Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aripiprazole

Proprietary Product Name: Abilify

Sponsor: Bristol-Myers Squibb Pharmaceuticals Pty Ltd

April 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	3 March 2011
Active ingredient(s):	Aripiprazole
Product Name(s):	Abilify
Sponsor's Name and Address:	Bristol-Myers Squibb Pty Ltd 556 Princes Highway Noble Park Vic 3174
Dose form(s):	Abilify: Tablets Abilify ODT: Oral Disintegrating Tablets
Strength(s):	Abilify: 2, 5, 10, 15, 20 and 30 mg Abilify ODT: 10, 15, 20 and 30 mg
Container(s):	Abilify, Abilify ODT: aluminium blisters in cartons
Pack size(s):	Abilify, Abilify ODT: pack of 30
Approved Therapeutic use:	For the Tablet and Oral Disintegrating Tablet presentations: Abilify is indicated for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy. Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate; Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy.
Route(s) of administration:	Abilify, Abilify ODT: oral
Dosage:	15 – 30 mg daily
ARTG Number (s):	90925, 90997, 90998, 90999, 91000, 91001, 128893, 128898, 128903, 128904

Product Background

This AusPAR describes the evaluation of a proposed extension of indications for Abilify (aripiprazole) to include treatment of patients with Bipolar I disorder, manic or mixed, at starting doses of 15 mg as monotherapy or in combination with lithium or valproate.

Aripiprazole is an atypical antipsychotic medication. It was registered in 2003 for the treatment of schizophrenia. It has been proposed that the efficacy of aripiprazole in the treatment of schizophrenia is mediated through a combination of partial agonist activity at

dopamine D_2 and serotonin $5HT_{1A}$-receptors and antagonist activity at serotonin $5HT_{2A}$-receptors.

In recent years the indications for other atypical antipsychotic medications have been extended to include treatment of aspects of Bipolar I Disorder, including treatment of acute mania and mixed episodes, prevention of relapse or recurrence and maintenance of effect. These medicines have indications that allow for monotherapy and/ or combination therapy with lithium or valproate. Other atypical antipsychotics with indications in Bipolar I Disorder include olanzapine, quetiapine, risperidone, zuclopenthixol and ziprasidone.

A previous submission for monotherapy treatment of acute mania in Bipolar I Disorder with aripiprazole was rejected after a negative recommendation from the Australian Drug Evaluation Committee (ADEC). At its 244th meeting in February 2006 the Committee considered that the evidence of efficacy rested on the acute short-term placebo-controlled trials. In view of these trials' lack of active comparator as well as the fact that evidence from the longer term active comparator study was lacking, given that the high dose of haloperidol (used in that study) may have biased the results in favour of aripiprazole, there was considered to be insufficient evidence of efficacy in the population in which this drug is intended to be used to recommend approval.

This current submission relies on studies previously submitted in that application and three new safety and efficacy studies. The proposed indication is broader, including acute and maintenance treatment, the addition of a claim for efficacy in episodes with and without psychotic features and a claim for adjuvant treatment with lithium or valproate for both acute and maintenance treatment.

The proposed Indications are:

Abilify monotherapy is indicated for acute and maintenance treatment of manic and mixed episodes with Bipolar I Disorder with or without psychotic features.

Abilify is indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features.

Regulatory Status

The product received initial ARTG Registration on 2003.

An application for use in Bipolar I disorder was approved in the US in September 2004, the European Union (EU) in March 2008, Switzerland in October 2008 and New Zealand in September 2010. In Canada, acute use was approved in July 2009.

There is some variation in the Bipolar I Disorder indication: In the EU the indication is for acute mania (monotherapy or combination therapy) and recurrence prevention of manic episodes in Bipolar I Disorder (in those who experience predominantly manic episodes) while in the USA the indication is for acute manic or mixed episodes (monotherapy or combination therapy) and maintenance treatment of Bipolar I Disorder.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

In this application the sponsor has submitted the same studies as submitted in the previous application as well as data from three new studies. The new studies are as follows:

CN138134 – Efficacy of aripiprazole in combination with valproate or lithium in the treatment of mania in patients with Bipolar I Disorder partially nonresponsive to valproate or lithium monotherapy.

CN138135 – A multicentre, randomised, double-blind, placebo-controlled study of aripiprazole monotherapy in the treatment of acutely manic patients with Bipolar I Disorder.

CN138162 – A multicentre, randomised, double-blind, placebo-controlled study of aripiprazole monotherapy in the treatment of acutely manic patients with Bipolar I Disorder.

The following studies that were previously evaluated by the TGA were also submitted:

- three double-blind three-week placebo-controlled studies (fixed-dose ***CN138007***, and flexible-dose ***CN138009*** and ***CN138074***)
- two flexible-dose 12-week double-blind studies with a 3 week placebo-controlled phase and an additional nine week active-controlled phase (***CN138135*** and ***CN138162***, with active-control groups of lithium and haloperidol, respectively).
- A flexible-dose 12-week double-blind haloperidol-controlled study with a 14-week extension phase (***CN138008***)
- A flexible-dose six-week double-blind, placebo-controlled combination study of aripiprazole with lithium or valproate (***CN138134***) with an ongoing 46-week open-label extension phase
- A flexible-dose, 26-week, double-blind, placebo-substitution maintenance treatment study (***CN138010***) for the prevention of recurrence, with a 74-week, double-blind, placebo-controlled, extension phase
- An open-label, flexible-dose, uncontrolled extension study (***CN138037***).

Studies CN138062 and CN138077 are bipolar mania studies that were terminated early (very few patients were enrolled in these studies by the time they were terminated). The safety data from these two studies are part of safety database, but no efficacy data were submitted.

Studies CN138096 and CN138146 were also submitted; however these studies were conducted in patients with depressive episodes and therefore are not directly relevant to the proposed extension of indication. These studies will not be discussed in this evaluation report.

In addition, safety data only from the open-label phases of two ongoing combination maintenance treatment studies, a flexible-dose study of aripiprazole with lithium or valproate (CN138189) and a flexible-dose study of aripiprazole with lamotrigine (CN138392) were included in the dataset.

Pharmacokinetics/Pharmacodynamics

No new pharmacokinetic/pharmacodynamic data were submitted.

Efficacy

Main (pivotal) studies

Study CN138135 – Acute treatment and maintenance of effect

This was a multicentre, randomised, double-blind, placebo-controlled and active-controlled flexible-dose study with three parallel treatment groups. Patients requiring inpatient hospitalisation were randomly assigned to receive either aripiprazole (starting dose of 15 mg/day with an option to increase to 30 mg/day on Day 4 or beyond), placebo, or lithium (starting dose of 900 mg/day with option to increase to 1200 mg/day at Day 4 and 1500 mg/day at Day 7) in a 1:1:1 ratio, for three weeks, and either double-blind aripiprazole or lithium for an additional 9 weeks. At any time during the study, the patient's aripiprazole or lithium dose could be decreased for tolerability reasons. Patients randomised to placebo were blindly switched to receive aripiprazole treatment at the end of Week 3 (these patients were not included in the maintenance of effect analyses). All patients continuing in the study were expected to be discharged from the hospital as of Week 3. Patients completing 12 weeks of double-blind study medication had the option to continue on blinded study medication (aripiprazole or lithium) for an additional extension phase of 40 weeks. The extension phase is currently ongoing. There were 715 patients enrolled at 48 study centres in the US from 20 April 2004 through 17 July 2006. The study was conducted according to Good Clinical Practice (GCP) guidelines. There were no major protocol amendments.

Objectives

The primary objective was to evaluate the efficacy of aripiprazole monotherapy as acute and maintenance therapy for the treatment of acutely manic patients with Bipolar I Disorder, manic or mixed.

The secondary objective was to evaluate the safety and tolerability of aripiprazole in this same patient population.

Study participants

The population in this study included male and female hospitalised patients ≥ 18 years of age, who had Bipolar I Disorder and displayed an acute manic or mixed episode, with or without psychotic features, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).

The main inclusion criteria were as follows:

- Patients with Bipolar I Disorder, manic or mixed episode with or without psychotic features, as defined by DSM-IV-TR and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I).
- Patients with a history of at least one previous manic or mixed episode of sufficient severity to require hospitalisation, and/or treatment with a mood stabiliser or antipsychotic agent;
- Patients with a Y-MRS Total Score ≥ 20 at screening and at the end of Phase 1 (baseline) with less than a 25% decrease between these two visits[1]
- Patients with a MADRS Total Score ≤ 17 at the end of Phase 1 (baseline), with no more than a 4-point increase between screening and baseline, with measurements at least two days apart[1]

[1] For more information on these scores, see next page.

- Women of childbearing potential (WOCBP) must have been using an adequate method of contraception to avoid pregnancy throughout the study and for up to four weeks after completion of the study in such a manner that the risk of pregnancy was minimised.

There was an extensive list of exclusion criteria.

Treatments

Aripiprazole was initiated on Day 1 (after baseline assessments) at 15 mg/day once a day (qd) with the option to increase to 30 mg/day on Day 4 or beyond. Lithium was initiated at 900 mg/day in divided doses (3 times a day [tds]) with the option to increase to 1200 mg/day at Day 4, and 1500 mg/day at Day 7.

Study medication dose increases and decreases could occur as follows:

- The patient's dose could be increased starting at Day 4 and again from Day 7 onward, for efficacy reasons. If a dose increase was warranted, both the capsules and tablets were to be increased at the same time unless the maximum dose had already been reached (2 tablets/5 capsules)
- At any time during the study, the patient's dose could be decreased for tolerability reasons. If a dose decrease was warranted, both the capsules and tablets were to be decreased at the same time unless the minimum dose had already been reached (1 tablets/3 capsules)
- Lithium dosing may have been increased or decreased at any time during the study based on lithium level results. In these cases, if a dose increase or decrease was warranted only the lithium dosing (capsules) was adjusted.

Outcomes/endpoints

The following outcome measures were used:

Young-Mania Rating Scale (Y-MRS): The Y-MRS consists of 11 items assessing the core symptoms of mania. Patients were rated on this scale at Screening, Baseline visits, and at each assessment during Double-blind Treatment Phase to evaluate patients for the emergence of manic symptomatology. The Y-MRS was the first efficacy evaluation performed at the baseline visit.

Montgomery Asberg Depression Rating Scale (MADRS): The MADRS was used as the primary assessment of a patient's level of depressive symptoms and was administered using a structured interview guide. Detailed instructions for administration of the structured interview guide were provided. This scale consists of 10 items each with 7 defined grades of severity.

Clinical Global Impression - Bipolar Version (CGI-BP): Patients were rated on Severity of Illness, Depression, Mania and Overall Bipolar Illness items, and Change from Preceding Phase, Depression, Mania and Overall Bipolar Illness items; these are 7-point scales. Severity of Illness was rated at the Baseline visit and at each weekly study visit after randomisation. The Change from Preceding Phase was rated at each visit in the Double-blind Treatment Phase, with respect to the patient's condition at the baseline visit beginning at Day 4.

Positive and Negative Syndrome Scale (PANSS): An experienced rater administered the PANSS. Scores for this scale were entered directly onto the form, which served as the source document. Patients were rated on this scale at Baseline and at Week 3 and Week 12/Early Termination during the Double-blind Treatment Phase. This scale consists of a Positive Scale (7 positive symptom constructs), a Negative Scale (7 negative symptom constructs), and a

General Psychopathology Scale (16 symptom constructs). Subscales of interest were the Hostility Subscale and the Cognitive Subscale.

The primary efficacy endpoint was the mean change from baseline to Week 3 (using Last Observation Carried Forward [LOCF] methodology) in Y-MRS Total Score. This was evaluated by analysis of covariance (ANCOVA). The model included the baseline measurement as covariate and treatment and study centre as main effects. The overall alpha level for testing that both aripiprazole and lithium were statistically significantly different from placebo was 0.05. This was accomplished by hierarchically testing the hypotheses at the 0.05 level. The mean change from baseline in Y-MRS Total score at Week 3 was first to be compared between aripiprazole and placebo using an alpha level of 0.05. If aripiprazole was statistically significantly different from placebo, lithium was to be compared to placebo at the alpha level of 0.05.

A hierarchical testing procedure was used for the comparison between aripiprazole and placebo of the key secondary efficacy outcome measure, mean change from baseline to Week 3 (LOCF) in CGI-BP Severity of Illness score (mania), in order to keep the overall experiment-wise Type I error at 0.05. If the difference between aripiprazole and placebo in the primary efficacy measure was statistically significant ($p \geq 0.05$), the difference between lithium and placebo in mean change from baseline in Y-MRS Total Score at Week 3 (LOCF) was tested. If that difference was also statistically significant ($p \geq 0.05$) then testing of the difference between aripiprazole and placebo in mean change from baseline to Week 3 (LOCF) in CGI-BP Severity of Illness score (mania) proceeded at alpha = 0.05.

Maintenance of effect was evaluated by comparing the originally randomised aripiprazole treatment group and the lithium treatment group during the 12-Week Double-blind Treatment Phase using the Efficacy Sample. For the Week 3 Responder Sample, differences between the estimated treatment means and corresponding 95% CIs were presented at all time points for the continuous outcome measures, using the LOCF and the Observed Case (OC) data sets. Percent remitters, percent responders, CGI Change from Preceding Phase response rate, and percentage of patients on treatment and in response, were evaluated for the Week 3 Responder Sample at all time points using the LOCF and OC data sets.

In order to further assess the comparability of the aripiprazole and the lithium treatment group up to and including Week 12, the mean change from baseline in Y-MRS Total Score was analysed using the Per Protocol Sample on both the OC and LOCF data sets.

The ANCOVA model included the baseline measure as covariate and treatment as main effect; it, however, did not include a term for centre effect for the Per Protocol Sample. To corroborate the results of the LOCF and the OC analyses, a longitudinal analysis using direct likelihood estimation was performed on the mean change from baseline in Y-MRS Total Score up to Week 12, using the OC data set and including only the aripiprazole and lithium treatment group.

The interaction between treatment and presence/absence of psychotic features at baseline were assessed for the mean change from baseline in Y-MRS Total Score at Week 12 (LOCF) and separately for the mean change from baseline in CGI-BP Severity (mania) at Week 12 (LOCF). This was done using an ANCOVA model including baseline as covariate, treatment and presence/absence of psychotic features as main effects, and the treatment by presence/absence of psychotic features interaction term. A subgroup analysis by presence/absence of psychotic symptoms at baseline was performed on the mean change from baseline in Y-MRS Total Score at Week 12 (LOCF) and on the mean change from baseline in

CGI-BP Severity (mania) at Week 12 (LOCF). The analysis was performed per subgroup using ANCOVA with baseline as covariate and treatment as main effect.

Other Secondary Efficacy Endpoints

Other secondary efficacy outcome measures for the 3-Week and the 12-Week Double-blind Treatment Phases were as follows:

- Mean change from baseline in Y-MRS Total Score
- Response Rate on the Y-MRS Total Score (response was defined as ≥ 50% improvement from baseline in Y-MRS Total Score)
- Percent Remitters on the Y-MRS Total Score (remission was defined as Y-MRS Total score ≥ 12)
- Percentage of patients achieving Response or Remission on the Y-MRS Total Score
- Percentage of patients in response on the Y-MRS Total Score who did not discontinue at or before Week 12
- Mean change from baseline in the CGI-BP Severity of Illness score (mania)
- Mean change from baseline in the CGI-BP Severity of Illness score (depression)
- Mean change from baseline in the CGI-BP Severity of Illness score (overall)
- Mean CGI-BP Change from Preceding Phase Score (mania)
- Response Rate on the CGI-BP Change from Preceding Phase Score (mania) (response is defined as “much” or “very much” improved from baseline)
- Mean CGI-BP Change from Preceding Phase Score (depression)
- Mean CGI-BP Change from Preceding Phase Score (overall)
- Mean change from baseline in PANSS Total Score
- Mean change from baseline in PANSS Positive Subscale Score
- Mean change from baseline in PANSS Negative Subscale Score
- Mean change from baseline in PANSS Cognitive Subscale Scores
- Mean change from baseline in PANSS Hostility Subscale Score
- Mean change from baseline in MADRS Total Score
- Time from randomisation to discontinuation due to lack of efficacy, defined as discontinuation due to manic, depressive or mixed symptoms.
- Time from randomisation to discontinuation due to any reason
- Time from randomisation to remission of mania (first occurrence of Y-MRS Total Score ≤ 12 during 12-week study phase)
- Time from randomisation to remission of mania and depression (first occurrence of Y-MRS Total Score ≤ 12 and MADRS Total Score ≥ 8 at the same observation during 12-week study phase)
- Incidence of emergent depression within the first three weeks as defined by a MADRS Total Score ≥ 18 with an increase from baseline ≥ 4 at any two consecutive

assessments within first three weeks or at the last observation within the first three weeks

- Incidence of emergent depression within the 12-Week study phase, defined as a MADRS Total Score ≥ 18 with an increase from baseline ≥ 4 at any two consecutive assessments within the 12-week study phase or at last observation within the 12-week study phase

Sample size

The mean change from baseline in Y-MRS Total Score at Week 3 was first compared between aripiprazole and placebo. The study was powered at 95% to detect a difference of 5.5 in the mean change from baseline in Y-MRS at Week 3 between aripiprazole and placebo, using an alpha level of 0.05. If aripiprazole was statistically significantly different from placebo, lithium was compared to placebo at the alpha level of 0.05. The sample size of 156 patients per treatment group yielded 90% power to detect a difference of 5.5 in the mean change from baseline in Y-MRS at Week 3 between lithium and placebo. The power of 90% was calculated as the product of the power of the individual tests, that is, under the assumption of independence. The above calculations assumed a standard deviation of 13.4 and the use of a 2-sided t-test for the difference between aripiprazole and placebo, and between lithium and placebo.

Randomisation

After written informed consent had been obtained, the investigator or designated site personnel enrolled the patient in the study by accessing the call-in interactive voice response system (IVRS), and a patient number was assigned. At the end of screening, the investigator or designated site personnel again accessed the IVRS, and patients were randomised to receive either aripiprazole, placebo, or lithium. Treatment assignments were governed by a fixed block randomisation schedule designed to allocate patients between the three treatment arms in a 1:1:1 ratio. Within each centre, approximately equal numbers of patients were to be assigned to each treatment group

Statistical methods

This study had three parallel arms up to and including Week 3. After Week 3, the patients who were randomised to placebo received aripiprazole as study medication. The results for the 12-Week Treatment Phase were tabulated for:

1) All time points up to and including Week 3 results per treatment group for all three treatment groups.

2) Week 4 to Week 12 results for the aripiprazole treatment group (only patients originally randomised to aripiprazole) and the lithium treatment group.

The patients randomised to placebo were not included in the tables for the results beyond Week 3; instead, separate tables were presented for the placebo treatment group to summarise the results after reassignment to aripiprazole.

For time points up to and including Week 3, comparisons were focused on aripiprazole versus placebo and lithium versus placebo (p-values were provided for these comparisons). The evaluation of maintenance of effect was based on the comparison of aripiprazole versus lithium at all time points during the 12-week double-blind phase. No p-values were provided for the efficacy comparisons of aripiprazole versus lithium, however, 95% Confidence Intervals (CI) for the treatment differences were given.

The following datasets were used in this study and were defined as follows:

- The Enrolled Sample comprised all patients who signed informed consent
- The Randomised Sample comprised all patients who were randomized to treatment
- The Safety Sample comprised all patients in the Randomised Sample who took at least one dose of study medication, as indicated on the study therapy form
- The Efficacy Sample comprised all patients who were in the Safety Sample and had at least one efficacy evaluation after the start of study drug
- The Week 3 Responder Sample comprised all patients who were randomised to aripiprazole or lithium and were on study and in response (decrease in Y-MRS Total Score of ≥ 50%) at Week 3 and had an efficacy evaluation beyond Week 3
- The Per Protocol Sample was a subset of the Efficacy Sample and excluded patients/efficacy ratings due to any of the following:
    - Patients without mood stabiliser levels prior to randomisation or exclusionary detectable mood stabiliser levels at the last measurement prior to randomisation, that is, ≥0.15 mmol/L lithium, ≥ 3.0 µg/mL valproic acid, ≥ 0.5 µg/mL carbamazepine, or≥ 2.0 µg/ml oxcarbazepine or without available results for levels of lithium, valproic acid, carbamazepine or oxcarbazepine prior to randomisation (protocol deviation)
    - Patients who started study drug within 30 days after taking fluoxetine or Symbyax (fluoxetine/olanzapine) or within 14 days after other antidepressants (protocol deviation)
    - Patients with a Y-MRS Total score of < 20 at screening or baseline (protocol deviation)
    - Patients with ≥ 25% decrease in Y-MRS Total score between screening and baseline (protocol deviation)
    - Patients with MADRS Total score ≥ 18 at baseline (protocol deviation)
    - Patients with > 4 point increase in MADRS Total Score between screening and baseline (protocol deviation)
    - Patients with < 4 days of study medication

In addition it excluded:

- Y-MRS efficacy ratings within 8 hours after benzodiazepine use (protocol deviation)
- All Y-MRS efficacy ratings at all time points after a positive cocaine test result
- All Y-MRS efficacy ratings at all time points after receiving the wrong study medication (that is, medication different from the randomised treatment)
- The Outcomes Research Sample comprised all patients in the Safety Sample who had at least one outcomes research evaluation after the start of study drug.
- The Placebo-to-Aripiprazole Sample comprised all patients in the placebo treatment group who received at least 1 dose of aripiprazole medication.

Results

Participant flow

Of the 715 patients enrolled, 480 were randomised to the 3 groups; 165 to placebo, 160 to lithium, and 155 to aripiprazole. Of the 480 randomised patients, 251 (52.3%) discontinued from the study prior to the end of Week 3. The incidence of discontinuations was similar in the 3 groups with approximately 50% of the patients in each group discontinuing prior to end of Week 3. The most frequently reported reason for discontinuation prior to the end of Week 3 in the aripiprazole group and the lithium group was withdrawal of consent (32 patients [20.6%] and 28 patients [17.5%], respectively), compared with 25 (15.2%) in the placebo group, whereas in the placebo group it was lack of efficacy (36 [21.8%] patients) versus 26 (16.3%) in the lithium group and 9 (5.8%) in the aripiprazole group. In all, 56 (11.7%) patients discontinued because of adverse events (AEs) prior to end of Week 3, 23 (14.8%) in the aripiprazole group, 20 (12.5%) in the lithium group, and 13 (7.9%) in the placebo group.

A total of 229 (47.7%) patients completed Week 3 and the percentage of patients that completed Week 3 was similar in the 3 groups (47% - 49%). Eighty-six (17.9%) patients discontinued after end of Week 3: 31 (20.0%) in the aripiprazole group, 24 (15.0%) in the lithium group, and 31 (18.8%) who were randomised to placebo and were blindly switched to aripiprazole after Week 3. For patients who discontinued treatment beyond Week 3, the most frequently reported reason for discontinuation was AE (29 [6.0%] patients): 8 (5.2%) patients in the aripiprazole group, 8 (5.0%) patients in the lithium group, and 13 (7.9%) patients who were randomised to placebo and were blindly switched to aripiprazole after Week 3.

A total of 143 (29.8%) patients completed the 12-week double-blind phase of the study: 42 (27.1%) patients in the aripiprazole group, 54 (33.8%) patients in the lithium group, and 47 (28.5%) patients who were randomised to placebo and were switched to aripiprazole after Week 3.

Of the 95 patients in the Week-3 Responder Sample, 44 were in the aripiprazole group and 51 were in the lithium group. From these 95 responders, 33 (34.7%) patients discontinued from the study after Week 3: 19 (43.2%) patients in the aripiprazole group and 14 (27.5%) patients in the lithium group. The most frequently reported reason for discontinuation after Week 3 was an AE (15 [15.8%] patients): 7 (15.9%) patients in the aripiprazole group and 8 (15.7%) patients in the lithium group.

