 70% versus 30%	aripiprazole 30mg/day (reduced to 15mg/day if required) versus placebo	**Primary outcome:** **Time to relapse[§] (manic, depressive or mixed) in phase 2:** HR 0.523 (0.30 to 0.91), p=0.02 **Secondary outcome*:** **Time to manic relapse in phase 2:** HR 0.31 (0.12 to 0.77), p=0.01 **Time to depressive relapse in phase 2:** HR 0.83 (0.35 to 2.01), p=0.68 **Proportion of patients relapsed in phase 2:** 25% versus 43% **Mean change in YMRS total score in phase 2[¶]:** 3.42 versus 7.5; Treatment difference -4.08 p=0.009. **Mean change in YMRS total score in phase 3[¶]:** 3.14 versus 5.9; Treatment difference NS **Time to relapse (combined phase 2 & 3):** HR 0.53 (0.32 to 0.87), p=0.01

Table 1A. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (aripiprazole versus placebo)
Combination therapy in acute mania						
CN138134 15, 23	Randomised, placebo-controlled, double-blind, 4 phase study; 1: Wash out (3-30 days), 2: Baseline mood stabiliser therapy (2wks), 3: Double-blind (6wks), 4: Open label (46wks). Where was this study conducted?	Entered phase 1, n=623 Entered phase 2, n=437 Entered phase 3, n=384 (Assigned to: aripiprazole n=253, placebo n=131). Completed phase 3: Aripiprazole 79%, placebo 85%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode requiring hospitalisation &/or treatment with mood stabiliser/antisychotic, no serious risk of suicide; At end of screening, YMRS score ≥16.	Male: 51% White: 91% Mean age: 42.1yr (18-68yr) Current episode manic versus mixed: 75% versus 25%	Adjunctive aripiprazole 15mg/day (increased to 30mg/day if required) in combination with valproate or lithium** versus adjunctive placebo in combination with valproate or lithium**.	**Primary outcome:** **Mean change in YMRS total score at end of phase 3†:** -13.31 (n=247) versus -10.7 (n=130); Treatment difference -2.62, p<0.01.

DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MADRS= Montgomery-Asberg Depression Rating Scale; NS= Not significant; YMRS: Young Mania Rating Scale; *= Refer to corresponding references for additional secondary outcomes; †= Last observation carried forward (LOCF); §= As defined by discontinuation due to lack of efficacy; ¶= From last stabilisation visit; **= Therapeutic serum level of lithium (0.6-1.0mmol/L) or valproate (50-125µg/ml) required at end of screening.

Table 1B. Non-aripiprazole studies included in the Company's indirect comparisons

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (treatment versus placebo)
Monotherapy in acute mania						
15, 24	Randomised, placebo-controlled, double-blind 3wk study. Where conducted?	Randomised, n=139 (olanzapine n=70, placebo n=69). Completed: Olanzapine 61%, placebo 35%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode, YMRS score ≥20, no serious risk of suicide	Male: 51.8% White: 72.7% Mean age: 39.5yr (18-65yr) Current episode manic versus mixed: 82.7% versus 17.3%	Olanzapine 5-20mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score†:** -10.26 versus -4.88; Treatment difference -5.38 (-10.31 to -0.93), p=0.02.
15, 25	Randomised, placebo-controlled, double-blind, multi-centre 3wk study. Where conducted?	Randomised, n=262 Completed: Risperidone 56%, placebo 42%.	Age ≥18yr DSM-IV bipolar disorder, prior manic or mixed episode, current episode pure mania YMRS score ≥20, MADRS score ≤20, no serious risk of suicide	Male: 57% White: 72% Mean age: 39yr (18-65) Current episode manic versus mixed: 100% versus 0%	Risperidone 1-6mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score†:** -10.6 (n=127) versus -4.8 (n=119); Treatment difference -5.8, p<0.001.
15, 26	Randomised, placebo-controlled, double-blind, 3wk study. Conducted at 8 centres in India.	Randomised, n=291 Received dose: Risperidone n=146, placebo n=144. Completed: Risperidone 89%, placebo 71%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode, YMRS score ≥20, no serious risk of suicide	Male: 56-68% Mean age: 35yr Current episode manic versus mixed: 94-97% versus 3-6%	Risperidone 1-6mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score†:** -22.7 versus -10.5; Treatment difference -12.2, p<0.001.