Of the patients in the Week 3 Responder Sample, 62 (65.3%) completed the 12-week double-blind phase: 25 (56.8%) patients in the aripiprazole group and 37 (72.5%) patients in the lithium group. For the patients who discontinued prior to end of Week 3, the most frequently reported mood symptoms as reason for discontinuation were manic symptoms (57 [11.9%] patients); 9 (5.8%) patients in the aripiprazole group, 21 (13.1%) patients in the lithium group, and 27 (16.4%) patients in the placebo group. Mixed symptoms were reported for 32 (6.7%) patients: 5 (3.2%) in the aripiprazole group, 12 (7.5%) patients in the lithium group, and 15 (9.1%) in the placebo group. Depressive symptoms were reported for 10 (2.1%) patients: 5 (3.2%) patients in the aripiprazole group, 2 (1.3%) patients in the lithium group, and 3 (1.8%) in the placebo group.

Baseline data

The mean age of the randomised patients was 39.7 years. Fifty-two percent of the patients were male and 66% were White. The demographic characteristics of the randomised patients were similar among the 3 treatment groups. For the Week 3 Responder Sample the demography was not notably different from that of the total randomised population or when comparing the individual treatment groups.

Patients had a DMS-IV-TR diagnosis of Bipolar I Disorder (manic [61%] or mixed [39%]); 23% had experienced psychotic symptoms at baseline and the distribution of those with

manic or mixed symptoms and the presence of psychotic symptoms was similar in the 3 treatment groups. The mean age of the onset of manic or mixed symptoms was 21.6 years and the mean age of the onset of depressive symptoms was 20.4 years; the mean age of onset of manic or mixed and depressive symptoms was similar in the 3 treatment groups. The 3 treatment groups were similar with respect to the other baseline psychiatric evaluations. The baseline psychiatric evaluation of the Week 3 Responder Sample was similar to the randomised population.

Outcomes

A summary of the main efficacy results from study CN138135 at Week 3 and Week 12 is provided in Table 1.

Overall summary of efficacy at Week 3

For the primary efficacy endpoint, the mean change from baseline to Week 3 in the Y-MRS Total Score (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference = -3.63 [95% CI -5.75, -1.51], p <0.001), as did the lithium group (treatment difference = -3.03 [95% CI -5.13, -0.92], p = 0.005).

For the key secondary efficacy endpoint, the mean change from baseline to Week 3 in CGI-BP Severity of Illness Score (mania) (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference = -0.43 [95% CI -0.70, -0.15], p = 0.002), as did the lithium group (treatment difference = -0.28 [95% CI -0.56, -0.01], p = 0.041). A statistically significantly greater percentage of aripiprazole-treated patients (46.8%) than placebo-treated patients (34.4%) showed response on the Y-MRS score (p = 0.036); the same was true for lithium-treated patients (45.8%) compared with placebo-treated patients (p = 0.032). A statistically significantly greater percentage of aripiprazole-treated patients (40.3%) than placebo-treated patients (28.2%) showed remission on the Y-MRS (p = 0.037) at Week 3; the same was true for lithium-treated patients (40.0%) compared with placebo-treated patients (p = 0.024).

The mean change from baseline to Week 3 in CGI-BP Severity of Illness Score (depression) (LOCF) was not statistically significantly different for either aripiprazole or lithium treatment versus placebo. The treatment differences between the aripiprazole and placebo groups in the mean change from baseline to Week 3 in CGI-BP Severity of Illness Score, overall (LOCF), was statistically significant in favour of the aripiprazole group (p < 0.001); the treatment difference between the lithium and placebo groups was not significant.

Table 1: CN138135 - Key efficacy results

	Placebo	Lithium	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 163	N = 155	N = 154
Mean Baseline	28.90	29.22	28.53
Mean Change at Week 3 (LOCF)	-9.01	-12.03**	-12.64**
Key Secondary Efficacy Measure			
CGI-BP Severity of Illness (mania) Score	N = 162	N = 154	N = 153
Mean Baseline	4.60	4.54	4.55
Mean Change at Week 3 (LOCF)	-1.06	-1.34*	-1.48**
Other Secondary Efficacy Measure at Week 3			
Response Rate (LOCF)	N = 163	N = 155	N = 154
Number of Responders[a] at Week 3 (%)	56 (34.4)	71 (45.8)	72 (46.8)
Ratio of Response Rates vs Placebo	--	1.33*	1.31*
Secondary Efficacy Measures at Week 12			
Y-MRS Total Score	--	N = 155	N = 154
Mean Baseline	--	29.22	28.53
Mean Change at Week 12 (LOCF)	--	-12.71	-14.48
Treatment Difference[b] (95% CI)			-1.78 (-4.02, 0.47)
CGI-BP Severity of Illness (mania) Score		N = 154	N = 153
Mean Baseline	--	4.54	4.55
Mean Change at Week 12 (LOCF)	--	-1.53	-1.70
Treatment Difference[b] (95% CI)			-0.18 (-0.47, 0.12)
Response Rate (LOCF)		N = 155	N = 154
Number of Responders[a] at Week 12 (%)	--	76 (49.0)	87 (56.5)
Ratio of Response Rates vs lithium (95% CI)			1.13 (0.92, 1.39)

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-lithium.

There was a statistically significantly greater percentage of aripiprazole-treated patients than placebo-treated patients in response at Week 3 on the CGI-BP Change from Preceding Phase (mania) Score ($p = 0.010$), but not lithium-treated patients ($p = 0.381$). At Week 3, the mean CGI-BP Change from Preceding Phase (depression) Score (LOCF) was not statistically significantly different for either the aripiprazole or lithium groups compared with the placebo group (Table 2); however, the treatment difference between the aripiprazole and placebo groups was statistically significant in favour of aripiprazole in the mean CGI-BP Change from Preceding Phase Scores, overall and mania, (LOCF).

Table 2: Mean Change from Baseline to Week 3 on CGI-BP Severity of Illness (Depression) Score: (CN138007, CN138009, CN138074, CN138135, CN138162), LOCF Data Set, Efficacy Sample

	CGI-BP Severity of Illness (Depression) Score[a]				
Protocol/ Treatment	N	Mean Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138007					
Placebo	129	2.45	-0.31	--	--
Aripiprazole 15 mg	125	2.51	-0.43	-0.12 (-0.36, 0.11)	0.308
Aripiprazole 30 mg	128	2.27	-0.53	-0.23 (-0.46, 0.01)	0.060
CN138009					
Placebo	122	2.35	0.07	--	--
Aripiprazole 30 mg to 15 mg	124	2.11	-0.24	-0.31 (-0.58, -0.04)	0.026
CN138074					
Placebo	129	2.59	-0.31	--	--
Aripiprazole 30 mg to 15 mg	135	2.66	-0.60	-0.30 (-0.56, -0.03)	0.026
CN138135					
Placebo	162	2.25	-0.17	--	
Aripiprazole 15 mg to 30 mg	153	2.25	-0.34	-0.17 (-0.39, 0.05)	0.137
Lithium	154	2.26	-0.22	-0.05 (-0.27, 0.17)	0.655
CN138162					
Placebo	151	1.54	-0.18	--	
Aripiprazole 15 mg to 30 mg	166	1.66	-0.12	0.06 (-0.07, 0.20)	0.362
Haloperidol	161	1.54	-0.11	0.08 (-0.06, 0.22)	0.268

[a] CGI-BP Severity of Illness (depression) Score ranges from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.

ANOVA model, controlling for treatment is used for baseline.

ANCOVA model, controlling for treatment and baseline value is used for mean change from baseline. Means, differences in means, 95% CI for the differences, and p-values are based on the ANOVA/ANCOVA model.

The treatment difference on the mean change from baseline to Week 3 in the MADRS Total Score (LOCF) was not statistically significantly different for either the aripiprazole or the lithium groups compared with the placebo group (Table 3). However, in the aripiprazole-treated patients there was no indication of worsening of depression symptoms.

The treatment differences between the aripiprazole group and the placebo group were statistically significant in favour of the aripiprazole group in the mean change from baseline to Week 3 in the PANSS Total Score (p = 0.011), Positive Subscale Score (p = 0.006), Negative Subscale Score (p = 0.021), Cognitive Subscale Score (p = 0.026), and Hostility Subscale Score (p = 0.006). The lithium group showed a significant treatment difference compared with the placebo group only on the PANSS Positive Subscale Score (p = 0.047).

During the first 3 weeks, the time to discontinuation for any reason was not statistically significantly different for either the aripiprazole group or the lithium group compared with the placebo group; approximately 50% of the patients in each group discontinued before the end of Week 3. The time to discontinuation for lack of efficacy based on the evaluation of the mood status at study discontinuation was statistically significantly longer for aripiprazole

treatment than placebo ($p < 0.001$), but not for lithium treatment ($p = 0.182$). The percentage of patients discontinuing with presence of mood symptoms (manic, mixed, or depressed) at study discontinuation up to the end of Week 3 was: aripiprazole, 11.7%; lithium, 22.6%, and placebo, 27.6%.

Table 3: Mean Change from Baseline to Week 3 in MADRS Total Score: (CN138007, CN138009, CN138074, CN138135, CN138162), LOCF Data Set, Efficacy Sample

	MADRS Total Score[a]				
Protocol/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138007[b]					
Placebo	87	14.50	-3.32	--	--
Aripiprazole 15 mg	102	16.26	-3.07	0.24 (-2.15, 2.64)	0.841
Aripiprazole 30 mg	94	14.97	-5.32	-2.00 (-4.41, 0.41)	0.103
CN138009[b]					
Placebo	79	14.26	-1.20	--	--
Aripiprazole 30 mg to 15 mg	99	13.80	-1.30	-0.10 (-2.38, 2.19)	0.934
CN138074					
Placebo	127	15.44	-3.02	--	--
Aripiprazole 30 mg to 15 mg	132	14.93	-4.33	-1.31 (-3.24, 0.62)	0.183
CN138135					
Placebo	163	11.39	-0.68	--	
Aripiprazole 15 mg to 30 mg	154	11.30	-2.12	-1.44 (-2.96, 0.08)	0.063
Lithium	155	11.35	-1.10	-0.41 (-1.92, 1.10)	0.590
CN138162					
Placebo	152	8.11	-2.09	--	
Aripiprazole 15 mg to 30 mg	166	8.34	-1.78	0.31 (-0.67, 1.28)	0.537
Haloperidol	161	8.14	-2.51	-0.42 (-1.40, 0.55)	0.395

[a] MADRS Total Score is from 0 to 60. A negative change score signifies improvement.

[b] Patients who received open-label rescue treatment in these studies, were not evaluated on the MADRS during the double-blind phase and therefore are not part of this analysis

ANOVA model controlling for treatment is used for baseline value in CN138007 and CN138009. ANOVA model, controlling for treatment and center, is used for baseline value in CN138074, CN138135 and CN138162. ANCOVA model, controlling for treatment and baseline value is used for mean change from baseline in CN138007, CN138009, and for treatment, center and baseline value in CN138074, CN138135 and CN138162. Means, differences in means, 95% CI for the differences, and P-values are based on the ANOVA/ANCOVA model.

Summary of Efficacy Results at Week 12

The aripiprazole treatment benefit demonstrated at end of Week 3 was maintained at Week 12. The mean change from baseline in the Y-MRS Total Score at Week 12 for the aripiprazole group was -14.48 and -12.71 for the lithium group. The mean change from baseline to Week 12 in CGI-BP Severity of Illness (mania) Score for the aripiprazole group was -1.70 and for the lithium group it was -1.53. The response rate (RR) ($\geq$ 50% improvement from baseline on Y-MRS Total Score) at Week 12 for aripiprazole treatment

was 56.5% and 49.0% for lithium treatment; the response ratio of aripiprazole/lithium (RR) was 1.13.

The percentage of patients in remission at Week 12 for the aripiprazole group was 49.4% and for the lithium group it was 39.4%; RR = 1.24.

The percentage of patients in response at Week 12 and not discontinued in the aripiprazole group (OC data set at Week 12) was 25.3% and in the lithium group it was 27.1%; RR = 0.93. The percentage of patients in remission or response at Week 12 was similar for the aripiprazole group (56.5%) and the lithium group (50.3%); RR = 1.10. The percentage of patients with remission of mania at Week 12 was numerically higher for aripiprazole treatment (61.7%) than lithium treatment (55.5%); time to remission of mania was similar in the aripiprazole group and the lithium group - Hazard Ratio (HR) = 1.21.

The mean change from baseline to Week 12 in CGI-BP Severity of Illness Scores (depression and overall) was similar for the aripiprazole and the lithium groups. The mean CGI-BP Change from Preceding Phase (mania) Score at Week 12 was statistically significant in favour of the aripiprazole group compared with the lithium group (95% CI: -0.62, -0.02). The response rate on CGI-BP Change from Preceding Phase (mania) was similar for aripiprazole treatment (56.5%) and lithium treatment (51.3%); RR = 1.09. At Week 12, the mean CGI-BP Change from Preceding Phase (depression and overall) Scores was similar for the 2 treatment groups.

The mean change from baseline to Week 12 on the MADRS Total Score was similar for the 2 treatment groups. The rate of emergent depression up to the end of Week 12 was similar for aripiprazole treatment and lithium treatment (RR = 0.85); 18.2% of aripiprazole treated patients and 21.3% of lithium treated patients had emergent depression up to the end of Week 12. The time to remission of mania or depression was similar for aripiprazole treatment and lithium treatment (RR = 1.22); 53.2% of aripiprazole-treated patients and 48.4% of lithium-treated patients had remission of mania up to the end of Week 12.

The improvements demonstrated on the PANSS Total Score and the subscale scores (positive, negative, cognitive, and hostility) were maintained at Week 12.

The time to discontinuation for any reason was similar for the aripiprazole group and the lithium group (HR = 1.18); 81.2% of patients in the aripiprazole group and 75.5% of patients in the lithium group discontinued for any reason up to the end of Week 12. Fewer aripiprazole-treated patients (27 [17.5%]) than lithium-treated patients (39 [25.2%]) discontinued for lack of efficacy up to the end of Week 12. The difference in time to discontinuation due to lack of efficacy was similar in the 2 groups (HR = 0.73).

Longitudinal Analysis on Mean Change in Y-MRS Total Score

In CN138135, the improvement observed at Week 3 in the mean change from baseline in Y-MRS Total Score was maintained up to Week 12 by LOCF data set analyses. To corroborate the results of the LOCF analyses, a longitudinal analysis using direct likelihood estimation was performed on the mean change from baseline in Y-MRS Total Score up to Week 12, using the OC data set and including only the aripiprazole and the respective active control groups. The mean change from baseline to the end of Week 12 on the Y-MRS Total Score (longitudinal repeated measures, OC data set) was similar between the aripiprazole (-18.89) and the lithium group (-17.03) in CN138135 (95% CI: [-4.69, 0.96]).

Evaluator Comment

In study CN138135 in acutely manic patients with Bipolar I Disorder (manic or mixed), aripiprazole dosed starting at 15 mg/day with allowed titration up to 30 mg/day was

statistically significantly superior in comparison with placebo in the primary endpoint, the mean change from baseline to Week 3 (LOCF) in Y-MRS Total Score. Treatment with lithium was also statistically significantly superior to placebo for the primary endpoint. The efficacy of treatment with aripiprazole compared with placebo and also lithium compared with placebo at the end of Week 3 was corroborated by the results in the key secondary endpoint, the mean change from baseline to Week 3 (LOCF) in CGI BP Severity of Illness Score (mania). The efficacy observed at Week 3 in both the aripiprazole group and the lithium group was maintained and was similar in both groups through Week 12. The completion rates at Week 3 were similar for all treatments.

Study CN138162 – Acute treatment and maintenance of effect

Study CN138162 had an identical design to CN138135 except haloperidol was used as an active control and there was no extension phase. The starting dose of haloperidol was 5 mg/day with an option to increase to 10 mg/day and 15 mg/day. Inclusion and exclusion criteria were the same as for study CN138135. Study populations analysed were identical to those in study CN138135. There were 614 patients enrolled at 61 study centres (7 in Bulgaria, 4 in Croatia, 8 in Mexico, 3 in Peru, 16 in Russia, 5 in South Africa, and 18 in the US) from 6 December 2004 to 13 October 2006. Fifty-nine study centres randomised patients. The study was conducted according to Good Clinical Practice (GCP) guidelines. There were no major protocol amendments.

Treatments

Aripiprazole was initiated on Day 1 (after baseline assessments) at 15 mg/day qd with the option to increase to 30 mg/day on Day 4 or beyond. Haloperidol was initiated at 5 mg/day qd with the option to increase to 10 mg/day at Day 4 or beyond, and 15 mg/day at Day 7 or beyond.

Outcomes/endpoints

Endpoints assessed were the same as for study CN138135.

Sample size and statistical methods

Sample size and statistical methods used were identical to study CN138135**.**

Results

Participant flow

Of the 614 patients enrolled, 485 were randomised to the three groups; 153 to placebo, 165 to haloperidol, and 167 to aripiprazole. Of the 485 randomised patients, 129 (26.6%) discontinued from the study prior to the end of Week 3. The incidence of discontinuations was similar in the three groups. The most frequently reported reason for discontinuation prior to the end of Week 3 in the aripiprazole group was withdrawal of consent and an AE (both 8.4%); in the placebo group, this was AE (10.5%); and in the haloperidol group this was withdrawal of consent (11.5%).

A total of 356 (73.4%) patients completed Week 3 and the percentage of patients that completed Week 3 was similar in the three groups (71% - 75%). Eighty-two (16.9%) patients discontinued after end of Week 3: 31 (18.6%) in the aripiprazole group, 26 (15.8%) in the haloperidol group, and 25 (16.3%) who were randomised to placebo and were blindly switched to aripiprazole after Week 3 (placebo-to-aripiprazole group). For patients who discontinued treatment beyond Week 3, the most frequently reported reason for

discontinuation was AE: 10 (6.0%) patients in the aripiprazole group, 10 (6.1%) patients in the haloperidol group, and 9 (5.9%) in the placebo-to-aripiprazole group.

A total of 274 (56.5%) patients completed the 12-week double-blind phase of the study: 95 (56.9%) patients in the aripiprazole group, 95 (57.6%) patients in the haloperidol group, and 84 (54.9%) patients who were randomised to placebo and were switched to aripiprazole after Week 3.

Of the 134 patients in the Week-3 Responder Sample, 67 each were in the aripiprazole and in the haloperidol group. From these 134 responders, 27 (20.1%) patients discontinued from the study after Week 3: 14 (20.9%) patients in the aripiprazole group and 13 (19.4%) patients in the haloperidol group.

The most frequently reported reason for discontinuation after Week 3 was AE: 4 (6.0%) patients in the aripiprazole group and 7 (10.4%) patients in the haloperidol group. Of the patients in the Week 3 Responder Sample, 53 (79.1%) patients in the aripiprazole group and 54 (80.6%) patients in the haloperidol group completed the 12-week double-blind phase.

Baseline data

The mean age of the randomised patients was 40.8 years; 56% of the patients were female and 78% were White. The mean weight of the patients was 78.0 kg and the mean body mass index (BMI) was 27.5 kg/m^2. The majority (43%) of patients were in the BMI category of > 27. The demographic characteristics of the randomised patients were similar among the 3 treatment groups. In the Week 3 Responder Sample the demography was not notably different, except in gender (overall, 67% were female) from that of the total randomised population or when comparing the individual treatment groups.

Patients had a DMS-IV-TR diagnosis of Bipolar I Disorder (manic [81%] or mixed [19%]); 10% experienced psychotic symptoms at baseline and the distribution of those with manic or mixed symptoms and the presence of psychotic symptoms was similar in the three treatment groups. The mean age of the onset of manic or mixed symptoms was 26.9 years and the mean age of the onset of depressive symptoms was 26.6 years; the mean age of onset of manic or mixed and depressive symptoms was similar in the three treatment groups. The three treatment groups were similar with respect to the other baseline psychiatric evaluations.

The baseline psychiatric evaluation of the Week 3 Responder Sample were notably different from those of the total randomised population in the time since the start of the most recent (non-current) manic episode (Randomised Sample 687.5 days versus 3-Week Responder Sample 840.8 days). Otherwise there were no major differences between the Week 3 Responder Sample and the Randomised Sample.

Outcomes

A summary of the main efficacy results from study CN138162 at Week 3 and Week 12 is provided in Table 4.

Table 4: Key efficacy results CN138162

	Placebo	Haloperidol	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 152	N = 161	N = 166
Mean Baseline	28.82	28.01	28.35
Mean Change at Week 3 (LOCF)	-9.70	-12.83**	-11.98*
Key Secondary Efficacy Measures			
CGI-BP Severity of Illness (mania) Score	N = 151	N = 161	N = 166
Mean Baseline	4.60	4.46	4.50
Mean Change at Week 3 (LOCF)	-1.17	-1.56**	-1.44*
Other Secondary Efficacy Measure at Week 3			
Response Rate (LOCF)	N = 152	N = 161	N = 166
Number of Responders[a] at Week 3 (%)	58 (38.2)	80 (49.7)	78 (47.0)
Ratio of Response Rates vs Placebo	--	1.26	1.19
Secondary Efficacy Measures at Week 12			
Y-MRS Total Score		N = 161	N = 166
Mean Baseline	--	28.01	28.35
Mean Change at Week 12 (LOCF)	--	-17.84	-17.16
Treatment Difference[b] (95% CI)			0.68 (-1.64, 3.00)
CGI-BP Severity of Illness (mania) Score		N = 161	N = 166
Mean Baseline		4.46	4.50
Mean Change at Week 12 (LOCF)	--	-2.19	-2.11
Treatment Difference[b] (95% CI)			0.08 (-0.22, 0.37)
Response Rate		N = 161	N = 166
Number of Responders[a] at Week 12 (%)	--	119 (73.9)	120 (72.3)
Ratio of Response Rates vs haloperidol (95%CI)			1.01 (0.89, 1.14)

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-haloperidol.

Overall Summary of Efficacy at Week 3

For the primary efficacy endpoint, the mean change from baseline to Week 3 in the Y-MRS Total Score (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference = -2.28 (95% CI [-4.44, -0.11]), p = 0.039), as did the haloperidol group (treatment difference = -3.13 (95% CI [-5.31, -0.94]), p = 0.005).

For the key secondary efficacy endpoint, the mean change from baseline to Week 3 in CGI-BP Severity of Illness score (mania) (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference = -0.27 (95% CI [-0.54, -0.01], p = 0.044), as did the haloperidol group (treatment difference = -0.39 (95% CI [-0.66, -0.13], p = 0.004). The percentage of aripiprazole-treated patients who showed response on the Y-MRS score was 47.0%; however, the percentage was not statistically significantly greater than for placebo-treated patients (38.2%, p = 0.145); the same was true for haloperidol-treated patients (49.7%) compared with placebo-treated patients (p = 0.069). The percentage of aripiprazole-treated patients (44.0%) who showed remission on the Y-MRS was not statistically significantly greater than for placebo-treated patients (36.8%, p =

0.242) at Week 3; the same was true for haloperidol-treated patients (45.3%) compared with placebo-treated patients (p = 0.206).

The percentage of aripiprazole-treated patients (49.4%) who showed remission or response on the Y-MRS was also not statistically significantly greater than for the placebo-treated patients (39.5%, p = 0.095); however, the haloperidol-treated patients (52.2%) did experience statistically significantly greater remission or response rate than the placebo-treated group (p = 0.042).

The mean change from baseline to Week 3 in CGI-BP Severity of Illness Score (depression) (LOCF) was not statistically significantly different for either aripiprazole or haloperidol treatment versus placebo. The treatment difference on the mean change from baseline to Week 3 in CGI-BP Severity of Illness Scores (overall) (LOCF) was statistically significant in favour of the aripiprazole group compared to the placebo group (p = 0.043), which was the same for the haloperidol group (p = 0.010).

At Week 3, the mean CGI-BP Change from Preceding Phase (depression) Score (LOCF) was not statistically significantly different for either the aripiprazole or haloperidol groups compared with the placebo group (see Table 2); however, the treatment difference on the mean CGI-BP Change from Preceding Phase (mania and overall) Score (LOCF) was statistically significant in favour of aripiprazole and haloperidol.

At Week 3, the response rate on CGI-BP Change from Preceding Phase (mania) Score (LOCF) was not statistically significantly different for either the aripiprazole or haloperidol groups compared with placebo.

The treatment difference on the mean change from baseline to Week 3 in the MADRS Total Score (LOCF) was not statistically significantly different for either the aripiprazole or the haloperidol groups compared with the placebo group (see Table 3).

The treatment differences between both active treatment groups and the placebo group in the mean change from baseline to Week 3 on the PANSS Total Score, the Positive Subscale Score, the Cognitive Subscale Score, and the Hostility Subscale Score were statistically significant in favour of both active treatment groups. The treatment difference on the mean change from baseline to Week 3 in the PANSS Negative Subscale Score (LOCF) was not statistically significantly different for either the aripiprazole or the haloperidol groups compared with the placebo group.

During the first 3 weeks, the time to discontinuation for any reason was not statistically significantly different for either the aripiprazole group or the haloperidol group compared with the placebo group; approximately 25% of the patients in each group discontinued before the end of Week 3. The time to discontinuation for lack of efficacy based on the evaluation of the mood status at study discontinuation was statistically significantly longer for aripiprazole treatment than placebo (p = 0.022), which was also true for haloperidol treatment (p = 0.001).

In terms of onset of efficacy, there were statistically significant treatment differences in favour of aripiprazole as early as Day 2. However in this study, differences in favour of aripiprazole were not statistically significant at Day 4, Week 1, and Day 10. In CN138162, the active control group of haloperidol was superior to the placebo group starting Day 2 through Week 3, and results were statistically significant at all time points thereafter to Week 3.

<u>Summary of Efficacy Results at Week 12</u>

A summary of efficacy results at Week 12 (LOCF data set) is presented in Tables 2 (Efficacy Sample) and 3 (Week 3 Responder Sample).

The improvement observed at Week 3 in the mean change from baseline in Y-MRS Total Score (-11.98 for aripiprazole and -12.83 for haloperidol) was maintained up to Week 12 for both the haloperidol group and the aripiprazole group (LOCF). The mean change from baseline to the end of Week 12 on the Y-MRS Total Score was similar for aripiprazole (-17.16) compared with haloperidol treatment (-17.84; 95% CI [-1.64, 3.00]). The trend of improvement from Week 3 to end of Week 12 was also seen for both groups with the OC data set.

Improvement on the Y-MRS Total Score was maintained to the end of Week 12 in both the aripiprazole and the haloperidol treatment groups. The trend of improvement was also seen for both groups in the adjusted mean change from baseline up to the end of Week 12 (aripiprazole -16.73, haloperidol -19.08, 95% CI [-0.16, 4.86]) in Y-MRS Total Score, LOCF data set, for the Per Protocol Sample.

The mean change from baseline to the end of Week 12 on the Y-MRS Total Score (longitudinal repeated measures, OC data set) was similar for aripiprazole treatment (-22.32) and haloperidol treatment (-22.68; 95% CI [-1.19, 1.91].

At the end of Week 3 (LOCF), 47.0% of patients in the aripiprazole group were in response (patients with $\geq$ 50% improvement from baseline in Y-MRS Total Score) and 49.7% of patients in the haloperidol group were in response; RR = 0.94, 95% CI (0.77, 1.16). At the end of Week 12 (LOCF), the percentage increased to 72.3% in the aripiprazole group and 73.9% in the haloperidol group; RR = 1.01, 95% CI (0.89, 1.14).

At the end of Week 3 (LOCF), 44.0% of patients in the aripiprazole group were in remission (patients with a Y-MRS Total Score $\leq$ 12) and 45.3% of patients in the haloperidol group were in remission; RR = 0.97, 95% CI (0.76, 1.23). In the aripiprazole group, the remission rate increased from 44.0% at Week 3 to 69.9% at Week 12. In the haloperidol group, the remission rate also increased from 45.3% at Week 3 to 71.4% at Week 12; RR = 1.01, 95% CI (0.88, 1.15).

At the end of Week 3 (LOCF), 49.4% of patients in the aripiprazole group and 52.2% in the haloperidol group were either in response or remission; RR = 0.93. At the end of Week 12 (LOCF), the percentage of patients in response or remission increased to 72.3% in the aripiprazole group and to 74.5% in the haloperidol group; RR = 1.00.

During the 12-week double-blind treatment phase, 77.7% of patients in the aripiprazole group and 75.8% in the haloperidol group were in remission. The time to remission (defined as the time taken from start of study medication to first occurrence of a Y-MRS score $\leq$ 12) was similar in the aripiprazole group and the haloperidol group, HR = 1.07 (95% CI [0.83, 1.37]).

During the 12-week double-blind treatment phase, 42.8% of patients in the aripiprazole group and 41.0% in the haloperidol group discontinued study medication due to any reason. Time to discontinuation for any reason was similar in the aripiprazole group and the haloperidol group, HR = 1.04 (95% CI [0.74, 1.45]).

In the analysis of time to discontinuation due to lack of efficacy, 19.3% of patients in the aripiprazole group and 10.6% of patients in the haloperidol group discontinued study medication due to lack of efficacy based on mood status, HR = 1.81 (95% CI [1.01, 3.27]).

Longitudinal Analysis on Mean Change in Y-MRS Total Score

In CN138162, the improvement observed at Week 3 in the mean change from baseline in Y-MRS Total Score was maintained up to Week 12 by LOCF data set analyses. To corroborate the results of the LOCF analyses, a longitudinal analysis using direct likelihood estimation was performed on the mean change from baseline in Y-MRS Total Score up to Week 12, using the OC data set and including only the aripiprazole and the respective active control groups. The mean change from baseline to the end of Week 12 on the Y-MRS Total Score (longitudinal repeated measures, OC data set) was similar between the aripiprazole (-22.32) and the haloperidol group (-22.68) in CN138162 (95% CI: [-1.19, 1.91]).

Evaluator Comment

In acutely manic patients with Bipolar I Disorder (manic or mixed), aripiprazole, at a starting dose of 15 mg/day with allowed titration up to 30 mg/day was superior to placebo in the primary endpoint, the mean change from baseline to Week 3 (LOCF) in Y-MRS Total Score. Treatment with haloperidol was also superior to placebo for the primary endpoint. The efficacy of treatment with aripiprazole compared with placebo and also haloperidol compared with placebo at the end of Week 3 was supported by the results in the key secondary endpoint, the mean change from baseline to Week 3 (LOCF) in CGI-BP Severity of Illness Score (mania). The efficacy observed at Week 3 in both the aripiprazole group and the haloperidol group was maintained and was similar in both groups through Week 12.

Study CN138009 – Acute treatment

Study CN138009 was a 3-week, randomised, double-blind, placebo-controlled flexible-dose study in hospitalised patients with Bipolar I Disorder, manic- or mixed-type. Patients randomised to aripiprazole were started at a dose of 30 mg/day, with the option to decrease to 15 mg/day based on tolerability, and to subsequently increase to 30 mg/day based on clinical response at any time during the study. At the end of Week 2 patients with CGI-BP Change from Preceding Phase (mania) score of 4 to 7 (no change to very much worse) were dropped from the blinded placebo-controlled treatment phase and offered the option to receive open-label aripiprazole (30 mg with dose decreased to 15 mg if needed based on tolerability) for Week 3. These patients and those who completed 3 weeks of double-blind therapy were eligible to enter one of two long-term studies (CN138010 or CN138037). A total of 358 patients were enrolled at 38 centres (all in the US) from 22 March 2000 through 18 June 2001. The study was conducted according to Good Clinical Practice (GCP) guidelines. There were a number of protocol amendments.

Inclusion and exclusion criteria were similar to the two previously discussed trials.

Objectives

The primary objective was to compare the efficacy of a flexible dosing regimen of aripiprazole to placebo on the Y-MRS monotherapy in the treatment of acutely relapsed patients with Bipolar I Disorder, manic or mixed.

The secondary objective was to evaluate the safety and tolerability of aripiprazole in this same patient population.

Treatments

Patients were randomised to one of two treatment groups: aripiprazole or placebo.

Aripiprazole was given as a full dose (30 mg/day) from the first day of treatment. Patients who were unable to tolerate the initial dose were allowed to reduce the dose to 15 mg/day. At

the end of Week 2 patients with lack of clinical response were dropped from the blinded treatment phase.

Treatments were covered by a fixed randomisation schedule to allocate patients among two treatment arms in a 1:1 ratio. Within each centre equal numbers of patients were assigned to each group.

Outcomes

The primary endpoint was the mean change from baseline to Week 3 in the Y-MRS. Secondary measures were CGI-PB Severity (Mania) score at Week 3 and the rate of discontinuation due to lack of efficacy or entry into the open label aripiprazole treatment at Week 2. Additional key efficacy measures included response rate (defined as reduction of ≥ 50% in the Y-MRS Total Score at any time point) and the mean change in the PANSS scores.

Sample size

The sample size for the study was based on the Y-MRS Total Score and assumptions obtained from the literature. The study was powered at 90% to detect a difference of 5.5 between placebo and aripiprazole on the mean change from baseline to Week 3 (LOCF) in the Y-MRS Total Score. The assumed standard deviation was 13.4.

Analysis Data Sets

The LOCF data set included data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous visit. Baseline data were not carried forward or averaged with on-treatment data to impute missing values for the LOCF data set. For patients who entered the open-label aripiprazole phase CN138009, efficacy evaluations at Week 2 were carried forward for the Week 3 analysis (that is, their open-label Week 3 efficacy results were not used in the double-blind analysis). The Observed Case (OC) data set consisted of the actual observations at each visit. Efficacy analyses per time point were performed using both the LOCF and OC data sets. The LOCF data set was the primary data set for the efficacy analyses per time point. The analyses of the OC data set were considered secondary and were performed to corroborate those on the LOCF data set.

Statistical methods

Baseline data for continuous outcome measures were evaluated by Analysis of Variance (ANOVA) with treatment and study centre as main effects. Change scores were derived by subtracting the baseline score from the score at each follow up visit. Continuous measurements (changes from baseline) were evaluated at each time point by ANCOVA, with baseline score as the covariate and terms for study centre and treatment. All analyses on the LOCF data set included study centre in the model except for the following: the analyses on the LOCF data set of MADRS Total score and in PANSS Hostility Subscale score in.

Results

Participant flow

In CN138009, a total of 262 patients were randomised to the aripiprazole group (130 patients) and the placebo group (132 patients). Twice as many aripiprazole-treated patients (42%) completed the 3-week double-blind treatment as did placebo-treated patients (21%). In this study, at the end of Week 2, patients with CGI-BP Change from Preceding Phase (mania) score of 4 to 7 (no change to very much worse) were dropped from the blinded treatment phase and offered the option to receive open-label aripiprazole for Week 3 (open-label rescue). Thus, non-responders could discontinue early from the placebo-controlled acute phase of the study and receive open-label aripiprazole hence the overall completion rates

were low in this study. The percentage of patients who entered the open-label treatment was lower in the aripiprazole group (13%) than in the placebo group (28%). The most frequently reported reasons for discontinuation in CN138009 were withdrawal of consent, lack of efficacy and AEs. The rates of discontinuations due to these reasons were similar between treatment groups.

Baseline data

Treatment groups were comparable in terms of age, race and body weight. A total of 8 of the 262 randomised patients were excluded from the Safety Sample. 14 out of 254 patients in the Safety Sample were excluded from the Efficacy Sample. The main reason for exclusion from analyses was patient withdrawing consent.

Outcomes

Key efficacy results from study CN138009 are summarised in Table 5.

Table 5: CN138009 – Key efficacy results

	Placebo	Aripiprazole
Primary Efficacy Measure		
Y-MRS Total Score	N = 122	N = 123
Mean Baseline	29.68	28.16
Mean Change at Week 3 (LOCF)	-3.35	-8.15**
Secondary Efficacy Measure		
CGI-BP Severity of Illness (mania) Score	N = 122	N = 124
Mean Baseline	4.74	4.56
Mean Change at Week 3 (LOCF)	-0.39	-1.00**
Other Efficacy Measures		
Response Rate at Week 3 (LOCF)	N = 122	N = 123
Number of Responders[a] (%)	23 (19)	49 (40)
Ratio of Response Rates vs Placebo		2.11**
PANSS Hostility Subscale Score	N = 78	N = 99
Mean Baseline	12.29	10.80
Mean Change at Week 3 (LOCF)	0.49	-1.61**
CGI-BP Change from Preceding Phase (mania) Score	N = 123	N = 124
Mean Score at Week 3 (LOCF)	4.09	3.31**

Source: CN138009 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least 50% decrease from baseline on Y-MRS Total Score.

Primary endpoint

In CN138009, where aripiprazole was administered at a starting dose of 30 mg/day, the mean change from baseline to Week 3 (LOCF) was statistically significant for the aripiprazole group versus the placebo group (P = 0.002). These results were not corroborated by analyses conducted on the OC data set for CN138009 (P = 0.700). However, the results of the OC analyses in CN138009 for Week 2 were significantly in favour of aripiprazole (P = 0.001); mean change from baseline in Y-MRS Total Score for aripiprazole was -11.54 versus placebo -5.74. A possible explanation for the inconsistent results reported between the LOCF and OC data sets at Week 3 in CN138009 is that as per the protocol patients who demonstrated "no change" to "very worse" (score of 4 to 7) on the CGI-BP Change from Preceding Phase Scale at the end of Week 2 were dropped from the double-blind treatment phase and offered the opportunity to receive open-label aripiprazole for Week 3. Once the patients entered the open-label rescue phase they were considered discontinued from the double-blind phase and thus contributed to the high drop-out rate of this study. The proportion of patients in the placebo group who entered the open-label treatment phase was higher (28%) than the aripiprazole group (13%).

Secondary endpoints

Results for the change from baseline in CGI-PB Severity of Illness (Mania) Score (LOCF Data set) are shown in Table 6. There were significantly greater improvements for the aripiprazole group compared to the placebo group from Day 4 through Week 3. Results for the OC were similar.

Table 6: Mean change from baseline in the CGI-BP Severity of Illness (mania) Score, LOCF Data Set, Efficacy Sample (CN138009)

	Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score[a]		Pairwise Comparisons P-values[b]
Phase/Variable	**Placebo N = 122[c]**	**Aripiprazole N = 124[c]**	**Aripiprazole vs Placebo**
Mean Baseline	4.74	4.56	0.051
Double-Blind Treatment Phase			
Day 4	-0.22	-0.53	0.005
Week 1	-0.30	-0.71	0.002
Day 10	-0.31	-0.85	0.001
Week 2	-0.32	-1.02	< 0.001
Week 3	-0.39	-1.00	0.001
Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo)			-0.61 (-0.98, -0.24)

Protocol CN138-009

Source: Appendices 10.2.1A and 10.2.1B

[a] CGI-BP Severity of Illness (mania) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.

[b] ANCOVA, controlling for treatment, center, and baseline value. LS Means P-values for comparisons.

[c] At Day 4, N = 119 for placebo, N = 119 for aripiprazole.

For CN138009, response rates in the aripiprazole group were superior to the placebo group (P = 0.001) (Table 7).

Table 7: Response rate on the Y-MRS Total Score, Primary LOCF Data Set, Efficacy Sample

	LOCF Data Set				
	Number Responding[a]/Number Assessed (%)				Pairwise Comparisons P-values[b]
	Placebo		Aripiprazole		Aripiprazole vs Placebo
Day 4	6/118	(5)	17/118	(14)	0.011
Week 1	16/121	(13)	34/123	(28)	0.004
Day 10	23/122	(19)	45/123	(37)	0.001
Week 2	22/122	(18)	46/123	(37)	0.001
Week 3	23/122	(19)	49/123	(40)	0.001
Week 3: 95% confidence interval for response ratio vs placebo					2.11 (1.38, 3.21)

Protocol CN138-009

Source: Appendices 10.3.6, 10.1.1A

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] CMH General Association test.

Results for the mean change from baseline to Week 3 in CGI-BP Severity of Illness Score (depression) (LOCF) favoured aripiprazole (Table 8).

Table 8: Mean change from baseline in CGI-BP Severity of Illness Score (depression) (LOCF data set)(CN138009) , Efficacy Sample

	Mean Change from Baseline in CGI-BP Severity of Illness (Depression) Score[a]		Pairwise Comparisons P-values[b]
Phase/Variable	Placebo N = 122[c]	Aripiprazole N = 124[c]	Aripiprazole vs. Placebo
Mean Baseline	2.35	2.11	0.090
Double-Blind Treatment Phase			
Day 4	0.00	-0.16	0.101
Week 1	-0.01	-0.25	0.020
Day 10	-0.02	-0.20	0.151
Week 2	0.04	-0.30	0.014
Week 3	0.07	-0.24	0.026
Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo)			-0.31 (-0.58, -0.04)

Protocol CN138-009

Source: Appendix 10.2.1A

[a] CGI-BP Severity of Illness (depression) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.

[b] ANCOVA, controlling for treatment, center, and baseline value. LS Means P-values for comparisons.

[c] At Day 4, N = 119 for placebo, N = 119 for aripiprazole.

Aripiprazole was superior at Week 3 over the placebo group on the PANSS Hostility Subscale Score (P = 0.003).

In terms of onset of efficacy, there were statistically significant treatment differences in favour of aripiprazole as early as Day 4, and results were statistically significant at all time points thereafter to Week 3. In CN138009, the aripiprazole group showed superior response compared to the placebo group from Day 4 through Week 3; at the end of Week 3, 40% of the aripiprazole-treated patients were in response (placebo 19%).

Evaluator Comment

In study CN138009, results for all primary and secondary endpoints favoured aripiprazole over placebo. Aripiprazole was shown to be effective in the treatment of patients with acute mania; however there was a large drop-out rate in the study. For this reason results from the study should be interpreted with caution.

Study CN138074 – Acute treatment

This study has been previously evaluated by the TGA and therefore will be discussed more briefly. It had an identical design to CN138009 except this study did not include the open-label treatment option for Week 3. This study did not require patients with CGI-BP Change from Preceding Phase (mania) Score 4 to 7 to drop out at the end of Week 2. Patients could continue in the study as outpatients during Week 3 if the following criteria were met at the end of Week 2: CGI BP Severity (mania) Score $\leq$ 3 and CGI-BP Change from Preceding

Phase (mania) Score ≤ 2. All patients who completed 3 weeks of double-blind therapy were eligible to enter 1 of 2 long-term studies (CN138010 or CN138037).

The primary endpoint was the mean change from baseline to Week 3 in the Y-MRS Total Score.

Sample size

For CN138074, a hierarchical testing procedure was used for the analysis of the key secondary efficacy variables in order to keep the overall experiment-wise Type I Error at 0.05. If the difference between placebo and aripiprazole in the primary analysis was statistically significant (P≤0.05), then testing of the key secondary endpoints could proceed sequentially in the following order: (1) analysis of responders; (2) CGI-BP Severity of Illness Score (mania), (3) PANSS16 Hostility Subscale Score; and (4) CGI-BP Change from Preceding Phase (mania) Score. Analysis was to stop with the first treatment comparison that failed to reach statistical significance.

Results

Participant flow

A total of 272 patients were randomised (aripiprazole, 137 and placebo, 135).

Outcomes

Key efficacy results from CN138074 are summarised in Table 9.

Table 9: CN138074 – Key efficacy results

	Placebo	Aripiprazole
Primary Efficacy Measure		
Y-MRS Total Score	N = 132	N = 136
Mean Baseline	28.45	28.80
Mean Change at Week 3, LOCF	-7.19	-12.52**
Key Secondary Efficacy Measures		
Response Rate at Week 3 (LOCF)	N = 132	N = 136
Number of Responders[a] (%)	42 (32)	72 (53)
Ratio of Response Rates vs Placebo		1.66**
CGI-BP Severity of Illness (mania) Score	N = 129	N = 135
Mean Baseline	4.71	4.69
Mean Change at Week 3 (LOCF)	-1.12	-1.59**
PANSS Hostility Subscale Score	N = 122	N = 124
Mean Baseline	10.74	10.60
Mean Change at Week 3 (LOCF)	-0.82	-2.21**
CGI-BP Change from Preceding Phase (mania) Score	N = 129	N = 135
Mean Score at Week 3 (LOCF)	3.22	2.63**

Source: CN138074 CSR. ** (P ≤ 0.01), * (0.01 < P ≤ 0.05), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline to Week 3 on the Y-MRS Total Score.

For the primary endpoint in CN138074 the mean change from baseline to Week 3 (LOCF) was statistically significant for the aripiprazole group versus the placebo group (P < 0.001).

These results were corroborated by analyses conducted on the OC data set for CN138074 (p = 0.004).

For CN138074 response rates in the aripiprazole group were superior to the placebo group (p = 0.001).

The aripiprazole group showed superiority in CGI-BP Severity of Illness (mania) Scores versus the placebo group (CN138074, P = 0.009).

Aripiprazole was superior at Week 3 over the placebo group on the PANSS Hostility Subscale Score. (P = 0.002).

In relation to CGI-BP change from preceding Phase (Mania) Score the aripiprazole group was superior to the placebo group (P = 0.001).

In terms of onset of efficacy, statistically significant treatment differences in favour of aripiprazole in Y-MRS Total Score were observed as early as Day 4 in CN138074. At every time point thereafter, results were of statistical significance in the aripiprazole group compared to the placebo group.

Response to treatment was defined as a ≥ 50% decrease from baseline in the Y-MRS Total Score. In CN138074, the aripiprazole group demonstrated superior response from Week 1 through Week 3 as compared to the placebo group; at the end of Week 3, 53% of aripiprazole-treated patients were in response (placebo 32%).

The CGI-BP Severity of Illness (depression) scale was used to assess the severity of the depression component in bipolar illness. Results showed that at the end of Week 3, there was a statistically significant treatment difference in favour of aripiprazole (P = 0.026).

Evaluator Comment

> The results from this study support that aripiprazole is effective in the acute treatment of patients with Bipolar I Disorder.

Study CN138010 - Maintenance treatment for prevention of recurrence

Study CN138010 was a randomised, double-blind, multicentre, flexible-dose, placebo-controlled study of aripiprazole in the maintenance treatment for the prevention of recurrence of Bipolar Disorder. There were 2 routes of entry into this study. Patients who had experienced a manic-or mixed-type episode and had recently completed an acute mania study of aripiprazole were eligible to enter (CN138007, CN138009, CN138062, CN138074, or CN138077) and also patients who had recently experienced a manic or mixed-type episode but had not participated in an aripiprazole study were eligible to enter this study. A total of 633 patients were enrolled at 76 centres in 3 countries (3 Argentina, 2 Mexico, 71 United States) from 5 March 2000 through 16 September 2002. The study was conducted according to Good Clinical Practice (GCP) guidelines. There were no major protocol amendments. There were 3 phases as follows:

Stabilisation phase: Open-label treatment with aripiprazole at a starting dose of 30 mg/day; could be decreased to 15 mg/day at any time, if necessary, for tolerability. Duration was from 6 to 18 weeks with visits every 2 weeks. Patients continued in this phase until their manic symptoms were stable as defined by pre-specified criteria (Y-MRS Total Score ≤ 10 and a MADRS Total Score ≤ 13 during 4 consecutive visits) over a minimum of 6 weeks.

Maintenance phase: Once stabilised, eligible patients were then randomised to aripiprazole or placebo. Patients assigned to aripiprazole started this phase at the same dose they were taking at the end of the Stabilisation phase. The dose of aripiprazole was 15 mg/day or 30 mg/day

and could be changed at any time during the study, as necessary, based on therapeutic effect and tolerability. The primary efficacy outcome measure was the time to relapse (as defined by discontinuation due to lack of efficacy) from randomisation. Patients were discontinued from the study because of lack of efficacy if they were hospitalised for manic or depressive symptoms, or required an addition to or increase in their psychotropic medications other than study medication (that is, predefined criteria for relapse). Benzodiazepines (lorazepam unless not locally available) were the only psychotropic medications allowed in the Maintenance phase, and only in small doses and limited frequency. Patients continued in this phase of the study for up to 26 weeks.