Table 1B. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (treatment versus placebo)
15, 27	Randomised, placebo-controlled, double-blind, parallel, 3wk study. Followed by 9wk double-blind study. Conducted in 10 countries in Europe and Asia.	Randomised, n=438 (risperidone n=154, haloperidol n=144, placebo n=140). Completed 3wks: Risperidone 89%, haloperidol 90%, placebo 85%. Completed 12wks: Risperidone 86%, haloperidol 88%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode, YMRS score ≥20, MADRS score ≤20, no serious risk of suicide	Male: 51-54% White: 62-66% Mean age: 38.5-41.3yr	Risperidone 1-6mg/day versus haloperidol 2-12mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score at 3wks†:** Risperidone versus placebo: -15.1 (n=153) versus -9.4 (n=138); p<0.001. Haloperidol vs placebo: -13.9 (n=144) versus -9.4 (n=138); p<0.001. **Mean YMRS total score at 3wks†**: Risperidone versus haloperidol vs placebo: 17.0 versus 17.4 versus 22.1 **Mean change in YMRS total score at 12wks†:** Risperidone vs haloperidol: -20.7 versus -18.4 (-3.94 to 1.03); NS **Mean YMRS total score at 12wks†:** Risperidone versus haloperidol: 11.4 (n=153) versus 12.9 (n=144); NS
15, 28	Randomised, placebo-controlled, double-blind, parallel, 12wk study. Conducted in 49 centres in South America, Asia and Europe	Randomised, n=302. ITT: Quetiapine n=101; haloperidol n=98; Placebo n=100 Completed: Quetiapine 54%, haloperidol 55%.	Age ≥18yr DSM-IV bipolar disorder, prior manic or mixed episode episode, current manic episode requiring hospitalisation, not rapid cycling, YMRS score ≥20,	Male: 36.8% Mean age: 42.9yr (18-79yr) Current episode manic versus mixed: 100% versus 0%	Quetiapine 100-800mg/day versus haloperidol 2-8mg/day versus placebo	**Primary outcome:** **Mean change in YMRS total score at 3wks†**: Quetiapine vs placebo: -12.29 versus -8.32; p<0.01. Haloperidol vs placebo: -15.71 versus -8.32; p<0.001. **Secondary outcome*:** **Mean change in YMRS total score at 12wks†**: Quetiapine vs placebo: -17.52 versus -9.48; p<0.001. Haloperidol vs placebo: -18.92 versus -9.48; p<0.001.

Table 1B. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (treatment versus placebo)
Monotherapy in relapse prevention						
15, 29	Randomised, placebo-controlled, double-blind, parallel, 48wk study (following 6-12wk open-label acute phase). Conducted in 44 sites in USA and 5 sites in Romania.	Open-label olanzapine, n=731. Randomised for double-blind study, n=361 (olanzapine n=225, placebo n=136). Completed: Olanzapine 21%, placebo 7%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode, YMRS score ≥20.	Male: 38.8% White: 87.3% Mean age: 39.8-41.1yr Current episode manic versus mixed: 66% versus 34%	Olanzapine 5-20mg/day versus placebo	**Primary outcome:** **Time to symptomatic relapse[§]:** 174days versus 22days[¶]; log-rank χ^2= 56.3, df=1, p<0.001; HR 2.67 (2.03-3.50).
15, 31	Randomised, placebo-controlled, double-blind, parallel, 52wk study (following ≤3months open-label acute phase). Conducted in 37 centres.	Open-label phase, n=571. Randomised for double-blind study, n=372 (divalproex n=187, lithium n=91, placebo n=94). ITT: divalproex n=187, lithium n=89, placebo n=93. Completed: Divalproex 38%, lithium 24%, placebo 25%.	Age 18-75yr DSM-III bipolar disorder, manic episode (plus 1 prior), no serious risk of suicide.	Male: 49% White: 92% Mean age: 38.7-40.3yr	Divalproex – serum trough concentration valproate 71-125µg/ml versus lithium – serum trough concentration 0.8-1.2mmol/L versus placebo	**Primary outcome:** **Time to manic/depressive episode:** Divalproex versus placebo: Wilcoxon χ^2_1= 0.95, p=0.33 Lithium versus placebo: Wilcoxon χ^2_1= 1.03, p=0.31 Divalproex versus lithium: Wilcoxon χ^2_1= 3.54, p=0.06.

Table 1B. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes* (treatment versus placebo)
15, 32	Randomised, double-blind, 52wk study (4wk double-blind taper phase + 48wk double-blind monotherapy phase) (following 6-12wks open-label phase) Conducted in 87 sites in Europe, Canada, S Africa, Israel, Australia, New Zealand.	Open-label phase, n=543. Randomised for double-blind study: olanzapine n=217, lithium n=214. Completed: Olanzapine 47%, lithium 33%.	Age ≥18yr DSM-IV bipolar disorder, manic or mixed episode, YMRS score ≥20, no serious risk of suicide.	Male: 47.1% White: 99.3% Mean age: 42yr Current episode manic versus mixed: 94% versus 6% History not rapid cycling versus rapid cycling: 97% versus 3%	Olanzapine 5-20mg/day versus lithium – target blood level 0.6-1.2meq/L	**Primary outcome:** **Symptomatic relapse/recurrence**:** Olanzapine versus lithium: 30% versus 38.8%; Fisher's exact p 0.055; OR 1.5 (1.0 to 2.2); 8.8% absolute risk reduction (-0.1% to 17.8%) **Time to symptomatic relapse**:** Log-rank χ^2= 3.4, df=1, p=0.07

df= degrees of freedom; DSM-III= Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HR: Hazard ratio; ITT= Intention to treat; MADRS= Montgomery-Asberg Depression Rating Scale; OR= Odds ratio; *= Refer to corresponding references for additional secondary outcomes; †= Last observation carried forward (LOCF); §= Symptomatic relapse into any mood episode defined as a YMRS total score ≥15, Hamilton Depression Rating Scale (HAM-D) score <15, or hospitalisation for a manic, mixed or depressive episode; ¶= Median time; **= defined by YMRS and/or HAM-D score ≥15.