Extension phase: Eligible patients continued on the blinded study drug treatment they were receiving at the end of the Maintenance phase, either aripiprazole (15 or 30 mg/day) or placebo, and their dose could be adjusted at any time during the study, as necessary, to enhance therapeutic effect or tolerability. Patients continued in the Extension phase of the study for up to 74 weeks. Criteria for relapse in this phase were the same as in the Maintenance phase. Patients unable to tolerate the lowest dose of study medication or who relapsed at any time during the phase were discontinued.

The primary objective of the study was to compare the maintenance of stability of aripiprazole versus placebo as measured by the time to relapse (discontinuation due to lack of efficacy) during the Maintenance phase. Patients were discontinued from the study due to lack of efficacy if they were hospitalised for manic or depressive symptoms or required an addition to or increase in their allowed psychotropic medications.

Study participants

Inclusion criteria for the Stabilisation Phase of the study included patients with DSM-IV diagnosis of Bipolar I disorder who had experienced at least two previous manic or mixed episodes including their most recent episode and who had experienced a recent manic or mixed episode requiring hospitalisation that began no more than three months before entry into the Stabilisation Phase. There were some additional requirements for entry into the Maintenance Phase and the Extension Phase. There was an extensive list of exclusion criteria.

Treatments

The dose of aripiprazole was 15 mg/day or 30 mg/day and could be changed at any time during the study, as necessary, based on therapeutic effect and tolerability.

Outcomes

The primary efficacy outcome measure was the time to relapse from randomisation into the Maintenance phase. Key additional efficacy measures included mean change from randomisation to endpoint in Y-MRS Total Score, CGI-BP Improvement and Severity of Illness scales, PANSS Total Score, hostility and cognitive subscale scores, and MADRS Total Scores.

Sample size

For CN138010, it was expected that the 6-month placebo relapse rate would be 45% and the aripiprazole relapse rate would be 20%. A total of 45 events would be required to yield 87% power to detect the expected 25% difference in the percentage of patients relapsing between placebo and the aripiprazole treatment groups, assuming these relapse rates, a dropout rate for reasons other than relapse of 18%, and a 2-sided test at the 0.05 level. These assumptions were based on results from three previous studies: a 52-week maintenance study comparing valproate, lithium, and placebo in bipolar patients, a maintenance study evaluating the prophylactic efficacy of lithium compared with placebo in manic-depressive illness, and a

placebo-controlled maintenance study evaluating the prophylaxis effect of lamotrigine in rapid-cycling bipolar disorder over 6 months. Based on these assumptions, it was expected that 152 patients would have to be randomised to obtain 150 evaluable patients (75 per treatment group) to yield 45 events (total number of patients who relapsed). The HR for these relapse rates and sample size was 2.7 based on a ratio of placebo/aripiprazole.

Key secondary endpoints were time to manic and time to depressive relapse. For these key secondary analyses, a hierarchical testing procedure was used so to maintain the overall experiment-wise Type I error at 0.05. If aripiprazole was superior to placebo in the primary efficacy analysis, then testing of the key secondary endpoints proceeded as follows: First, time to manic relapse was tested. If aripiprazole was significant versus placebo for the time-to-manic-relapse analysis, then time to depressive relapse was tested. The procedure stopped on the first treatment comparison that was not statistically significant. All testing of the key secondary endpoints was 2-sided at the 0.05 significance level.

Randomisation

At baseline eligible patients entered the Stabilisation Phase and received open-label aripiprazole. Eligible patients were randomised into the Maintenance phase to receive either aripiprazole or placebo according to a computer-generated randomisation schedule**.** Treatments were covered by a fixed randomisation schedule to allocate patients among two treatment arms in a 1:1 ratio. Within each centre equal numbers of patients were assigned to each group.

Statistical methods

Samples for the study were defined as follows:

- Stabilisation (Enrolled) Sample: included all patients enrolled into the studies.
- Randomised Sample: included all patients randomised to treatment after 1 January 2001. The 35 patients who received unblinded study medication in the double-blind Maintenance phase prior to 1 January 2001 were not included in the analyses of efficacy or in the Maintenance Safety Sample but were analysed separately.
- The Maintenance Safety Sample in CN138010 comprised all patients in the Randomised Sample who took at least one dose of maintenance study medication, as identified on the dosing record. The Maintenance Safety Sample was used to summarise extent of exposure and to assess the primary efficacy endpoint, time to relapse. The data for the patients who inadvertently received unblinded Maintenance phase study medication and subsequently discontinued from the study were not included in the Maintenance Safety Sample.

Baseline data for continuous outcome measures were evaluated by ANOVA with treatment group as the main effect. Change scores were derived by subtracting the baseline score from the score at each follow up visit. Since the study had more than one phase, and not all evaluations were performed at the same visit, the definition of baseline might vary from analysis to analysis.

The Cochran-Mantel Haenszel (CMH) General Association Test was used to analyse the percent of patients that discontinued (due to relapse or any reason).

The primary analysis of time from randomisation to relapse during the Maintenance phase was performed on the Maintenance Safety Sample. All other efficacy analyses were performed on the Efficacy Sample at baseline or randomisation, at endpoint, and at each

specified study week. Efficacy analyses were performed using both the LOCF and OC data sets..

Results

Participant flow

Five hundred sixty-seven patients entered the open-label Stabilisation phase, 206 (36%) completed this phase. The Randomised Sample had 161 patients: 78 in the aripiprazole group and 83 in the placebo group. Fifty-eight percent of the 161 patients discontinued from the Maintenance phase of the study: 50% of aripiprazole-treated patients and 66% of placebo-treated patients. The most common reason for discontinuing from therapy in both treatment groups was lack of efficacy (24% aripiprazole; 43% placebo).

A total of 67 (42%) patients completed the Maintenance phase of the study and 66 of these patients entered the Extension phase. Enrolment in the Extension phase of the study was terminated after 45 patients had relapsed, and patients were allowed to continue in the study only until the last randomized patient had completed the Maintenance phase, at which time, the study was terminated.

Baseline data

Within the Randomised Sample, the demographic characteristics of the treatment groups were similar with the exception of gender: fewer women were randomised to the aripiprazole group (62%) than to the placebo group (72%).

Within the Randomised Sample, the treatment groups were balanced for all psychiatric variables except for the proportion of patients experiencing a manic-type episode which was 78% in the placebo group and 62% in the aripiprazole group. More patients experienced a manic-type episode (70%) than a mixed-type episode (30%) at baseline. Patients entered the Maintenance Phase when they were determined to be stable over a period of 6 consecutive weeks (in the Stabilisation Phase) as defined by pre-specified criteria (Y-MRS Total Score ≤ 10 and a MADRS Total Score ≤ 13 during 4 consecutive visits).

Of the 161 patients randomised to the double-blind Maintenance Phase, 158 were included in the Maintenance Efficacy Sample.

Outcomes

Key efficacy results from study CN138010 are summarised in Table 10.

Table 10: CN138010 – Summary of efficacy results at endpoint, LOCF data set, Maintenance Phase

	Treatment Group	
	Placebo	Aripiprazole
Variable	**N=83**	**N=77**
PRIMARY EFFICACY ENDPOINT		
Time to relapse for any event[a]		
Hazard ratio (95% CI)[b]	0.523 (0.300, 0.913)	
P-value[c]	0.020*	
KEY SECONDARY ENDPOINTS		
Time to manic relapse		
Hazard ratio (95% CI)[b]	0.309 (0.123, 0.774)	
P-value[c]	0.008**	
Time to depressive relapse		
Hazard ratio (95% CI)[b]	0.833 (0.345, 2.011)	
P-value[c]	0.684	
OTHER EFFICACY ENDPOINTS		
Number of Relapses (%)[d]	36 (43%)	19 (25%)*
Relative Risk (Aripiprazole:Placebo) (95% CI)[e]	0.569 (0.359, 0.902)	
Number of manic relapses (%)	19 (23%)	6 (8%)
Number of depressive relapses (%)	11 (13%)	9 (12%)
Number of mixed relapses (%)	5 (6%)	4 (5%)
Number of relapses of unknown type (%)	1 (1%)	0 (0%)
Y-MRS		
Mean Score at Last Stabilization Visit	2.06	2.55
(95% CI)	(1.51, 2.62)	(1.98, 3.13)
Mean Change at Week 26	7.50	3.42**
(95% CI)	(5.39, 9.61)	(1.23, 5.62)

Table 10 (cont): CN138010 – Summary of efficacy results at endpoint, LOCF data set, Maintenance Phase

	Treatment Group	
	Placebo	Aripiprazole
Variable	**N=83**	**N=77**
MADRS		
Mean Score at Last Stabilization Visit	4.51	3.87
(95% CI)	(3.67, 5.35)	(3.00, 4.74)
Mean Change at Week 26	6.43	5.11
(95% CI)	(4.12, 8.75)	(2.71, 7.52)
PANSS Total Score		
Mean Score at Randomization	36.41	35.85
(95% CI)	(34.96, 37.86)	(34.36, 37.33)
Mean Change at Week 26	9.13	5.22
(95% CI on treatment differences)	(-8.27, 0.43)	
PANSS Cognitive Subscale Score		
Mean Score at Randomization	8.57	8.62
(95% CI)	(8.11, 9.04)	(8.14, 9.10)
Mean Change at Week 26	2.48	0.84*
(95% CI on treatment differences)	(-2.96, -0.34)	
PANSS Hostility Subscale Score		
Mean Score at Randomization	4.38	4.38
(95% CI)	(4.18, 4.57)	(4.18, 4.58)
Mean Change at Week 26	1.78	0.78*
(95% CI on treatment differences)	(-1.90, -0.09)	
CGI -BP Severity of Illness (mania)		
Mean Score at Last Stabilization Visit	1.28	1.34
Mean Change from Last Stabilization at Week 26	0.89	0.39*
(95% CI on treatment differences)	(-0.89, -0.11)	
CGI -BP Severity of Illness (depression)		
Mean Score at Last Stabilization Visit	1.45	1.34
(95% CI)	(1.30, 1.60)	(1.18, 1.50)
Mean Change from Last Stabilization at Week 26	0.69	0.67

Table 10 (cont): CN138010 – Summary of efficacy results at endpoint, LOCF data set, Maintenance Phase

	Treatment Group	
	Placebo	Aripiprazole
Variable	**N=83**	**N=77**
(95% CI on treatment differences)	(-0.42, 0.39)	
CGI -BP Severity of Illness (overall)		
Mean Score at Last Stabilization Visit	1.41	1.42
(95% CI)	(1.26, 1.56)	(1.27, 1.58)
Mean Change at Week 26	1.28	0.74*
(95% CI on treatment differences)	(-0.98, -0.11)	
Mean CGI-BP Change from Preceding Phase (mania) Score[f] at Week 26	3.71	3.29
Mean CGI-BP Change from Preceding Phase (depression) Score[g] at Week 26	4.07	3.84
Mean CGI-BP Change from Preceding Phase (overall) Score[h] at Week 26	4.15	3.71

Protocol CN138010

Source: Appendices 10.1A, 10.2A-1, 10.2A-2, 10.3.3, 10.3.4, 10.3.5, 10.3.6

**($p \leq 0.01$), * ($0.01 < p \leq 0.05$), compared with placebo

[a] Defined as discontinuation due to lack of efficacy.

[b] Cox's Proportional Hazards model, aripiprazole:placebo. A hazard ratio < 1 favors aripiprazole.

[c] Log-Rank Test for equality of Kaplan-Meier survival curves.

[d] Statistical testing not done on specific relapse type.

[e] CMH General Association Test, aripiprazole:placebo. A relative risk < 1 favors aripiprazole.

[f] CGI-BP mania change score is from 1 (very much improved) to 7 (very much worse).

[g] CGI-BP depression change score is from 1 (very much improved) to 7 (very much worse).

[h] CGI-BP overall change score is from 1 (very much improved) to 7 (very much worse).

The primary efficacy endpoint of CN138010 was the time from randomisation to relapse during the Maintenance phase (as defined by discontinuation due to lack of efficacy). Patients were discontinued from the study because of lack of efficacy if they were hospitalised and/or required an addition to or increase in their allowed psychotropic medications, other than study medication, for manic or depressive symptoms. Benzodiazepines (lorazepam unless not locally available) were the only psychotropic medications allowed in the Maintenance phase, and only in small doses and limited frequency. As shown in Table 10, the proportion of relapses was lower in the aripiprazole group (25%) than the placebo group (43%) in the Maintenance phase.

Aripiprazole treatment reduced the risk of relapse compared to placebo by approximately half as indicated by the HR: 0.523, 95% CI (0.300, 0.913).

The results showed a statistically significant difference in favour of aripiprazole, in time to manic relapse (P = 0.008), but no significant difference in time to depressive relapse (P = 0.684) during the Maintenance phase. The number of patients who had a manic-type relapse was approximately 3 times less in the aripiprazole group than the placebo group (8% in aripiprazole versus 23% in placebo).

The proportion of patients without relapse at Week 26 was 49% for placebo and 72% for aripiprazole. There were also significant benefits with aripiprazole vs placebo in the number of patients with relapses (p=0.013), rate of notable worsening in Y-MRS Total Score at Weeks 1,4, and 12-26 (p<0.03) PANSS cognitive subscale score at Week 26 (p=0.014) and CGI-BP Severity of Illness (mania) Score at Weeks 18-26 (p<0.05). There were no significant differences in MADRS Total Score, rate of notable worsening in MADRS Total Score, CGI-BP Severity of Illness (depression) Score and CGI-BP change from the preceding phase (mania, depression and overall) scores.

Maintenance of treatment greater than 1 year

A total of 67 patients completed the Maintenance phase, and 66 of these patients entered the Extension phase. These patients were followed for relapse during the Extension phase for an additional period of up to 17 months or a total of up to 23 months from randomisation in the Maintenance phase. The pre-specified analysis of time from randomisation to relapse (as defined by discontinuation due to lack of efficacy) for a period greater than 1 year was evaluated during the combined Maintenance and Extension phases.

Consistent with findings in the Maintenance phase, aripiprazole was superior to placebo in delaying the time to relapse during the combined Maintenance and Extension phases, further supporting the efficacy of aripiprazole in maintaining the effect in prevention of relapse in patients with Bipolar I Disorder. The proportion of relapses was lower in the aripiprazole group (32%) than the placebo group (52%). Aripiprazole treatment reduced the risk of relapse compared to placebo as indicated by the HR: 0.531, 95% CI (0.324, 0.871). These results support efficacy of aripiprazole in maintaining the stability of patients with Bipolar I Disorder. In the Maintenance/Extension phases aripiprazole was shown to be superior to placebo in delaying the time to a manic relapse (HR: 0.348 [95%CI: 0.161, 0.754], p=0.005), however there was no difference between the groups with respect to time to a depressive relapse (HR: 0.808, [95%CI: 0.361, 1.808], p=0.602).

A post-hoc analysis was conducted on the combined Maintenance and Extension phases. It included rating scales to document the recurrence of bipolar symptoms after stabilisation of the patient's bipolar disorder. Specifically, this analysis used a modified definition of relapse to confirm the investigator-judged relapse in the combined Maintenance and Extension phases (relapse was defined as discontinuation due to lack of efficacy confirmed by hospitalisation for mood episode and/or confirmed by a Y-MRS Total Score ≥ 15 or a MADRS Total Score≥ 18 on or within 7 days of the date of discontinuation).

The post-hoc analysis showed that the proportion of patients in relapse was less in the aripiprazole group (27%) than in the placebo group (47%) in the combined Maintenance and Extension phase. Aripiprazole treatment significantly reduced the risk of relapse compared with placebo by half, as seen by the HR: 0.496, (95% CI 0.291, 0.845). The post-hoc analysis confirmed the results of the prospectively-defined analysis of time to relapse for any event over a time period greater than 1 year.

Evaluator Comment

> The results from CN138010 supported that patients treated with aripiprazole 15-30 mg/day had significantly fewer relapses and relapsed significantly later than patients who received placebo. Aripiprazole was superior to placebo in preventing manic relapse but not depressive relapse. Results were similar at 6 months and 17 months.
>
> There are aspects of this study that indicate that results should be interpreted with some caution. In particular, there was potential for selection bias in the Maintenance and Extension phases of the study. There was also only a small number of patients entered

in the Extension phase (n=66).Overall however results do support efficacy of aripiprazole as maintenance treatment.

Study CN138134 - 6-Week combination therapy study

Study CN138134 was a multicentre, randomised, double-blind, flexible-dose, placebo-controlled study with 2 parallel treatment groups. Patients who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned to receive either aripiprazole or placebo in a 2:1 ratio, in combination with lithium or valproate for 6 weeks. Patients considered appropriate by the investigator (that is, able to be treatment compliant; might benefit from longer-term treatment) could continue in the study for an additional 46 weeks on open-label aripiprazole in combination with lithium or valproate. There were 623 patients enrolled at 89 study centres in 16 countries from 19 October 2004 through 06 November 2006. The study was conducted according to Good Clinical Practice (GCP) guidelines. There were no major protocol amendments.

Phase 1: It was a 3-day to 4-week phase to achieve the therapeutic levels of lithium or valproate as well as screening and psychotropic washout phase. Patients who were receiving lithium or valproate, just prior to entering the study as well as those not receiving these treatments prior to entering the study, were eligible to participate. All patients received lithium or valproate during this phase. A Y-MRS total score of ≤ 16 was required for patients to enter Phase 2.

Phase 2: This phase lasted 2 weeks and was used to confirm that patients were partially nonresponsive to mood stabilisers (defined by a Y-MRS Total Score ≤ 16 during Phase 1 and at the end of Phase 2, with a decrease of ≤ 25% between Phases 1 and 2).

Phase 3: Patients who met partial nonresponse criteria were randomised to receive either aripiprazole or placebo in combination with lithium or valproate in a 6-week, double-blind phase. Patients were randomised in a 2:1 ratio (aripiprazole:placebo), stratified by mood stabiliser treatment and study centre, and started treatment with either placebo or with aripiprazole at 15 mg/day with the option to increase to 30 mg/day at Day 7 (Week 1) or beyond for clinical response.

Phase 4: This was a 46-week open-label extension phase. Patients who completed the double-blind treatment phase could enter this phase with aripiprazole and either lithium or valproate. The extension phase is currently ongoing.

The primary objective was to compare the efficacy of aripiprazole in combination with lithium or valproate to lithium or valproate monotherapy, as measured by the Y-MRS, in the treatment of patients with Bipolar I Disorder, manic or mixed episode, with or without psychotic features, partially nonresponsive to lithium or valproate monotherapy. The secondary objective was to evaluate the safety and tolerability of aripiprazole in combination with lithium or valproate in this same patient population.

Study participants

Inclusion criteria for the study were included patients with Bipolar I Disorder, manic or mixed episode, with or without psychotic features, as defined by DSM-IV-TR and confirmed by the Mini International Neuropsychiatric Interview (MINI) who were partially nonresponsive to lithium or valproate monotherapy and who had a history of at least one previous manic or mixed episode of sufficient severity to require hospitalisation, or treatment with a mood stabiliser or antipsychotic agent. There were additional inclusion criteria assessed prior to entry into Phase 2 and Phase 3. There was an extensive list of exclusion criteria.

Treatments

Patients were randomised, using a 2:1 (aripiprazole:placebo) scheme, to 1 of 2 treatment groups: 1) double-blind aripiprazole, 1 tablet per day (15 mg/day), co-administered with open-label lithium or valproate or 2) double-blind placebo (1 matching tablet per day) co-administered with open-label lithium or valproate. Study medication was administered orally. Doses were to be taken at approximately the same time each day without regard to meals.

Sample size

A sample size of 240 patients in the combination therapy with aripiprazole treatment group and 120 patients in the monotherapy treatment group yielded 90% power to detect a difference of 3.23 in the mean change from baseline in Y-MRS at Week 6 between combination therapy with aripiprazole and monotherapy. The above calculations assumed a standard deviation of 8.82 and a 2-sided t-test for the difference between aripiprazole and placebo at the 0.05 significance level. In the literature a treatment difference of 3.23 was observed between co-therapy of olanzapine and lithium and monotherapy with lithium. A common standard deviation of 8.82 was observed for the full sample in the same trial.

The following samples were defined for analyses purposes:

- The Enrolled Sample comprised all patients who signed informed consent
- The Randomised Sample comprised all patients who were randomised to treatment
- The Safety Sample comprised all patients in the Randomised Sample who took at least one dose of study medication, as indicated on the study therapy form
- The Efficacy Sample comprised all patients who were in the Safety Sample and had at least one efficacy evaluation after the start of study drug
- The Outcomes Research Sample comprised all patients in the Safety Sample who had at least 1 outcomes research evaluation after the start of study drug
- The Per Protocol Sample was a subset of the Efficacy Sample and excluded patients/efficacy ratings due to any of the following protocol deviations:
    - Patients with serum levels of lithium outside the therapeutic range (0.6 to 1.0 mmol/l) or with serum levels of valproate outside the therapeutic range (50 to 125 μg/mL) at randomisation
    - Patients with Y-MRS Total Score < 16 at the end of Phase 1 or at the end of Phase 2
    - Patients with decrease in Y-MRS Total Score of more than 25% between end of Phase 1 and end of Phase 2
    - Patients who started Phase 2 within 30 days of taking fluoxetine or within 14 days of other antidepressants
    - Patients with < 4 days of study medication

The following were also excluded:

- Y-MRS efficacy rating within 8 hours after benzodiazepine use
- All Y-MRS efficacy rating at all time points after a positive cocaine test result
- All Y-MRS efficacy ratings at all time points after receiving the wrong study medication (medication different from the randomised treatment)

The Last Observation Carried Forward (LOCF) dataset included data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous visit. Baseline data were not carried forward or averaged with on-treatment data to impute missing values for the LOCF dataset. Data from the first 2 phases of the study were not used to impute missing values in Phase 3 analyses. The Observed Case (OC) dataset consisted of the actual observation at each visit.

Randomisation

Treatment assignments were governed by a fixed randomisation schedule designed to allocate patients between the 2 treatment groups in a 2:1 (aripiprazole:placebo) ratio. Randomisation was stratified by site and mood stabiliser (lithium or valproate) using an interactive voice response system (IVRS). Within each stratum, patients were assigned to each treatment group in approximately a 2:1 (aripiprazole:placebo) ratio.

Statistical methods

The primary efficacy endpoint was evaluated on the Efficacy Sample by an ANCOVA model with baseline score as covariate and type of mood stabilizer (lithium or valproate) and treatment as main effects. The treatment by mood stabilizer interaction was assessed at Week 6 LOCF by including the treatment by mood stabilizer interaction in the ANCOVA model. The key secondary efficacy endpoint was evaluated using a hierarchical testing procedure in order to keep the overall experiment-wise Type I Error at 0.05. If the difference between combination therapy with aripiprazole and monotherapy in the primary efficacy measure was statistically significant ($P \leq 0.05$), then the testing of the difference between aripiprazole and placebo in mean change from baseline to Week 6 LOCF in CGI-BP Severity of Illness Score (mania) proceeded at alpha = 0.05.The results were presented by treatment group, and by treatment group and type of mood stabiliser (lithium and valproate). P-values for comparisons corresponded to 2-tailed tests of significance and were rounded to 3 decimal places. No P-values were provided for subgroup analyses since this study was not powered to detect treatment differences in subgroup analyses.

Results

Participant flow

Of the 623 patients enrolled, 384 were randomised to double-blind treatment in Phase 3: 253 to the adjunctive aripiprazole group and 131 to the adjunctive placebo group.

Of these patients, 54 (21.3%) in the aripiprazole group and 20 (15.3%) in the placebo group discontinued during double-blind treatment. The two most frequently reported reasons for discontinuation in Phase 3 across groups were AE (aripiprazole 23 patients, 9.1%; placebo 7 patients, 5.3%) and lack of efficacy (aripiprazole 12 patients, 4.7%; placebo 6 patients, 4.6%).

A total of 199 (78.7%) patients in the aripiprazole group and 111 (84.7%) patients in the placebo group completed the 6-week double-blind phase of the study. Mood status reported at study discontinuation was comparable between treatment groups.

Baseline data

Within the Randomised Sample, the demographic characteristics of the treatment groups were similar. More women (54%) than men (46%) were randomised. The mean age at the start of manic or mixed symptoms was 27.0 years; 75% of patients were experiencing a manic-type episode and 25% were mixed-type episode at baseline. Therapeutic levels of lithium and valproate were confirmed at the end of medication washout Phase 1, prior to

entering the mood stabiliser monotherapy Phase 2 and in addition only patients with a Y-MRS ≥ 16 were eligible to enter Phase 2. The mean Y-MRS Total Score was 23.9 at the end of Phase 1. The mean duration of Phase 1 mood stabiliser dosing was 18.9 days. The treatment groups were similar with respect to the baseline psychiatric evaluations.

The mean baseline (end of Phase 2) Y-MRS Total Score of the Randomised Sample was 23.1. The mean baseline CGI-BP Severity of Illness Score (mania) for all randomised patients was 4.2. Baseline assessment scores of psychiatric rating scales were similar for the aripiprazole and placebo groups. Patients who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned in a 2:1 ratio (aripiprazole:placebo) for 6 weeks in combination with lithium or valproate, stratified by mood stabiliser treatment; 41% of the randomised patients were on lithium and 59% were on valproate.

There were 384 patients randomised according to 2:1 (aripiprazole: placebo) ratio to the6-week combination treatment phase (Phase 3): 131 to the placebo group and 253 to the aripiprazole group. Seven of the 384 patients were excluded from the Efficacy Sample, resulting in a total of 377 patients in the Efficacy Sample.

Outcomes

For the primary efficacy endpoint, the mean change from baseline to Week 6 (Phase 3) in the Y-MRS Total Score (LOCF), aripiprazole added to lithium or valproate showed statistically significantly greater improvement than placebo added to lithium or valproate; the treatment difference was -2.62 (P = 0.002).

For the key secondary efficacy endpoint, the mean change from baseline to Week 6 in CGI-BP Severity of Illness score (mania) (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference -0.33, P = 0.014).

A statistically significantly greater percentage of aripiprazole-treated patients (62.8%) than placebo-treated patients (48.5%) showed response on the Y-MRS Total Score. The relative risk (aripiprazole/placebo) was 1.29 (P = 0.008). A statistically significantly greater percentage of aripiprazole- treated patients (66.0%) than placebo-treated patients (50.8%) showed remission on the Y-MRS at Week 6. The relative risk was 1.30 (P = 0.004).

The time to response in the aripiprazole group was significantly different from the placebo group (P = 0.005, HR [aripiprazole/placebo] = 1.45) as was the time to remission (P = 0.003, HR = 1.48).

Treatment-by-subgroup interactions for the subgroups defined by type of mood stabiliser (lithium and valproate) were investigated for the primary (mean change from baseline to Week 6 in Y-MRS Total Score) and the key secondary efficacy (change from baseline to Week 6 in CGI-BP Severity of Illness [mania] Score) endpoints at Week 6 (LOCF). The treatment-by-mood stabiliser interactions assessed at Week 6 for both the primary and secondary efficacy endpoints were not statistically significant (P = 0.332, and P = 0.203, respectively).

Evaluator Comment

> This study demonstrated the efficacy of aripiprazole in combination with lithium or valproate in the treatment of patients with Bipolar I Disorder who are partially nonresponsive to lithium or valproate monotherapy. Aripiprazole, at a starting dose of 15 mg/day with allowed titration up to 30 mg/day, was statistically significantly superior to placebo on the primary efficacy measure (mean change from baseline at Week 6 on Y-MRS Total Score). A statistically significant difference was observed

beginning at Week 1 and continuing through Week 6. Aripiprazole was superior to placebo on the key secondary efficacy measure (mean change from baseline in the CGI-BP Severity of Illness Score [mania]) at Week 6.

Analysis performed across trials (pooled analyses and meta-analysis)

Subgroup analyses

The sponsor presented the model-based mean change from baseline to Week 3 in the Y-MRS Total Score for the LOCF data set in various population sample subsets of the pooled 3-week placebo-controlled comparisons. These population sample subsets include gender, age, race, psychiatric characteristics (type of episode and rapid cycling) and baseline psychiatric status as evaluated by the Y-MRS Total Score. Statistical significance for the interaction term was interpreted at the 10 % level ($P \leq 0.1$).

Results were consistently in favour of aripiprazole across subsets. The treatment-by-subgroup interaction terms were not statistically significant for any of the subgroups, except for the subgroup according to baseline Y-MRS Total Score (≤ median score [28] or > median score) and type of episode (manic or mixed).

Supportive studies

Study CN138007 – Acute treatment

Study CN138007 was a 3-week, randomised, double-blind, placebo-controlled, fixed-dose (3 parallel treatment groups: 15 mg/day aripiprazole, 30 mg/day aripiprazole, and placebo) study in hospitalised patients with Bipolar I Disorder, manic- or mixed-type. At the end of Week 2, patients with Clinical Global Impressions-Bipolar (CGI-BP) Change from Preceding Phase (mania) score of 4 to 7 (no change to very much worse) were dropped from the blinded placebo-controlled treatment phase and offered the option to receive open-label aripiprazole (30 mg with dose decreased to 15 mg if needed based on tolerability) for Week 3. These patients and those who completed three weeks of double-blind therapy were eligible to enter one of two long-term studies (CN138010 or CN138037).

Study participants

In CN138007, 256 patients received fixed doses of aripiprazole (127 patients received 15 mg/day and 129 received 30 mg/day). The retention rate in CN138007 was similar across all three treatment groups (45.7% to 49.6%). CN138007 also offered open-label rescue at Week 2. The percentage of patients who switched from double-blind treatment to open-label treatment at Week 2 was lower for the 15 mg aripiprazole group (11%) than for either the 30 mg aripiprazole group (19%) or the placebo group (20%).

Results

The key results from CN138007 are presented in Table 11. In CN138007, which used fixed-doses of 15 mg/day or 30 mg/day, aripiprazole did not differentiate from placebo at Week 3 (LOCF) on the primary or secondary efficacy measures.

Aripiprazole 15 mg and 30 mg were not superior to placebo in reduction in Y-MRS Total Scores, CGI-BP criteria and response rates in this study.

Table 11: CN138007 - Key Efficacy Results

	Placebo	Aripiprazole 15 mg	Aripiprazole 30 mg
Primary Efficacy Measure			
Y-MRS Total Score	N = 130	N = 127	N = 129
Mean Baseline	28.27	27.94	27.83
Mean Change at Week 3 (LOCF)	-10.12	-10.01	-10.80
Secondary and Other Efficacy Measures			
CGI-BP Severity of Illness (mania) Score	N = 129	N = 125	N = 128
Mean Baseline	4.68	4.66	4.70
Mean Change at Week 3 (LOCF)	-1.17	-1.29	-1.33
Response Rate at Week 3 (LOCF)	N = 130	N = 127	N = 129
Number of Responders[a] (%)	49 (38)	52 (41)	58 (45)
Ratio of Response Rates vs Placebo	--	1.06	1.21
PANSS Hostility Subscale Score	N = 87	N = 101	N = 93
Mean Baseline	10.58	10.71	10.89
Mean Change at Week 3 (LOCF)	-2.31	-1.86	-2.53
CGI-BP Change from Preceding Phase (mania) Score	N = 130	N = 127	N = 129
Mean Score at Week 3 (LOCF)	3.26	3.20	3.20

Source: CN138007 Clinical Study Report (CSR). ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

LOCF: Last Observation Carried Forward, PANSS: Positive and Negative Syndrome Scale

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS total score.

Study CN138008 – Maintenance of effect

Study 138008 was a flexible-dose active-controlled study with a 12-week acute phase and a 14-week extension phase comparing aripiprazole (15 mg/day to 30 mg/day) with haloperidol (10 mg/day to 15 mg/day) in outpatients or inpatients with a diagnosis of Bipolar I Disorder who were experiencing an acute manic episode. Patients with a CGI-BP (mania) Change from Preceding Phase Score of ≤ 3 at the end of Weeks 1 or 2 could increase their dose of aripiprazole from 15 mg to 30 mg or haloperidol from 10 mg to 15 mg. At the end of the initial three-week period, patients meeting eligibility criteria (CGI-BP Severity of Illness [mania] Score < 4 and Montgomery-Asberg Depression Rating Scale14 [MADRS] Total Score < 18) continued in the same treatment group at the same dose level for the remainder of the study. The dose of study medication could not be increased during subsequent weeks of the study, but could be decreased to 15 mg of aripiprazole or 10 mg of haloperidol, if necessary, for tolerability. Patients not tolerating these lower doses were to be discontinued from the study. Anticholinergic medications were not permitted in this study. A total of 372 patients were enrolled at 76 centres in Europe, Australia, the UK and South Africa between 20 November 2000 to 28 September 2001. The study was conducted according to GCP guidelines.

Extension phase: patients who completed this 12-week portion of the study and met pre-specified criteria could continue treatment in a 14-week, double-blind extension phase. In the 12-week portion, discontinuation rates due to adverse events were high in the haloperidol arm because of the protocol-specified inability to lower the haloperidol dose below 10 mg and also because anticholinergic agents were not permitted in this study. The 14-week extension phase data are not presented in this document. Efficacy analyses were not performed during the 14-week extension phase because only a small number of patients continued in the extension phase (30 in the aripiprazole group and 9 in the haloperidol group). Data reported on CN138008 in this document pertains to the 12-week acute phase.

The primary objective was to compare the number of patients receiving aripiprazole 15-30mg/day vs haloperidol 10-15mg/day who continued treatment and maintained a response at Week 12 (defined as ≥ 50% improvement from baseline Y-MRS). The secondary objectives were to compare the response rate at the end of Week 3, the response rate at the end of Week 12 within the subgroup of patients who completed week 3 with CGI-BP Severity of Illness (mania) Score <4 and MADRS score <18, and to assess safety.

Inclusion criteria included patients with a DSM-IV diagnosis of Bipolar I disorder who currently displayed an acute manic or mixed episode and a score of ≥ 20 on the Y -MRS at screening and on reassessment at baseline prior to randomisation. There was an extensive list of exclusion criteria.

Treatments and randomisation

At baseline eligible patients were randomised to receive either aripiprazole or haloperidol according to a computer-generated randomisation schedule. Treatment assignment was governed by a fixed randomisation schedule designed to allocate patients between two treatment arms in a 1:1 ratio. Within each centre equal numbers of patients were randomised to each arm

Outcomes

The primary efficacy endpoint was the response rate at Week 12, defined as the proportion of patients who completed the 12 week phase and who had at least 50% improvement from baseline in the Y-MRS Total Score. Patients who discontinued from the study during the 12 week phase, and without a Week-12 Y-MRS Total Score (<50% improvement) were considered non-responders.

The main secondary endpoints were: 1) response rate at Week 3, defined as the proportion of patients who completed Week 3 and who had at least 50% improvement from baseline in Y-MRS Total Score. Patients who discontinued at or prior to Week 3 and patients without a Y-MRS Total Score at Week 3 were considered non-responders; and 2) response rate at Week 12 in the subgroup of patients who did not discontinue at or prior to Week 3 and who had a CGI-BP (mania) Severity Score < 4 and MADRS score <18 at Week 3.

Sample size

The planned sample size of 306 patients was powered at 90% to detect a treatment difference of 19% in the proportion of patients in response and on treatment at Week 12, between the aripiprazole group (54%) and the haloperidol group (35%). This assumed a 2-sided test at the 0.05 level. The estimated percentages of patients in response and on treatment at Week 12 were derived from an estimated response rate at the end of Week 3 of 60% in the aripiprazole group versus 50% in the haloperidol group, and the estimated number of patients who either dropped out after the end of Week 3 or were not in response at the end of Week 12 (10% in the aripiprazole group and 30% in the haloperidol group).

Statistical methods

The LOCF data set included data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous visit. The Observed Case (OC) data set consisted of the actual observations at each visit. Efficacy analyses per time point were performed using both the LOCF and OC data sets. The LOCF data set was the primary data set for the efficacy analyses per time point. The analyses of the OC data set were considered secondary and were performed to corroborate those on the LOCF data set.

Baseline data for continuous outcome measures were evaluated by ANOVA with treatment and study centre as main effects. Change scores were derived by subtracting the baseline score from the score at each follow up visit.

Results

Participant flow

In CN138008, 347 patients randomised to double-blind treatment: 175 patients to the aripiprazole group and 172 patients to the haloperidol group. Nine of the 347 patients randomised to treatment were excluded from the Efficacy Sample, resulting in a total of 338 patients in the Efficacy Sample (174 aripiprazole-treated and 164 haloperidol-treated).

Baseline data

The treatment groups were similar for variables of age, race, and weight. More men were randomised to the aripiprazole group (43%) compared with the haloperidol group (33%). The majority of patients were White (89%).

More patients experienced a manic-type episode than a mixed-type episode at baseline. The treatment groups were similar on the baseline ratings scales.

Outcomes

Key efficacy results from study CN138008 are summarised in Table 12.

Table 12: CN138008 – Key efficacy results

	Haloperidol	Aripiprazole
Primary Efficacy Measure		
Response Rate (Safety Sample)	N = 169	N = 175
Number of Responders[a] at Week 12 (%)	48 (28.4)	87 (49.7)
Ratio of Response Rates vs Haloperidol (95% CI)	1.75 (1.33, 2.30)**	
Secondary Efficacy Measures		
Response Rate (Safety Sample)	N = 169	N = 175
Number of Responders[b] at Week 3 (%)	72 (42.6)	89 (50.9)
Ratio of Response Rates vs Haloperidol (95% CI)	1.19 (0.95, 1.50)	
Responders at Week 12 in the Subset of Patients who Completed Week 3 with a CGI-BP Severity (mania) Score of < 4 and a MADRS Total Score < 18	N = 77	N = 112
Number of Responders[a] (%)	42 (54.6)	77 (68.8)
Ratio of Response Rates vs Haloperidol (95% CI)	1.26 (1.00, 1.58)*	
Other Secondary Efficacy Measures		
Remission Rate (Safety Sample)	N = 169	N = 175
Number in Remission[c] at Week 12 (%)	45 (27)	87 (50)**
Ratio of Remission Rates vs Haloperidol (95% CI)	1.87 (1.41, 2.47)**	
Time to discontinuation for any reason (Safety Sample)	N = 169	N = 175
Hazard Ratio	1.94 (1.47, 2.57)**	
Y-MRS Total Score (Efficacy Sample, LOCF)	N = 162	N = 174
Mean Baseline	31.39	31.07
Mean Change at Week 12 (LOCF)	-18.22	-19.93

Source: CN138008 Week 12 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with haloperidol

[a] A responder was a patient who had at least a 50% decrease from baseline on the Y-MRS Total Score and who did not discontinue at or before Week 12.

[b] A responder was a patient who had at least a 50% decrease from baseline on the Y-MRS Total Score and who did not discontinue at or before Week 3.

[c] A patient with remission in a specific study week was a patient with a Y-MRS Total Score < 12 who did not discontinue in, or prior to, that study week.

Due to the protocol-specified inability to lower the haloperidol dose below 10 mg or to prescribe anticholinergic agents in CN138008, there was a higher discontinuation rate in the haloperidol arm. The high discontinuation rate contributed to the differences between

treatment groups on the primary endpoint; the number of responders at Week 12 (patients with a ≥ 50% decrease from baseline in Y-MRS Total score) who remained in the study. In addition, CN138008 did not contain a placebo group hence this study is considered a supportive study for maintenance of effect rather than pivotal. The 12-week data from this study are presented to support aripiprazole's maintenance of effect observed in CN138135 and CN138162.

Aripiprazole was superior to haloperidol on the primary efficacy endpoint, percentage of patients on-treatment and in response at Week 12 ($P < 0.001$). For the secondary efficacy measure of percentage of patients on-treatment and in response at the end of Week 3, the aripiprazole group showed a higher response (51%) compared to the haloperidol group (43%); however; the difference was not statistically significant. For the cohort of patients who continued in the study by meeting eligibility criteria at Week 3 (CGI-BP Severity of Illness [mania] Score < 4 and MADRS Total Score < 18), the aripiprazole group (69%) was superior to the haloperidol group (55%) at the end of Week 12 ($P = 0.048$).

The proportion of patients on-treatment and remission (Y-MRS Total Score < 12) was greater in the aripiprazole group (50%) than in the haloperidol group (28%) at Week 12 ($P < 0.001$). Furthermore, aripiprazole was superior to haloperidol ($P < 0.001$) in time to discontinuation for any reason. The mean change from baseline to Week 12 in the Y-MRS Total Score (LOCF) was similar between the aripiprazole and the haloperidol group.

Evaluator Comment

The high drop-out rate in the haloperidol group may have influenced efficacy outcomes therefore results from this study should be interpreted with caution.

Evaluator's overall conclusions on clinical efficacy

Acute treatment

Primary endpoint

Results from four flexible-dose studies showed that aripiprazole was superior to placebo in the short-term (3 week) treatment of acute manic episodes on the primary efficacy measure, the mean change from baseline to Week 3 in the Young-Mania Rating Scale (Y-MRS) Total Score.

In CN138135 and CN138162 (starting dose of aripiprazole 15 mg/day), the aripiprazole group showed superiority over the placebo group on the mean change from baseline to Week 3 in Y-MRS Total Score ($P < 0.001$ and $P = 0.039$, respectively). The active-control groups of lithium (CN138135) and haloperidol (CN138162) also showed superiority over the placebo groups on the mean change from baseline to Week 3 in Y-MRS Total Score (both, $P = 0.005$). The fact that the active comparators showed superiority over placebo provides assay sensitivity, thereby validating the results of aripiprazole. Although the studies were not designed to assess dose response, the positive results in CN138135 and CN138162 support an aripiprazole starting dose of 15 mg/day for this population.

In CN138009 and CN138074 (aripiprazole at a starting dose of 30 mg/day), the mean change from baseline to Week 3 (LOCF) was statistically significant for the aripiprazole group versus the placebo group ($P = 0.002$ and $P < 0.001$, respectively).

Results of the fixed-dose study, CN138007 showed no differentiation from placebo for either dose of aripiprazole (15 mg/day or 30 mg/day) for the LOCF data set in the mean change from baseline in Y-MRS Total Score. In this study there was a notably high placebo response

rate, and this may have contributed to the failure to show superiority of aripiprazole treatment over placebo.

Secondary Endpoints

In terms of secondary endpoints, results were as follows:

Response Rates

For two studies, CN138009 and CN138074, response rates in the aripiprazole group were superior to the placebo group (both studies, P = 0.001). Similarly, in CN138135, response rates in the aripiprazole and the lithium group at Week 3 were superior to the placebo group (P = 0.036 and P = 0.032, respectively).

By contrast, in CN138162, the response rates in the aripiprazole and the haloperidol groups were numerically higher (47% and 50%, respectively, versus 38% in placebo) but were not statistically significantly different than the placebo group for either active treatment group (P = 0.145 and P = 0.069, respectively). In CN138007, the response rates for both the 15 mg or the 30 mg aripiprazole group were also not statistically significantly different from the placebo group.

CGI-BP Severity of Illness (Mania) Score

For CN138009 and CN138074, the aripiprazole group showed superiority in CGI-BP Severity of Illness (mania) Scores versus the placebo group (CN138009 P = 0.001; CN138074 P = 0.009). Similarly, in CN138135 and CN138162 (starting aripiprazole dose of 15 mg/day) statistically significant treatment differences between the aripiprazole and placebo groups were in favour of aripiprazole (P = 0.002 and P = 0.044, respectively). In these studies, the active-control groups of lithium (CN138135) and haloperidol (CN138162) were also superior to the placebo group (P = 0.041 and P = 0.004, respectively).

Once again, in CN138007 results were not favourable for aripiprazole; there were no statistically significant treatment differences for aripiprazole versus placebo.

PANSS Hostility Subscale Score

In CN138009 and CN138074, aripiprazole was superior at Week 3 over the placebo group on the PANSS Hostility Subscale Score (P = 0.003 and P = 0.002, respectively). Similarly, in CN138135, the aripiprazole group showed a statistically significant mean decrease from baseline on the PANSS Hostility Subscale Score at Week 3 (P = 0.006) compared with the placebo group; however, the treatment difference in the lithium group versus the placebo group was not statistically significant in this study. In CN138162, both the aripiprazole and the haloperidol groups showed superiority over the placebo group (P = 0.004 and P < 0.001, respectively).

In CN138007, there were no statistically significant differences between the aripiprazole and the placebo group on mean change in PANSS Hostility Subscale Score at Week 3.

CGI-BP Change from Preceding Phase (Mania) Score

In CN138009 and CN138074, the aripiprazole group was superior to the placebo group (both studies, P = 0.001) on the mean CGI-BP Change from Preceding Phase (mania) Score at Week 3. Similarly, in CN138135 and CN138162, the mean CGI-BP Change from Preceding Phase (mania) Score at Week 3 was significantly improved in the aripiprazole groups compared with the placebo groups (P < 0.001 and P = 0.031, respectively). For the active-control groups, the improvement at Week 3 versus the placebo group was statistically significant, in favour of the haloperidol group in CN138162 (P = 0.005), but not in favour of the lithium group in CN138135 (P = 0.197).

In the fixed-dose CN138007, there were no statistically significant treatment differences between the aripiprazole groups and the placebo group on this measure.

Onset of Efficacy

Early control of acute manic symptoms is important for patients. Aripiprazole demonstrated efficacy at Week 3 in 4 of the 5 placebo-controlled studies. In CN138007, aripiprazole did not differentiate from placebo at Week 3 (LOCF) on the primary and secondary efficacy measures.

In the two studies with a starting dose of 30-mg aripiprazole (CN138009, CN138074), onset was reported as early as Day 4 with continued efficacy at each time point through Week 3.

In the two studies with a starting dose of 15-mg aripiprazole (CN138135, CN138162), onset of efficacy was reported as early as Day 2. At every time point thereafter, statistically significant results in favour of the aripiprazole group were demonstrated in CN138135, but not in CN138162, where significance was not shown at Day 4, Week 1, or Day 10. In CN138162, the active-control group of haloperidol was superior to the placebo group starting at Day 2 through Week 3. In CN138135, the lithium group was superior to the placebo group starting at Week 1 through Week 3.

Subgroup analyses

Subgroup analyses on the model-based mean change from baseline to Week 3 in the Y-MRS Total Score for the LOCF data set were conducted in subsets of the pooled 3-week placebo-controlled comparisons including gender, age, race, psychiatric characteristics (type of episode and rapid cycling) and baseline psychiatric status as evaluated by the Y-MRS Total Score. Results were in favour of aripiprazole across all subsets. The treatment-by-subgroup interaction terms were not statistically significant for any of the subgroups.

Overall the evaluator considered that the data submitted for evaluation adequately support that aripiprazole is effective for the acute treatment of patients with Bipolar I Disorder.

Maintenance of effect (12-Week studies)

Two studies, CN1138135 and CN138162, were conducted to assess whether the efficacy of aripiprazole at Week 3 was maintained through Week 12. Maintenance of effect was evaluated by comparing the originally randomised aripiprazole treatment groups and the active-control treatment groups of lithium (CN138135) and haloperidol (CN138162) during the 12-week double-blind treatment phase for the Efficacy Sample and also by comparing the Week 3 Responder Sample (all patients who were randomised to aripiprazole or lithium/haloperidol and were on study and in response at Week 3 and had an efficacy evaluation beyond Week 3).

In both studies, the response seen in the aripiprazole group at Week 3 was maintained through Week 12 (Efficacy Sample), with similar results reported in the Week 3 Responder Sample. In CN138135, the percentages of patients in remission (defined as a Y-MRS Total Score ≤ 12) increased between Week 3 and Week 12, in the aripiprazole group (40.3% and 49.4%, respectively) and remained stable in the lithium group (40.0% and 39.4%, respectively). In CN138162, remission rates were higher at Week 12 than Week 3 in both the aripiprazole (69.9% vs 44.0%, respectively) and the haloperidol groups (71.4% vs 45.3%, respectively), but were similar between treatment groups at each time point.

An additional maintenance of effect study, CN138008, was conducted comparing aripiprazole with haloperidol. Two design features of this study that were different to CN138162 were the protocol-specified inability to lower the haloperidol dose below 10 mg

or to prescribe anticholinergic agents. These design features of CN138008 resulted in a higher discontinuation rate in the haloperidol arm. Also, CN138008 did not include a placebo group; hence, this study is not considered pivotal in support of the maintenance indication. Nevertheless, aripiprazole was superior to haloperidol on the primary efficacy endpoint, percentage of patients on-treatment and in response at Week 12 (49.7% vs 28.4%, P < 0.001).

The evaluator considered that the data from studies CN138135 and CN138162 adequately demonstrate that aripiprazole is effective for the maintenance treatment of patients with Bipolar I Disorder for a period of 12 weeks.

Maintenance Treatment for the Prevention of Recurrence

Maintenance up to 26 Weeks

In CN138010, aripiprazole was effective in maintaining the stability of patients with Bipolar I Disorder whose most recent episode was manic or mixed type. The proportion of patients in relapse was less in the aripiprazole group (25%) than the placebo group (43%) in the maintenance phase. Aripiprazole treatment significantly reduced the risk of relapse compared with placebo treatment by approximately half, as indicated by the HR: 0.523 (95% CI 0.300, 0.913).

Key secondary efficacy measures were the time to manic relapse and the time to depressive relapse during the maintenance phase. There was a statistically significant difference, in favour of aripiprazole, in time to delaying manic relapse (P = 0.008), but no significant difference in time to delaying depressive relapse (P = 0.684) during the maintenance phase. The number of patients who had a manic type relapse was approximately 3 times less in the aripiprazole group than the placebo group (8% in aripiprazole versus 23% in placebo). These results support efficacy of aripiprazole as maintenance treatment.

Study CN138010 was designed to detect a clinically meaningful difference between treatment groups for relapses of any bipolar event; it was not designed or powered to detect treatment differences for relapses specifically into depressive episodes. In order to evaluate whether aripiprazole prevents depressive relapses, patients with an index episode of bipolar depression would need to be studied.

Maintenance Treatment Greater Than 1 Year

The statistical analysis plan for study CN138010 pre-specified an analysis of time from randomisation to relapse (as defined by discontinuation due to lack of efficacy) for a period of greater than 1 year using data from the combined maintenance and extension phases. Of the 67 patients who completed the 26-week maintenance phase, 66 continued into the 74-week extension phase. This duration of treatment meets requirements of the TGA-adopted EU guidance for the evaluation of treatment for recurrence prevention in bipolar disorder.[2]

Consistent with findings in the maintenance phase, aripiprazole was superior to placebo in delaying the time to relapse during the combined maintenance and extension phases, further supporting the efficacy of aripiprazole in maintaining the effect in prevention of relapse in patients with Bipolar I Disorder, manic or mixed. The proportion of patients in relapse was less in the aripiprazole group (32%) than the placebo group (52%). Aripiprazole treatment reduced the risk of relapse compared with placebo by nearly half, as indicated by the HR: 0.531 (95% CI 0.324, 0.871).

[2] EMEA, Committee for Proprietary Medicinal Products (CPMP), 26 April 2001. Note for guidance on clinical investigation of medicinal products in the treatment and prevention of bipolar disorder (CPMP/EWP/567/98).

A post-hoc analysis was conducted on the combined maintenance and extension phases. It included rating scales to document the recurrence of bipolar symptoms after stabilisation of the patient's bipolar disorder. The post-hoc analysis showed that the proportion of patients in relapse was less in the aripiprazole group (27%) than in the placebo group (47%) in the combined maintenance and extension phase. Aripiprazole treatment significantly reduced the risk of relapse compared with placebo by half, as seen by the HR: 0.496, (95% CI 0.291, 0.845). The post-hoc analysis confirmed the results of the prospectively-defined analysis of time to relapse for any event over a time period greater than one year.

It is of some concern that the numbers of patients analysed for efficacy up to 1 year are not large. However, overall this study is considered supportive of an indication for the prevention of a new manic episode in patients whose manic episodes responded to aripiprazole treatment.

Combination Therapy

Data from a 6-Week combination therapy study, CN138134, were included in the submission. Patients who were partially nonresponsive to mood stabilisers (defined by a Y-MRS Total Score $\geq$ 16 during Phase 1 and at the end of Phase 2, with a decrease of $\leq$ 25% between Phases 1 and 2) were randomised to receive either aripiprazole or placebo in combination with lithium or valproate in a 6-week, double-blind phase (Phase 3).

The aripiprazole group (aripiprazole in combination with either lithium or valproate) showed statistically significantly greater improvement than the placebo group (placebo in combination with either lithium or valproate) on the primary efficacy endpoint, the mean change from baseline to Week 6 (Phase 3) in the Y-MRS Total Score (P = 0.002) and on the key secondary efficacy endpoint, the CGI-BP Severity of Illness (mania) Score (P = 0.014).

There was a statistically significant difference between treatment groups in the mean CGI-BP Change from Preceding Phase (mania) Score favouring aripiprazole at Week 6 (P = 0.037). The aripiprazole group was superior to the placebo group in PANSS Hostility Subscale Scores (P = 0.001). The mean changes from baseline to Week 6 in CGI-BP Severity of Illness (depression) Score and in MADRS Total Score were similar between the aripiprazole group and the placebo group.

Overall the results support that aripiprazole is efficacious when used in combination with lithium or valproate in the treatment of patients with Bipolar I Disorder.

Safety

Introduction

Safety data were presented as follows:

- 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania: Safety data were presented for 7 studies: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135 and CN138162. For administrative reasons, CN138062 and CN138077 were terminated early; however safety data from these studies were included in the submission.
- 6-Week Combination Therapy Study: Safety data are presented for CN138134.
- 12-Week Active-controlled Studies: Safety data were presented separately for 3 active-controlled studies that compared aripiprazole, administered at a starting dose of 15 mg/day (with the option to increase the dose to 30 mg/day for clinical response) with lithium (in CN138135) or haloperidol (in CN138162 and CN138008),

administered for up to 12 weeks in patients with a diagnosis of Bipolar I Disorder who were acutely manic.

- Maintenance Treatment Study: Safety data were presented from the maintenance phase of CN138010 comparing aripiprazole with placebo, administered for up to 26 weeks in patients who were previously stabilized on aripiprazole 15 mg/day or 30 mg/day. Additional summaries presented data for the combined 26-week maintenance phase and the 74-week extension phase.
- All Aripiprazole Safety Dataset: Cumulative data on patients exposed to aripiprazole in all Phase 2/3/4 studies were submitted, including the bipolar mania studies that have unblinded or open-label data (ongoing CN138134 extension, CN138135 extension, CN138189 and CN138392).

Patient exposure

A total of 2626 patients received aripiprazole tablets in the acute bipolar mania clinical trial program; 13543 patients received aripiprazole tablets across all Phase 2/3/4 studies in various indications. Table 13 presents a summary of the number of patients who received aripiprazole in the safety sample of these studies.

In most Phase 2/3/4 studies across the clinical program, aripiprazole was administered as monotherapy. In three studies of bipolar mania, aripiprazole was administered as adjunctive therapy: to lithium or valproate in CN138134 and CN138189 and to lamotrigine in CN138392. CN138189 and CN138392 are ongoing and blinded, but have open-label phases that contributed data to the All Aripiprazole Data Set. In studies of major depressive disorder (MDD), aripiprazole was administered as adjunctive therapy to antidepressant therapy (escitalopram, sertraline, venlafaxine, fluoxetine, paroxetine, mirtazapine, and bupropion). In one ongoing study in schizophrenia (CN138170), aripiprazole is administered as adjunctive therapy to clozapine; in another ongoing study in schizophrenia (CN138397) aripiprazole is administered as adjunctive therapy to patients on quetiapine or risperidone.

Table 13: Summary of All Studies, Aripiprazole (Oral Tablet), Safety Sample

Pools by Indication and Study Design	Enumeration of Patients by Treatment Group[a]			
	Placebo	Atypical[b]	Haloperidol, Perphenazine, or Lithium	Aripiprazole
Bipolar Mania				
3-Week Placebo-Controlled[c]	753	n/a	324	917
6-Week Combination Therapy	130	n/a	n/a	253
12-Week Active-Controlled[c]	n/a	n/a	169	175
Maintenance Treatment Study	[83][d]	n/a	n/a	[77][d]
Other	n/a	n/a	n/a	128 (63)[e]
Uncontrolled/Open Label	n/a	n/a	n/a	1637 (421)[e]
Total Bipolar Mania	883	n/a	493	2626
Major Depressive Disorder[f]				
6-Week Placebo-Controlled Trials	366	n/a	n/a	371
Ongoing, Uncontrolled/Open-Label	n/a	n/a	n/a	930 (246)[e]
Total Major Depressive Disorder	366	n/a	n/a	1055
Bipolar Depression				
8-Week Placebo-Controlled	367	n/a	n/a	360
Ongoing, Uncontrolled/Open-Label	n/a	n/a	n/a	407 (174)[e]
Total Bipolar Depression	367	n/a	n/a	593
Schizophrenia				
Short-Term Placebo-Controlled	500	99	200	1204
Short-Term Active-Controlled	n/a	n/a	144[g]	153
Long-Term Controlled	153	712	431	1731
Other	n/a	n/a	42	588 (88)[e]
Ongoing Uncontrolled/Open Label[h]	n/a	111	n/a	6025 (1398)[e]
Total Schizophrenia	653	922	817	8215

Table 13 (cont): Summary of All Studies, Aripiprazole (Oral Tablet), Safety Sample

	Enumeration of Patients by Treatment Group[a]			
Pools by Indication and Study Design	**Placebo**	**Atypical[b]**	**Haloperidol, Perphenazine, or Lithium**	**Aripiprazole**
Psychosis in Alzheimer's Disease				
Placebo-controlled	343	n/a	n/a	595
Ongoing Uncontrolled/Open-Label	n/a	n/a	n/a	859 (560)[e]
Total Psychosis	343	n/a	n/a	894
Other Indications				
Parkinson's	n/a	n/a	n/a	14
Alcoholism	143	n/a	n/a	146
Total Phase2/3/4 Exposure[i]	2755	922	1310	13,543[j]

Source: Appendices 1A and 1B

NOTE: Safety Sample includes all patients who received at least 1 dose of study medication as indicated on the dosing record.

[a] Excludes clinical studies conducted in Japan and other Asian countries, and pediatric data.

[b] Includes olanzapine and risperidone.

[c] In CN138135 and CN138162, patients were randomized to aripiprazole, active control, and placebo for the first 3 weeks; patients randomized to placebo were blindly switched to aripiprazole after Week 3 and all patients continued for an additional 9 weeks of double-blind, active-controlled treatment. Patients who switched from placebo to aripiprazole are enumerated in the uncontrolled/open-label row. Patients treated with lithium or haloperidol are enumerated in the 3-week row.

[d] The number in brackets represents patients participating in the double-blind placebo-substitution phase of CN138010 but who were already counted in the aripiprazole column under uncontrolled/open label. The numbers in brackets do not include patients who were unblinded due to mislabeling.

[e] The number in parentheses represents patients participating in open-label extension phases and studies, but who were already counted in the aripiprazole column under other study groups (eg, short-term and long-term controlled studies and other studies).

[f] In all studies of MDD, aripiprazole was administered as adjunctive therapy with antidepressant treatment. This claim is not being pursued in the EU, but was submitted as a separate sNDA in the US.

[g] Perphenazine-treated patients.

[h] Open-label CN138087, CN138100, and CN138152 had 674 patients randomized to a "standard of care" group.

[i] As of 1-Dec-2006, treatment was still blinded for a total of 344 patients from schizophrenia and MDD studies; and as of 14-Feb-2007, treatment was still blinded for a total of 152 patients from 2 adjunctive placebo-substitution studies in bipolar mania.

[j] All Aripiprazole Data Set.

3-Week Placebo-Controlled Comparisons: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162

Among all aripiprazole-treated patients across the 3-week placebo-controlled comparisons, 81.4% received drug for at least 8 to 14 days, and 58.8% received the drug for more than 15 days. Across the fixed and flexible dose studies, 32.7% received an overall mean dose of ≤17.5 mg/day, while 55.5% received a mean dose of > 25 mg/day.

6-Week Combination Therapy: CN138134

A total of 253 patients received aripiprazole (147 with valproate, 106 with lithium); 130 patients received placebo (80 with valproate, 50 with lithium). Most patients in both groups had at least 5 weeks of treatment (77.9% aripiprazole, 88.5% placebo). The majority (71.9%)

of aripiprazole-treated patients had an overall mean dose that reflected primarily the use of a 15 mg/day dose. Dosing patterns were similar between the 2 mood stabiliser groups.

Active-Controlled Studies: CN138008, CN138162, CN138135

In the 12-week active-controlled studies, aripiprazole was compared to haloperidol in CN138008 and CN138162 and to lithium in CN138135. The percentage of patients who remained on study therapy through 78 days was greater for aripiprazole (52.6%) than haloperidol (30.2%) in CN138008, was similar for aripiprazole and haloperidol in CN138162 (57.8% aripiprazole, 58.2% haloperidol), and was 26.6% for aripiprazole and 34.6% for lithium in CN138135.

The distribution of patients among mean dose categories showed that 49.1% and 40.4% of patients in the haloperidol studies (CN138008 and CN138162) and 37.7% of patients in the lithium study (CN138135) had an overall mean aripiprazole dose of≤ 17.5 mg/day.

Maintenance Treatment: CN138010

Among patients who entered the maintenance phase of CN138010, approximately half (37/77) continued on aripiprazole therapy for 6 months, while the mean daily dose remained stable through endpoint at approximately 24 mg/day). Among aripiprazole-treated patients, 35.0% of patients were on the 15 mg/day dose; 65.0% were on the 30 mg/day dose at endpoint. In the combined maintenance and extension phases, the proportion of patients with an overall mean dose between > 12.5 mg - ≤ 17.5 mg (reflecting a 15 mg/day dose) was 31.2%, while 58.4% had an overall mean dose between > 25 mg - ≤ 32.5 mg (reflecting a dose of 30 mg/day).

All Aripiprazole-Treated Patients

In the bipolar mania program, a total of 2626 patients received at least one dose of aripiprazole treatment; 1895 received aripiprazole for at least 3 weeks; and 1446 received aripiprazole for at least 6 weeks. The number of patient exposure years was 546.8. In the bipolar mania studies, most aripiprazole-treated patients were distributed evenly in overall mean dose categories of >12.5 to ≤ 17.5 mg/day (36.3%) and >25.0 to ≤ 32.5 mg/day (39.2%), reflecting 15 mg/day and 30 mg/day dose regimens, respectively.

Adverse events

3-Week Placebo-Controlled Comparisons: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162

Incidence of Treatment-Emergent Adverse Events

In the bipolar mania placebo-controlled comparisons (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), the incidence of treatment-emergent AEs was 82.8% in the aripiprazole group and 71.7% in the placebo group. Common AEs that occurred at an incidence of ≥ 5% (including numbers that equalled or were greater than 5% after rounding) and twice that of placebo included akathisia, sedation, extrapyramidal disorder and restlessness.

In the pooled bipolar mania placebo-controlled comparisons (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162) and placebo-controlled schizophrenia studies (31-93-202, 31-94-202, 31-97-201, 31-97-202, CN138001), the incidence of treatment-emergent AEs was 87.0% in the aripiprazole group and 77.4% in the placebo group.

In the pooled bipolar mania placebo-controlled comparisons (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), drug-related, treatment-emergent AEs that were reported in the aripiprazole group at a rate ≥ 1% greater than the rate

in the placebo group were (by MedDRA *System Organ Class* [SOC] and Preferred Term [PT])[3]:

Nervous System Disorders: headache, akathisia, sedation, tremor, extrapyramidal disorder, somnolence

Gastrointestinal Disorders: nausea, constipation, vomiting, dyspepsia, salivary hypersecretion, stomach discomfort

Psychiatric Disorders: restlessness, anxiety

Musculoskeletal and Connective Tissue Disorders: musculoskeletal stiffness

General Disorders and Administration Site Conditions: fatigue

Eye Disorders: vision blurred

In the pooled bipolar mania placebo-controlled comparisons (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162) and placebo-controlled schizophrenia studies (31-93-202, 31-94-202, 31-97-201, 31-97-202, CN138001, CN138047), drug-related, treatment-emergent AEs that were reported in the aripiprazole group at a rate ≥ 1% greater than the rate in the placebo group, by SOC, were:

Nervous System Disorders: headache, akathisia, dizziness, sedation, tremor, somnolence, extrapyramidal disorder

Gastrointestinal Disorders: nausea, vomiting, constipation, dyspepsia, salivary hypersecretion

Psychiatric Disorders: insomnia, anxiety, restlessness

General Disorders and Administration Site Conditions: fatigue

Eye Disorders: vision blurred

The adverse drug reactions (ADRs) of tachycardia and orthostatic hypotension were also reported in the pooled aripiprazole group, but did not occur at ≥ 1% placebo-subtracted rate; however these events are still considered to be clinically important events.

6-Week Combination Therapy: CN138134

Incidence of Treatment-Emergent Adverse Events

In the combination therapy study of aripiprazole or placebo co-administered with lithium or valproate, the overall incidence of treatment-emergent AEs was 62.1% for aripiprazole and 53.8% for placebo. AEs reported for patients in the aripiprazole group at an incidence of 5% or greater (including numbers that equalled or were greater than 5% after rounding) and twice that of placebo included akathisia, insomnia and extrapyramidal disorder.

Active-Controlled Studies: CN138008, CN138162, CN138135

Incidence of Treatment-Emergent Adverse Events

In the 12-week haloperidol-controlled studies, the aripiprazole group had lower incidences relative to the haloperidol group of akathisia, extrapyramidal disorder, tremor and parkinsonism, with the latter 2 primarily reported in CN138008. Patients in the aripiprazole group reported higher incidences of nausea (primarily in CN138008) and mania (primarily in CN138162).

[3] MedDRA: Medical Dictionary for Regulatory Activities

In the 12-week lithium-controlled study, patients in the aripiprazole group reported lower incidences than the lithium group of tremor, but higher incidences of akathisia, sedation, insomnia, agitation, restlessness, dry mouth, musculoskeletal stiffness and fatigue.

Maintenance Treatment: CN138010

Incidence of Treatment-Emergent Adverse Events

Among patients who received aripiprazole or placebo in the maintenance treatment study (CN138010), the incidence of treatment-emergent AEs was similar for the aripiprazole and placebo groups. In CN138010 there was no clear pattern of late-emerging AEs. The AE of weight increased was reported at a higher rate in the aripiprazole group than the placebo group; however, no definitive conclusion can be drawn because of the small sample sizes.

The incidences of drug-related AEs for the combined maintenance and extension phases were similar to those reported in the maintenance phase.

Adverse events of special interest

Extrapyramidal symptoms

In the 3-week placebo-controlled comparisons, the overall incidence of extrapyramidal symptoms (EPS)-related AEs was 26.5% in the aripiprazole group and 11.3% for the placebo group. Akathisia (13.0% vs 3.6%) and extrapyramidal disorder (5.3% vs 1.7%) were the most frequently reported EPS-related AEs in the aripiprazole group. The rate of discontinuation from study therapy because of an EPS-related AE was higher in the aripiprazole group (2.9%) than the placebo group (0.7%). Akathisia accounted for most of the discontinuations in the aripiprazole group (2.1% vs 0.3% for placebo).

In the 6-week combination therapy study, the incidence of EPS-related AEs was 28.1% in the aripiprazole group and 13.8% in the placebo group. Akathisia was higher in the aripiprazole group than the placebo group (18.6% vs 5.4%). EPS-related AEs led to discontinuation for 5.9% of patients in the aripiprazole group and 1.5% in the placebo group. In this study akathisia and tremor accounted for all discontinuations.

In the aripiprazole group, there was a difference in the incidence of akathisia and tremor, when analysed by mood stabiliser co-treatment. The incidence of treatment-emergent akathisia in patients on lithium-aripiprazole treatment was 28.3% versus 4.0% in the lithium-placebo group and 11.6% in patients on valproate-aripiprazole treatment versus 6.3% in the valproate-placebo group. The incidence of tremor in the lithium-aripiprazole group was 13.2% versus 8.0%in the lithium-placebo group and 6.1% in the valproate-aripiprazole group versus 5.0% in the valproate-placebo group.

In both haloperidol-controlled studies, the incidence of EPS-related AEs and the rate of discontinuation from therapy because of EPS-related events was lower in the aripiprazole groups than in the haloperidol groups. In the lithium-controlled study, the incidence of EPS-related AEs was higher in the aripiprazole group (26.6%) than in the lithium group (17.6%). Akathisia was the most frequently reported AE leading to discontinuation of aripiprazole treatment, while tremor was the most frequently reported reason for discontinuation of lithium treatment.

In the maintenance treatment study, the incidence of EPS-related AEs in the maintenance phase of CN138010 was similar for the treatment groups (aripiprazole 18.2%, placebo 15.7%). The most frequently reported (≥ 5%) EPS-related AEs in the aripiprazole group were tremor (9.1% vs 1.2%) and akathisia 6.5% vs 3.6%).

Seizure

The rate of seizure was low in the 3-week placebo-controlled comparisons, the 12-week maintenance of effect studies, the 6-week combination therapy study, the maintenance treatment study, and among all aripiprazole-treated patients with bipolar mania.

In the 3-week placebo-controlled comparisons in acute bipolar mania, 2 (0.2%) aripiprazole-treated patients experienced convulsions and 2 (0.3%) placebo-treated patients reported grand mal convulsions.

No patient reported a seizure-related AE in the 6-week placebo-controlled phase of CN138134. In the active controlled studies (CN138008, CN138162, CN1381350 one aripiprazole-treated patient (CN138135-44-137) reported a seizure-related AE in CN138135.

In the maintenance treatment study, CN138010, no seizure-related AEs were reported during the combined maintenance and extension phases.

Neuroleptic Malignant Syndrome (NMS)

All Aripiprazole-Treated Patients

A comprehensive search of the AE database for all Phase 2/3/4 studies was conducted to identify aripiprazole-treated patients who had NMS reported as an AE. Three out of 13543 patients (0.02%) exposed to aripiprazole in Phase 2/3/4 clinical studies reported an AE of NMS (98304-534-54, schizophrenia; CN138007-19-133, bipolar mania; CN138004-105-429, dementia). The events for all 3 patients were previously reported in the sponsor's aripiprazole *Integrated Summary of Safety* (October 2001) or *Summary of Safety* (June 2005). No new cases of NMS were reported in the sponsor's *120-Day Safety Update* (October 2005) or to the data cut-off date for the current submission.

Orthostasis

Orthostatic hypotension was defined as ≥ 20 mmHg decrease from baseline in systolic blood pressure measurements and ≥ 25 beats per minute (bpm) increase from baseline in heart rate, both taken from supine to standing. This was different to the definition previously used in aripiprazole submissions (≥ 30 mmHg decrease in systolic blood pressure and ≥ 25 bpm increase in heart rate).

There were no statistically significant differences between the aripiprazole groups and placebo groups in the incidence of orthostatic hypotension across any of the placebo-controlled studies in bipolar mania.

In the 3-week placebo controlled comparisons, the incidence of the treatment-emergent AE of "orthostatic hypotension" was higher in the aripiprazole group than the placebo group (aripiprazole 0.7%; placebo 0.1%); however no differences were observed in either the 6-week adjunctive therapy or 26-week maintenance treatment studies.

Weight Measurements

Potentially clinically relevant weight gain or loss was defined as a ≥ 7% increase or decrease from baseline, respectively.

In the 3-week placebo-controlled comparisons, the 12-week active-controlled studies (CN138008, CN138162, CN138135), and the 6-week combination therapy study (CN138134), there were no statistically significant differences between the aripiprazole groups and comparator groups in weight gain or loss, or body mass index (BMI).

In the maintenance treatment study (CN138010), the mean change from randomisation to endpoint (LOCF) in body weight showed an increase (0.47 kg) for aripiprazole-treated

patients and a decrease (-1.72 kg) for placebo-treated patients; however, the difference was not statistically significant (p=0.056). Aripiprazole-treated patients had a statistically significantly greater incidence of clinically relevant weight gain (12.5% vs 0% placebo, p = 0.005) and a statistically significantly lower incidence of clinically relevant weight loss (1.8% vs 16.7% placebo, p = 0.006) than placebo-treated patients. There were no clinical concerns raised in this study regarding significant changes in weight beyond what is currently labelled.

Among all aripiprazole-treated patients in bipolar mania studies, the incidence of clinically relevant weight gain increased over time, regardless of whether aripiprazole was given as monotherapy or given in combination with mood stabilisers. In addition the mean percent changes from baseline to endpoint in body weight, BMI, and waist circumference also increased through Week 26 and beyond.

Serious Adverse Events and Deaths

3-Week Placebo-Controlled Comparisons: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162

The incidence of treatment-emergent SAEs in the 3-week placebo-controlled comparisons in acute bipolar mania was similar between treatment groups (6.0% aripiprazole, 4.4% placebo). Mania was the only SAE reported in > 1% of patients (2.1% aripiprazole, 1.6% placebo).

6-Week Combination Therapy: CN138134

The incidence of treatment-emergent SAEs in CN138134 was low in both treatment groups (3.2% aripiprazole, 2.3% placebo). No SAE was reported in > 1% of aripiprazole-treated patients.

Active-Controlled Studies CN138008, CN138162, CN138135

In the haloperidol-controlled studies, the incidence of treatment-emergent SAEs during 12-weeks of treatment was 11.4% for the aripiprazole group and 3.0% for the haloperidol group in CN138162, and 2.3% and 7.1% for the aripiprazole and haloperidol groups, respectively, in CN138008. In the lithium-controlled study (CN138135), the incidence of treatment-emergent SAEs was 12.3% and 8.2% for the aripiprazole and lithium groups, respectively. Treatment-emergent SAEs reported for > 1% of patients in the aripiprazole group in any of the 3 studies were events associated with patients' underlying disease.

Maintenance Treatment: CN138010

During the maintenance phase of CN138010, the incidence of treatment-emergent SAEs was 7.8% in aripiprazole group and 13.3% in the placebo group. Mania was reported in 5.2% of aripiprazole-treated patients and 6.0% of placebo-treated patients. All other SAEs were reported in no more than one patient in either treatment group.

Deaths

3-Week Placebo-Controlled Comparisons: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162

There was one death in a patient who received aripiprazole during the 3-week placebo-controlled comparisons in acute bipolar mania. A 37-year old man (CN138074-18-252) was found dead at his home 5 days after his last dose of aripiprazole. An autopsy revealed hydrocodone intoxication, which was listed as the cause of death. The death was reported as unrelated to study medication.

6-Week Combination Therapy: CN138134

No deaths were reported in the 6-week placebo-controlled phase of CN138134.

Active-Controlled Studies

Three deaths were reported in the active-controlled studies. One of these deaths occurred prior to randomisation: the patient died of cardiac arrest after enrolment and before he was randomised or received any treatment. Two other deaths were reported. In both cases, patients were randomised to placebo in the placebo-controlled phase of CN138162 and switched to aripiprazole after Week 3 of the 12-week double-blind phase of the study. One patient died of pulmonary necrosis and lung abscess and both events were considered unrelated to study therapy. The remaining patient died of probable multiple drug effects (cocaine, alcohol, diphenhydramine, and aripiprazole).

Maintenance Treatment: CN138010

One patient died of heroin intoxication (overdose) during open-label aripiprazole treatment in the Stabilisation phase of CN138010. No patients died during the double-blind placebo-substitution phases (maintenance or extension) of CN138010.

All Aripiprazole-Treated Patients

As of 14 February 2007, five deaths were reported among 2626 patients in the acute bipolar mania studies. There were 546.8 patient years of exposure in these studies. The rate of deaths per PEY was 0.009.

Laboratory findings

Overall, there were no clinically meaningful differences between the treatment groups in the incidences of potentially clinically relevant cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides in the 3-week placebo-controlled comparisons, the 6-week combination therapy study, the 12-week active-controlled studies, or the maintenance treatment study. Among all aripiprazole-treated bipolar mania patients, the incidences of these abnormalities were similar to those reported for patients with schizophrenia. The incidence of hyperglycaemia- or diabetes-related AEs was low in bipolar mania studies.

Among patients in the 3-week placebo-controlled studies and CN138134 in acute bipolar mania who had normal values at baseline, the incidence of haematology abnormalities of potential clinical relevance was low for all parameters in both treatment groups. No aripiprazole-treated patient discontinued because of a haematological abnormality.

Safety related to drug-drug interactions and other interactions

No pharmacokinetic interaction studies of specific relevance to the bipolar mania population have been conducted. Two drug interaction studies conducted in patients with schizophrenia or schizoaffective disorder, which used lithium and valproate (CN13802121 and CN138023, respectively), showed that once daily doses had no clinically relevant effects on the pharmacokinetics of aripiprazole. One drug interaction study was conducted with carbamazepine/aripiprazole (CN138022) in chronically ill patients with schizophrenia or schizoaffective disorder. Results were previously reported in the *sponsor's Schizophrenia Integrated Summary of Safety/Marketing Authorisation Application.* Two interaction studies assessing valproate/aripiprazole (CN138126) and lithium/aripiprazole (CN138127) were conducted in healthy volunteers to determine the effect of aripiprazole on these agents. Pharmacokinetic results of these two studies showed no meaningful effects of aripiprazole on the plasma levels of these drugs. A pharmacokinetic interaction study in patients with Bipolar I Disorder (CN138402) was ongoing at the time of the evaluation but has now been completed. Pharmacokinetics, safety and tolerability of aripiprazole were to be assessed when co-administered with lamotrigine.

Discontinuation due to adverse events

Other Significant Adverse Events

3-Week Placebo-Controlled Comparisons: CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162

The incidence of treatment-emergent AEs that led to discontinuation of study therapy in the 3-week placebo-controlled comparisons in acute bipolar mania was 11.0% for the aripiprazole group and 9.6% for the placebo group. In the aripiprazole group, mania and akathisia were the most frequently reported AEs leading to medication discontinuation.

6-Week Combination Therapy: CN138134

The incidence of treatment-emergent AEs that led to discontinuation of study therapy in CN138134 was 11.9% for the aripiprazole group and 6.2% for the placebo group. Most of this treatment difference was accounted for by the higher incidence in the aripiprazole group of akathisia (aripiprazole 5.1%, placebo 0.8%) and tremor (aripiprazole 2.0%, placebo 0.8%). One patient (CN138134-135-575) was reported to have discontinued because of "hepatic failure." The investigator considered this event to be mild in nature. This patient had a history of hepatitis and was previously treated with valproate. The patient discontinued from the study on Day 19, while at doses of 15 mg aripiprazole and 500 mg valproate. The patient's blood levels of alanine aminotransferase (ALT) increased from 48 U/L at baseline to 96 U/L and aspartate aminotransferase (AST) increased from 20 U/L at baseline to 48 U/L. These values did not exceed the protocol-specified criteria for potential clinical relevance. No further treatment was required. The event persisted at the time of the last follow-up. Incidences of akathisia and tremor were 8.5% and 2.8%, respectively, in patients who received aripiprazole co-administered with lithium compared with 2.7% and 1.4%, respectively, in patients who received aripiprazole in combination with valproate.

Active-Controlled Studies: CN138008, CN138162, CN138135

In the 12-week haloperidol-controlled studies, the incidence of treatment-emergent AEs leading to discontinuation of study therapy was 18.9% for the aripiprazole group and 49.1% for the haloperidol group in CN138008, and 14.5% (aripiprazole) and 10.9% (haloperidol) in CN138162. The difference in these rates between studies was due to the allowed use of anticholinergics in CN138162, but not in CN138008. The most frequently reported AEs leading to discontinuation of aripiprazole treatment were akathisia and depression (primarily in CN138008), and mania (primarily in CN138162). In the 12-week lithium-controlled study (CN138135), the incidence of treatment-emergent AEs leading to discontinuation of study therapy was 20.1% for the aripiprazole group and 17.6% for the lithium group. The most frequently reported AE leading to discontinuation of aripiprazole treatment was akathisia (3.2% of patients).

Maintenance Treatment: CN138010

Adverse events leading to discontinuation of study therapy were reported for 10.4% of patients in the aripiprazole group and 19.3% of patients in the placebo group during the maintenance phase of CN138010. Mania was the most frequently reported AE leading to discontinuation of aripiprazole (3.9%) and placebo (6.0%). All other AEs leading to discontinuation of aripiprazole treatment were reported for no more than one patient per AE term.

Post marketing experience

Aripiprazole was first approved for the treatment of schizophrenia on 17 July 2002 (International Birth Date) in Mexico and subsequently in the United States on 15 November 2002 and the European Union on 4 June 2004. In addition, aripiprazole was approved in the United States on 29 September 2004 for the treatment of Bipolar I Disorder, manic or mixed.

AEs from postmarketing safety surveillance have been summarised in the Periodic Safety Update Reports (PSURs). No new detailed postmarketing data were presented in this submission.

Evaluator's overall conclusions on clinical safety

The safety and tolerability of aripiprazole was assessed in a total of 2626 patients who received aripiprazole in the acute bipolar mania studies and 13543 patients who received aripiprazole across all Phase 2/3/4 studies. Overall, the administration of aripiprazole was well tolerated; AEs were generally mild to moderate in severity, and infrequently led to study discontinuation. The incidence of treatment-emergent AEs was generally lower in studies that used a starting dose of 15 mg/day compared with those that used a starting dose of 30 mg/day. Among all-aripiprazole treated patients, the incidence of treatment-emergent AEs and discontinuations due to AEs in bipolar mania patients was generally similar to that reported in the other patient populations.

3-Week placebo-controlled comparisons

Data from the 3-week placebo-controlled comparisons in bipolar mania showed that the incidence of treatment-emergent AEs was 82.2% in the aripiprazole group and 71.7% in the placebo group. Events of akathisia, sedation, extrapyramidal disorder, and restlessness were reported at an incidence of ≥ 5% (including numbers that equalled or were greater than 5% after rounding) and twice that of placebo. ADRs that were reported in the aripiprazole group at a rate ≥ 1% the rate in the placebo group, by SOC, were:

Nervous System Disorders: headache, akathisia, sedation, tremor, extrapyramidal disorder, somnolence

Gastrointestinal Disorders: nausea, constipation, vomiting, dyspepsia, salivary hypersecretion, stomach discomfort

Psychiatric Disorders: restlessness, anxiety

Musculoskeletal and Connective Tissue Disorders: musculoskeletal stiffness

General Disorders and Administration Site Conditions: fatigue

Eye Disorders: vision blurred

Overall, this ADR profile was similar to that reported in the schizophrenia placebo-controlled studies.

In the 3-Week placebo-controlled studies the rates of death, SAEs, and discontinuation of therapy due to AEs were low. There was one death reported in an aripiprazole-treated patient (hydrocodone intoxication, unrelated to therapy). The incidence of treatment-emergent SAEs was similar between treatment groups (6.0% aripiprazole, 4.4% placebo), with the majority of events occurring in the system organ class of psychiatric disorders. The rates of treatment-emergent AEs that led to discontinuation of study therapy were also similar between treatment groups: 11.0% for the aripiprazole group and 9.6% for the placebo group. Mania and akathisia were the most frequently reported AEs leading to discontinuation of study therapy in the aripiprazole group.

In relation to laboratory findings, the safety profile of the aripiprazole group was similar to that of the placebo group, with low incidences of treatment- emergent serum chemistry, electrolyte, urinalysis, haematology vital sign, and electrocardiogram (ECG) abnormalities. No aripiprazole-treated patient discontinued because of a laboratory abnormality.

12-Week Active-Controlled Studies

In the 12-week lithium-controlled study (CN138135), the aripiprazole group reported lower incidences than the lithium group of tremor, but higher incidences of akathisia, sedation, insomnia, agitation, restlessness, dry mouth, musculoskeletal stiffness, and fatigue. In the 12-week haloperidol-controlled studies, the aripiprazole group reported lower incidences relative to the haloperidol group of akathisia, extrapyramidal disorder, tremor, and parkinsonism, with the latter 2 primarily reported in CN138008. The aripiprazole group reported higher incidences of nausea (primarily in CN138008) and mania (primarily in CN138162).

No deaths were reported during the 12-week phase of CN138135. Two deaths (pulmonary necrosis and lung abscess) were reported in CN138162 after patients were randomised to placebo in the placebo-controlled phase and switched to aripiprazole after Week 3 of the 12-week double-blind phase. The rates of SAEs were higher in the aripiprazole groups than the active-control groups in CN138162 (11.4% vs 3.0% haloperidol, respectively) and CN138135 (12.3% vs 8.2% lithium, respectively), but lower than the haloperidol group in CN138008 (2.3% vs 7.1%, respectively). Most events were reported in the system organ class (SOC) of psychiatric disorders.

The incidence of treatment-emergent AEs leading to discontinuation of study therapy in CN138008 was lower in the aripiprazole group than the haloperidol group (18.9% vs 49.1%), and higher than the haloperidol group in CN138162 (14.5% vs 10.9%). The different rates between these studies were due to the allowed use of anticholinergic medication in CN138162, but not in CN138008. The most frequently reported AEs leading to discontinuation of aripiprazole treatment were akathisia and depression (primarily in CN138008), and mania (primarily in CN138162). In the 12-week lithium-controlled study (CN138135), the incidence of treatment-emergent AEs leading to discontinuation of study therapy was 20.1% for the aripiprazole group and 17.6% for the lithium group. The most frequently reported AE leading to discontinuation of aripiprazole treatment was akathisia (3.2%).

6-Week Combination Therapy Study

In the combination therapy study of aripiprazole or placebo co-administered with lithium or valproate, the overall incidence of treatment-emergent AEs was 62.1% for aripiprazole and 53.8% for placebo. AEs reported for patients in the aripiprazole group at $\geq$ 5% (including numbers that equalled or were greater than 5% after rounding) and twice that of placebo included akathisia, insomnia, and extrapyramidal disorder.

No deaths were reported in the 6-week placebo-controlled phase of CN138134, and the incidence of SAEs was low (aripiprazole 3.2%, placebo 2.3%). More aripiprazole-treated (11.9%) than placebo-treated (6.2%) patients discontinued from study therapy because of an AE, with most of this treatment difference accounted for by the higher incidence in the aripiprazole group of akathisia (aripiprazole 5.1%, placebo 0.8%) and tremor (aripiprazole 2.0%, placebo 0.8%). One patient was reported to have discontinued because of "hepatic failure but the patient's blood levels of ALT and AST did not exceed protocol-specified criteria for potential clinical relevance.

The safety profile of the aripiprazole group was similar to that of the placebo group in terms of laboratory findings, with low incidences of treatment-emergent serum chemistry, electrolyte, haematology vital sign, and ECG abnormalities.

Maintenance Treatment Study

The incidence of treatment-emergent AEs during the maintenance phase of CN138010 was similar for the aripiprazole (74.0%) and placebo (69.9%) groups. There was a higher incidence of AEs in the aripiprazole group than the placebo group, which was largely accounted for by the higher incidence of tremor (aripiprazole 7.8%, placebo 1.2%) and musculoskeletal stiffness (aripiprazole 6.5%, placebo 1.2%). During the combined maintenance and extension phases, the incidences of AEs were similar to those reported in the maintenance phase.

One aripiprazole-treated patient died of heroin intoxication during the Stabilisation phase of CN138010. The incidence of SAEs was lower in the aripiprazole group (7.8%) than the placebo group (13.3%) during the maintenance phase, with most events reported in the SOC of *Psychiatric Disorders*. The incidence of discontinuation of study therapy was also lower in the aripiprazole group (10.4%) than the placebo group (19.3%), with mania the most frequently reported event leading to discontinuation in both groups.

In relation to laboratory findings, the safety profile of the aripiprazole group was similar to that of the placebo group, with low incidences of treatment-emergent serum chemistry, electrolyte, haematology vital sign, and ECG abnormalities.

Suicide

In the 3-week placebo-controlled studies, the pooled incidence of suicide-related AEs was low, but higher in the aripiprazole group than in the placebo group although this difference was not statistically different. The incidence of treatment-emergent suicide-related AEs was similar to previously reported rates for placebo-controlled studies in bipolar mania. Low rates of suicide-related AEs were also reported in the other controlled studies, though in the 26-week study with a 74-week extension, the rate of suicide-related events was lower in the aripiprazole group than in the placebo group. There were no completed suicides. These results are consistent with the known profile of the drug and disease.

Clinical Summary and Conclusions

Clinical efficacy

Results are summarised in the Efficacy section (Evaluator's overall conclusions on clinical efficacy)

Clinical safety

Results are summarised in the Safety section (Evaluator's overall conclusions on clinical safety).

Benefit risk assessment

Benefits

Acute Manic Episodes

The efficacy of aripiprazole in the acute treatment of bipolar mania was demonstrated by positive results in four of five short-term 3-Week placebo-controlled studies on the primary outcome measure, the mean change from baseline on the Y-MRS Total Score. Overall the secondary analyses supported this treatment effect. In two trials with active control (lithium or haloperidol), aripiprazole demonstrated similar effects on efficacy endpoints as the active

control. One trial did not demonstrate efficacy on either the primary or secondary endpoints. This fixed-dose trial showed a treatment response on aripiprazole on the primary endpoint that was similar to the treatment response on aripiprazole achieved in the flexible-dose trials; however, the response on placebo was greater than in the flexible-dose trials and contributed to the negative results in this study.

Maintenance treatment

Two of the 3-week placebo-controlled studies had double-blind treatment with aripiprazole or active control (lithium or haloperidol) for an additional 9 weeks. In both trials, aripiprazole and active control was statistically superior to placebo at 3-weeks on the mean change from baseline on the Y-MRS Total Score, and this treatment effect of aripiprazole and active control was maintained at all time points between Week 3 to Week 12. In each trial, aripiprazole had similar treatment effects as active control at Week 12 on other endpoints as well.

An additional study showed that aripiprazole was statistically superior to haloperidol on the primary endpoint of the percent of patients on treatment and in response at Week 12. This difference between treatment groups on the primary endpoint may have been partially the result of the higher discontinuation rate observed in the haloperidol arm, which itself may have resulted from the high starting dose of haloperidol (10 mg/day) and the fact that use of anticholinergic medications was not allowed during the trial. In addition, this study did not include a placebo-control. Therefore, data from this study are considered supportive rather than pivotal for maintenance of effect of aripiprazole.

Combination therapy

One study demonstrated the efficacy of aripiprazole in combination with lithium or valproate in the treatment of patients with Bipolar I Disorder who were partially nonresponsive to lithium or valproate monotherapy. Aripiprazole was superior to placebo on the primary efficacy measure (mean change from baseline at Week 6 on Y-MRS Total Score) beginning at Week 1 and continuing through Week 6. Aripiprazole was also superior to placebo on the key secondary efficacy measure (mean change from baseline in the CGI-BP Severity of Illness Score [mania]) at Week 6.

Maintenance treatment for the prevention of recurrence

Bipolar I Disorder is a lifelong episodic illness characterised by manic or depressive episodes followed by symptom-free or euthymic periods. Therefore, the prevention or delay of subsequent mood episodes is a primary objective in effectively treating this illness.

One study demonstrated that aripiprazole was efficacious in preventing bipolar relapse in patients whose manic episodes had responded to aripiprazole treatment. Aripiprazole was superior to placebo on the primary endpoint (time to relapse for any mood event) and on the secondary endpoint of time to manic relapse, though aripiprazole was not statistically superior to placebo in delaying the time to depressive relapse.

Risks

The safety and tolerability of aripiprazole was assessed in a total of 2626 patients who received aripiprazole in the acute bipolar mania studies and 13543 patients who received aripiprazole across all Phase 2/3/4 studies. In most of these studies, aripiprazole was administered as monotherapy; however, some aripiprazole-treated patients were treated with adjunctive therapy.

Overall, the administration of aripiprazole was well tolerated (for example, generally mild to moderate in severity) and infrequently led to study discontinuation. The incidence of treatment-emergent AEs was lower in studies that used a starting dose of 15 mg/day compared with those that used a starting dose of 30 mg/day. Among all-aripiprazole treated patients, the incidence of treatment-emergent AEs and discontinuations due to AEs in bipolar mania patients was generally similar to that reported in the other patient populations. No new safety signals emerged in the new studies submitted for evaluation.

Balance

The safety and efficacy data from this clinical trial program supports the use of aripiprazole tablets in the treatment of patients with Bipolar I Disorder. Acute efficacy for treatment of manic episodes was demonstrated in four short-term monotherapy trials, two of which showed maintenance of effect similar to lithium or haloperidol up to 12 weeks. One adjunctive therapy trial with lithium or valproate demonstrated the safe and effective use of aripiprazole in combination with mood stabilisers. The prevention of recurrence of bipolar disorder, particularly manic episodes, was demonstrated in a 26-week trial with a 74-week extension phase. The majority of these trials included patients with moderate to severe manic episodes, some of whom also had psychotic symptoms. In these trials, aripiprazole was shown to be generally well-tolerated. The adverse effects of aripiprazole were generally mild to moderate and similar to those previously observed in the schizophrenia population treated with aripiprazole. No unexpected safety concerns were identified.

Importantly, the adverse effect profile of aripiprazole was different from that of other atypical antipsychotic drugs that are commonly used to treat mania. EPS was more frequently reported in aripiprazole-treated than in placebo-treated patients, but at a rate lower than that of haloperidol-treated patients.

Overall the evaluator considered that aripiprazole has a favourable benefit-risk profile for the acute and maintenance treatment of manic or mixed episodes associated with Bipolar I Disorder.

It was also considered that the data adequately support a favourable benefit/risk profile when aripiprazole is used as an adjunctive therapy to lithium or valproate for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder.

Conclusions

The data submitted for evaluation adequately support efficacy of aripiprazole for the acute and maintenance treatment of patients with Bipolar I Disorder.

It was recommended that this application to extend the indication for aripiprazole should be approved. The indication as proposed by the sponsor was considered acceptable:

Abilify monotherapy is indicated for acute and maintenance treatment of manic and mixed episodes with Bipolar I Disorder with or without psychotic features.

Abilify is indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

It was an integrated RMP reflecting the current approved indications in the EU.

The following safety concerns were identified by the sponsor:

Important Identified Risks

- Extrapyramidal Symptoms (EPS), including tardive dyskinesia.
- Neuroleptic Malignant Syndrome (NMS).

Important Potential Risks

- Seizures.
- Hyperglycaemia/diabetes.
- Suicide-related events.
- Orthostatic hypotension.
- Dyslipidaemia.

Important Missing Information

- Pregnancy and lactation.
- Paediatrics patients with schizophrenia (< 13 years of age) and paediatric patients with bipolar mania.

The sponsor listed other potential concerns in the pharmacovigilance (PhV) plan:

- Cardiovascular related disorders.
- Conduction abnormalities.
- Weight gain.
- Growth (paediatric patients).
- Dysphagia.
- Lactose.
- Increased mortality and CVA in elderly patients with dementia.
- IMI solution: serious injection site reactions; serious hypersensitivity reaction to excipients.

Routine PhV was proposed for the safety concerns.[4] Results of additional PhV actions initiated in earlier RMP versions and now completed have been summarised. Additional PhV activities proposed in the current RMP relate to paediatric exposure. There were no additional risk minimisation activities proposed beyond cautionary statements in the product information (PI).[5]

Overall the RMP was acceptable. A number of issues were noted by the evaluator and recommendations are made to the Delegate that the sponsor:

- Should update the RMP with the following nonclinical safety data or substantiate the exclusion:

[4] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[5] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

- The findings of pituitary gland adenomas and mammary gland fibroadenomas, adenocarcinomas and adenoacanthomas from animal studies using doses or exposures in excess of the maximum recommended human dose (MRHD).
- Hyperprolactinaemia findings and the human risk relevance of prolactin-inducing endocrine tumours.
- Bilateral retinal degeneration observed in albino rats using doses or exposures in excess of the MRHD.

- Be requested to update the bipolar mania exposure data in subsequent versions of the Australian RMP to include that from paediatric bipolar trial data.
- Be requested to provide post-marketing exposure data for Australia in subsequent RMP versions.
- Be requested to update the relevant section of the draft Australian PI, or provide justification for not doing so, with respect to changes made to the European Summary of Product Characteristics (SmPC), outlined in the RMP as resulting from regulatory actions taken in the EU. However, it was recommended that the statements on the epidemiological study findings relating to suicidality not be included in the Australian PI as these may be misinterpreted by prescribers as conferring reduced risk thus potentially resulting in less clinical vigilance in the monitoring of suicidal thoughts and impulses.
- Closely monitor reports of overdoses and their outcomes, including reports from literature searches, and report on these cumulatively in future PSURs.
- Closely monitor reports of abuse, misuse and drug dependence, including reports from literature searches, and report on these cumulatively in future PSURs.
- Closely monitor reports of off-label use, including reports from literature searches, and report on these cumulatively in future PSURs.
- Closely monitor reports of paediatric use, including reports from literature searches and updates from paediatric trial data, and report on these cumulatively in future PSURs.
- Provide clarification about post-marketing studies and treatment-emergent depression.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Efficacy

Previously considered studies included:

- three double-blind, 3-week placebo-controlled studies;
- two flexibly dosed studies to 12 weeks with haloperidol and lithium as active controls;

- a flexible dose 12 week study with haloperidol as the active control which included a 14 week extension;
- a flexible dose 6 week double-blind, placebo-controlled combination study of aripiprazole with lithium or valproate which included a 46 week open label extension phase;
- a flexible dose, 26 week, double-blind, placebo-substitution maintenance treatment study for the prevention of recurrence with a 74-week, double-blind, placebo-controlled, extension phase;
- an open-label, flexible dose, uncontrolled extension study.

The newly submitted studies and study CN138010 are discussed below.

Study CN138134 was a multi-centre, multinational, randomised, double-blind study comparing aripiprazole + either lithium or valproate with placebo +lithium or valproate for 6 weeks followed by a 46-week open-label extension phase. Adult patients with Bipolar I Disorder with a manic or mixed episode, with or without psychotic features who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned to receive either aripiprazole or placebo in a 2:1 ratio, in combination with lithium or valproate for 6 weeks.

The study had an initial phase lasting from 3 days to 4 weeks in which all patients received lithium or valproate, therapeutic levels were achieved and screening and psychotropic medication washout occurred if required. Patients with a Y-MRS score of ≤16 at the end of Phase 1 were able to enter Phase 2 of the study. This was a 2 week continuation period in which partial non-responsiveness was assessed. Partial non-responsiveness to lithium or valproate was defined as a Y-MRS score of ≤ 16 during Phase 1 and with a decrease of ≤ 25% between Phases 1 and 2. Patients meeting these criteria then entered Phase 3, a 6 week period in which they were randomised to receive either double-blinded aripiprazole 15 – 30 mg daily according to response or placebo in addition to their lithium or valproate. At the end of Phase 3 there was a 46-week extension period where patients could continue with either open-label combination therapy or lithium or valproate monotherapy. That phase of the study was ongoing at the time of preparation of the submission.

The primary efficacy endpoint was mean change in Y-MRS score from baseline at the beginning of Phase 3 until the end of Phase 3. Clinical Global Impression – Bipolar Disorder (CGI-BP) was a key secondary efficacy endpoint. Response rates, defined as a 50% reduction from baseline in Y-MRS score and remission, defined as a reduction in Y-MRS to ≤12 were also secondary endpoints.

The reduction in mean Y-MRS scores was larger in patients given lithium compared with patients given valproate. Statistical significance was not reached for the subgroup of patients given lithium but was reached for the subgroup given valproate. Reductions in CGI-BP, response rates and remission rates were also statistically significantly greater in patients given aripiprazole compared with placebo in addition to lithium or valproate.

These differences were substantial with 62.8% of patients given aripiprazole vs 48.5% given placebo achieving a response and 66% aripiprazole vs 50.8% placebo achieving remission at the end of Phase 3.

Study CN138135 was intended to evaluate the efficacy of aripiprazole monotherapy in acute and maintenance therapy for acute manic or mixed episodes in patients with Bipolar I Disorder. This was a randomised, double-blind, placebo and active-controlled study comparing a flexible dose of aripiprazole (15 – 30 mg once daily) or lithium with placebo in adult patients with Bipolar I Disorder who had an acute manic or mixed episode with or

without psychotic features requiring initial in-hospital treatment. Patients received for aripiprazole or lithium or placebo for 3 weeks. Patients randomised to placebo were blindly switched to aripiprazole and treatment continued with either aripiprazole or lithium for a further 9 weeks. This was followed by an optional double-blind 40 week extension period of aripiprazole or lithium that was ongoing at the time the submission was prepared.

Patients were required to have a Y-MRS score of ≥ 20 at screening and at the end of Phase 1 (baseline) with a < 25% reduction in YMRS score between the screening and baseline visits. Patients with a MADRS of >17 at baseline or who had a > 4 point increase between screening and baseline with measurements at least 2 days apart were excluded from study. The primary efficacy endpoint was the mean change from baseline to Week 3 (LOCF) in Y-MRS score. However differences from placebo in mean change from baseline were presented for this endpoint. Maintenance of effect was evaluated by comparing the originally randomised aripiprazole treatment group and the lithium treatment group during the 12-week double-blind treatment phase. Responder and Remission rates and CGI-BP were included in the secondary endpoint measures.

By Week 12, 143 (29.8%) patients remained on study treatments, however 62 (65.3%) patients who responded in the initial 3 week period continued to complete the 12 week maintenance phase. At Week 12 mean Y-MRS scores had declined a further 0.68 from the Week 3 level in patients given lithium and a further 1.84 in patients given aripiprazole. There was no statistically significant difference in the mean changes in Y-MRS scores or in CGI-BP scores from baseline to Week 12 between aripiprazole and lithium. The 50% response rate at Week 12 was 49.0% for patients given lithium and 56.5% for patients given aripiprazole and this difference was statistically significantly different (95%CI 0.92, 1.39).

Study CN138162 had the same design as study CN138135 except that the active comparator was haloperidol given at a starting dose of 5 mg daily with an option to increase to 10 or 15 mg daily. The demographics and baseline Y-MRS scores are similar to those in study 135 as are the extent of reduction from baseline in Y-MRS scores at Weeks 3. Unlike study CN138135 the majority of patients, 274 (56.5%) completed the 12-week double-blind phase of the study, 56.9% given aripiprazole, 57.6% given haloperidol and 54.9% who were initially randomised to placebo and then switched to aripiprazole. Differences between aripiprazole vs placebo and haloperidol vs placebo at Week 3 were both statistically significant.

The changes in mean Y-MRS scores at Week 12 were somewhat greater in this study than in study CN138135 with mean change in Y-MRS scores of -17.16 for aripiprazole and -17.84 for haloperidol. Differences between aripiprazole and haloperidol at Week 12 in reduction in mean Y-MRS score and response rate were not statistically significant. An increase in the responder rates for both aripiprazole and haloperidol was apparent between Weeks 3 and 12 (from 47.0% to 72.3% for aripiprazole and from 49.7% to 73.9% for haloperidol).

Although it is not clear whether the sponsor intends to claim for prevention of recurrence in patients with Bipolar I Disorder, this was examined in **Study CN138010**. This was a placebo-controlled, randomised withdrawal study in patients who had experienced an acute manic or mixed episode. This study had an initial stabilisation phase where all patients received aripiprazole for from 6 to 18 weeks. Patients continued in this phase until symptoms were stable over a minimum of 6 weeks. They were then randomised to aripiprazole or placebo for a 26 week maintenance phase with the option of a further 74 weeks randomised treatment in an extension phase.

Only 12 patients completed the extension phase. The placebo group relapsed sooner than the aripiprazole group. In the maintenance phase the HR for recurrence for aripiprazole was 0.523 (95% CI: 0.300; 0.913).

Safety

A total of 2626 patients received aripiprazole in the acute bipolar mania clinical development program. Of particular note is that safety of aripiprazole in Bipolar I Disorder beyond 12 weeks treatment has not been adequately assessed. Study CN138010 assessed monotherapy aripiprazole for the longest duration. In that study 37 patients continued on aripiprazole for 6 months. Longer term safety data may be available from the extension phases of the newly submitted studies but these data were not available at the time of submission.

In the 3-week placebo-controlled comparisons, adverse events in patients given aripiprazole occurring with a frequency of≥ 5% and twice that of placebo included akathisia, sedation, extrapyramidal disorder and restlessness. Orthostatic hypotension and tachycardia were reported to be no more frequent than 1% greater than the rate in patients given placebo.

Extrapyramidal symptoms occurred in 26.5% of patients given aripiprazole compared with 11.3% given placebo. Withdrawal occurred in 2.9% of patients given aripiprazole and 0.7% given placebo due to an EPS-related adverse event.

In the 6-week combination therapy study the incidence of EPS-related adverse events was similar to that of the 3-week studies. But discontinuation rates due to EPS-related events were higher, at 5.9% and 1.5% for the aripiprazole and placebo groups respectively. Treatment-emergent akathisia in patients given lithium-aripiprazole was 28.3% compared with 11.6% in patients given valproate-aripiprazole, 6.3% in patients given valproate-placebo and 4.0% in patients given lithium-placebo. In the previously submitted haloperidol-controlled studies EPS-related adverse events were, as expected, more frequent in patients given haloperidol.

Weight gain of≥ 7% of body weight was not statistically significantly different from placebo in the 3 week studies. In the maintenance study 12.5% of patients given aripiprazole and 0% given placebo had this degree of weight gain (considered clinically significant). Five deaths were reported among the 2626 patients in acute bipolar mania studies. There was no clear relationship between aripiprazole and any of these deaths.

Risk Management Plan

The OPR reviewer has noted that the sponsor proposed routine PhV for the identified safety concerns. Additional PhV activities proposed in the current RMP relate to paediatric exposure. There were no additional risk minimisation activities proposed beyond cautionary statements in the Product Information (PI). With regard to the bipolar mania clinical development program the reviewer noted that:

- The majority of patients were in the 18 to 50 year old age group, with no patients less than 18 years exposed. There were 51 patients over the age of 65.
- Regarding race, the majority exposed were White, 356 were Black and 37 Asian.

Overall the RMP was acceptable. A number of issues were noted by the reviewer and these were addressed by the sponsor prior to consideration of the submission by the ACPM.

Risk-Benefit Analysis

Delegate Considerations

There are three components to the proposed indications that require consideration: acute treatment; maintenance of effect; and the specific claim for effect in episodes with and

without psychotic features. Each of these requires consideration of efficacy and safety as monotherapy and in combination with either lithium or valproate.

There were three previously submitted studies that examined efficacy and safety in acute mania or mixed episodes. As noted in the ADEC Minutes for the previous submission of these three short term, placebo-controlled studies, the first showed evidence of efficacy, the second showed evidence but a high dropout rate and the third did not support efficacy of aripiprazole compared to placebo. There are now a further three studies which have demonstrated clinically significant efficacy of the proposed dose of aripiprazole in the short term (3 week) treatment of manic or mixed episodes in patients with Bipolar I Disorder. Efficacy as monotherapy and in combination with lithium or valproate for acute manic or mixed episodes in Bipolar I Disorder has now been convincingly demonstrated.

Although the newly submitted studies included patients with and without psychotic features there was no primary analysis of efficacy by subgroup for these patients. Such an analysis would need to be pre-specified and to show statistically significant efficacy for each subgroup (that is, with and without psychotic features) to sustain the proposed claim for "with and without psychotic features". Furthermore this subgroup analysis would also have to show statistically significant efficacy as monotherapy and in combination with lithium or valproate for the acute (3-week) indication. This has not occurred.

The newly submitted studies CN138135 and CN138162 examined maintenance of effect of aripiprazole to 12 weeks as monotherapy. Study CN138135 had a very high dropout rate with only 29.8% of patients completing 12 weeks of study and so is of limited value. Study CN138162 satisfactorily demonstrated efficacy in maintenance of effect of an acute episode. Evidence of efficacy of combination therapy with lithium or valproate for maintenance of effect has only partially been met by study 134 in that maintenance of effect of combination therapy was demonstrated for 6 rather than 12 weeks.

Maintenance of treatment for the prevention of recurrence was assessed in the previously submitted study CN138010, a randomised withdrawal study, also described in this AusPAR. As noted in the previous ADEC Minutes, conclusions from this trial are that (monotherapy) aripiprazole is more efficacious than placebo in maintaining initial efficacy of treatment in the acute manic phase. However, concerns were raised with the large variation in stabilisation phase and the potential for selection bias in the maintenance extension phase. The ADEC also noted that this study did not include an active comparator and cannot therefore be regarded as providing sufficient evidence of maintenance effect against an appropriate standard treatment of known efficacy. This study has apparently been accepted some years ago by the FDA and EMEA as evidence of aripiprazole in prevention of recurrence of manic and mixed episodes.

Prevention of recurrence has not been requested as an indication and it is not clear if the sponsor intended to include prevention of recurrence as part of the claim for maintenance treatment of manic and mixed episodes in Bipolar I Disorder. The sponsor was requested to clarify its intention with regard to the maintenance indication in the Pre-ACPM response.

No new safety issues pertaining to aripiprazole were apparent from the acute bipolar mania clinical development program.

Efficacy of aripiprazole has been well demonstrated for acute treatment of manic or mixed episodes in Bipolar I Disorder as monotherapy and in combination with lithium or valproate. Maintenance of effect has been well demonstrated for monotherapy aripiprazole over a 12 week period but not for combination therapy.

To be consistent with the presentation of Bipolar I Disorder indications currently approved for other atypical antipsychotic medications the Delegate proposed that the indications be

presented by condition being treated rather than by whether the product is to be administered alone or in combination as is currently proposed. The Delegate also did not consider the additional claim for patients *with and without psychotic features* was sustained and proposed to omit it from the indications. The indications for aripiprazole with respect to Bipolar I Disorder should be amended to:

Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and in combination with lithium or valproate;

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder as monotherapy.

The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was specifically requested on:

- Whether indications that specify manic or mixed episodes *with or without psychotic features* can be sustained from the available data;
- Whether the indications should specify up to 12 weeks of treatment for manic or mixed episodes in Bipolar I Disorder, or should longer term use for prevention of recurrence be permitted for those patients who have had a manic or mixed episode and who achieved stability on aripiprazole;

Response from Sponsor

The sponsor noted that the Delegate has sought clarification of, and recommended amendments to, the proposed indication. The sponsor confirmed that it wished to include "prevention of recurrence" as part of the maintenance monotherapy indication. It had no objection to the removal of "with or without psychotic features" and had no objection to the Delegate's revised maintenance indication:

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder as monotherapy.

The sponsor also supported the Delegate's action to seek advice from the ACPM as to the appropriateness of a further revision to this indication and proposed the following:

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder as monotherapy; for the prevention of recurrence of manic and mixed episodes of Bipolar I Disorder.

The sponsor also discussed consequent amendments to the PI which are beyond the scope of this AusPAR.

The sponsor noted that as Bipolar I Disorder is a lifelong episodic illness characterised by manic and depressive episodes, management is complex and requires long-term treatment. Long-term maintenance treatment with atypical antipsychotics as monotherapy or in combination with lithium or valproate has been recommended in several international guidelines. Although CN138010 did not include an active comparison, the results from this study are comparable to other maintenance studies investigating relapse and recurrence. The sponsor performed a literature review which included a meta-analysis of 14 long-term studies conducted with other antipsychotics to support the efficacy of aripiprazole compared to other antipsychotics.

The sponsor indicated that CN138010 demonstrated that aripiprazole treatment prevented relapse for up to 26 weeks and to 2 years in patients previously stabilised on the drug. The sponsor further noted that in clinical practice, clinicians will continue prophylactic treatment in patients who have initially responded in the acute setting.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indications:

Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy

In making this recommendation the ACPM considered that the efficacy had been demonstrated for the acute treatment of manic and mixed episodes in Bipolar I Disorder as monotherapy and in combination with lithium or valproate. The ACPM noted that the evidence for maintenance of effect had been demonstrated for monotherapy over a 12 week period.

The ACPM supported the Delegate's view that the additional submitted claim for the prevention of recurrence of manic and mixed episodes of Bipolar I Disorder was not supported because the longest study was conducted for only 26 weeks. The sponsor was encouraged to conduct further trials to support an expanded indication.

The ACPM also supported the Delegate in the need to ensure consistency in the indications for the atypical antipsychotic class of medicines by presenting by condition being treated, rather than by whether the product is to be administered alone or in combination as proposed by the sponsor. The ACPM further advised there were insufficient data for treatment of patients under 18 years.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Abilify tablets containing aripiprazole 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg and Abilify ODT containing aripiprazole 10 mg, 15 mg, 20 mg and 30 mg Orally Disintegrating Tablets, for the new indication:

Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate;

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy.

The sponsor's acceptance to limit this extension of indication in this submission to be applicable for the tablets and the orally disintegrating tablets presentations only and to create a separate Product Information document for the injection presentation were noted.

As a condition of approval, the Risk Management Plan dated 1 March 2010, as agreed with the Office of Product Review, must be implemented.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Product Information Document

for

ABILIFY™

Aripiprazole Tablets & Orally Disintegrating Tablets

NAME OF THE DRUG

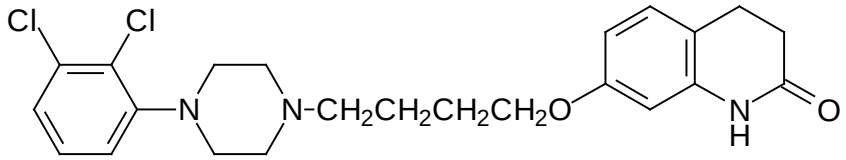
Aripiprazole.

Aripiprazole is 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-3, 4- dihydrocarbostyril .

DESCRIPTION

ABILIFY™ is a novel antipsychotic agent with unique pharmacologic properties and a chemical structure that differs from current antipsychotic agents.

The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.39. The chemical structure is:



The CAS registry number for aripiprazole is 129722-12-9.

Since aripiprazole is insoluble in water with its equilibrium solubility being about 0.00001% w/v, its pKa was established in 20% aqueous ethanol pKa = 7.6 (20% ethanol, at 25°C). The partition coefficients ($P_{o/w}$) of aripiprazole range from 3.4 at pH 2.0 to > 1000 at pH 6.0.

ABILIFY™ is available as 2mg* (green, scored), 5mg (blue, unscored), 10mg (pink, unscored), 15mg (yellow, unscored), 20mg (white, unscored), and 30mg (pink, unscored) tablets for oral administration. The inactive ingredients in the tablets are: lactose, maize starch, microcrystalline cellulose, hydroxypropylcellulose, and magnesium stearate. The following colorants are also contained in the tablets: 2mg* tablets - indigo carmine CI73015 aluminium lake and yellow iron oxide CI77492; 5mg tablets - indigo carmine CI73015 aluminium lake; 10mg tablets - red iron oxide CI77491; 15mg tablets – yellow iron oxide CI77492; 20mg tablets – nil; 30mg tablets – red iron oxide CI77491.

* Not currently marketed in Australia

ABILIFY™ is also available as orally disintegrating tablets (ODT) in the following strengths 10mg* (pink, unscored), 15mg* (yellow, unscored), 20mg* (white, unscored), and 30mg* (pink, unscored). These are intended to be placed on the tongue to disperse before being swallowed. Tablet disintegration occurs rapidly (median is approximately 1 minute) in saliva. They can also be placed in water and the dispersion swallowed immediately. The shape and markings used for the orally disintegrating tablets are described in the **PRESENTATION** section. The inactive ingredients in the orally disintegrating tablets are: acesulfame potassium, aspartame, calcium silicate, croscarmellose sodium, crospovidone, cre [illegible] magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid and xylitol. The following colorants are also contained in the orally disintegrating tablets: 10mg ODT - red iron oxide CI77491; 15mg ODT – yellow iron oxide CI77492; 20mg ODT – nil; 30mg ODT – red iron oxide CI77491.

* Not currently marketed in Australia

PHARMACOLOGY

Pharmacodynamics

The mechanism of action of ABILIFY™, as well as other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of ABILIFY™ is mediated through a combination of partial agonist activity at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist activity at serotonin $5HT_{2A}$ receptors.

ABILIFY™ activity is primarily due to the parent drug, aripiprazole

Aripiprazole exhibited higher affinity binding *in vitro* for dopamine D_2 and D_3, serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors (K_i values of 0.3, 0.8, 1.7, and 3.4nM, respectively), than for dopamine D_4, serotonin $5HT_{2C}$ and $5HT_7$, $alpha_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61nM, respectively) and the serotonin reuptake site (K_i value of 98nM). Aripiprazole exhibited no appreciable affinity for muscarinic receptors (IC_{50} >1000nM).

The predominant metabolite in human plasma, dehydro-aripiprazole has been shown to have a similar affinity for dopamine D_2 and D_3 receptors (K_i values 0.4 and 0.5nM, respectively) as the parent compound and a much lower affinity for the other receptor subtypes.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity.

Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of ABILIFY™.

Pharmacokinetics

Absorption

Oral Administration

Aripiprazole is well absorbed after oral administration of ABILIFY™, with peak plasma concentrations occurring within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation of ABILIFY™ is 87%. ABILIFY™ can be administered without regard to meals. Following administration of a 15 mg ABILIFY™ tablet with a standard high-fat meal, the Cmax of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed Tmax by 3 hours for aripiprazole and 12 hours for the active metabolite. Aripiprazole accumulation is predictable from single dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. There is no diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole.

Studies have shown that ABILIFY™ orally disintegrating tablets are bioequivalent to ABILIFY™ tablets.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg. At therapeutic concentrations, aripiprazole is highly bound (88 –97% to > 99%, as determined by polydimethylsiloxane-glass bead and equilibrium dialysis assays, respectively) to serum proteins, primarily albumin, *in vitro*. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of warfarin did not occur.

Metabolism

Aripiprazole undergoes minimal pre-systemic metabolism. Aripiprazole is extensively metabolized by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are primarily responsible for dehydrogenation and hydroxylation of aripiprazole, while N-dealkylation is primarily catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39% of aripiprazole AUC in plasma. Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are

extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Subjects were entered into clinical studies without knowledge of their metabolizer status and, therefore, the safety profile reflects experience in both EMs and PMs.

Excretion

Following a single, oral dose of [^{14}C]-labeled aripiprazole, approximately 27% and 60% of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the faeces. The total body clearance of aripiprazole is 0.7mL/min/kg, which is primarily hepatic.

In a bioavailability study comparing fasted and fed subjects at a dose of 15 mg, the elimination half-life of aripiprazole from human plasma was found to be 75 hours mean, range 32–146 hours, n=58, in fasted subjects and 84 hours mean, range 32-157 hours, n=57 in subjects taking a high-fat meal immediately before drug administration. Steady-state concentrations are attained within 14 days of dosing. The plasma elimination half-life of the chief metabolite, dehydro-aripiprazole, from human plasma was found to be approx. 100 hours.

Elderly

There were no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects nor was there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients. In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥ 65 years) subjects compared to younger adult subjects (18-64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young healthy subjects. No dosage adjustment is recommended for elderly patients. (See **PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Use in the Elderly**)

Gender

There were no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor was there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients. Cmax and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are

largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole.

Smoking

Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects of smoking on the pharmacokinetics of aripiprazole. Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

Renal Impairment

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects. In patients with severe renal impairment (creatinine clearance <30 mL/min), Cmax of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment

A study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole. In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

CLINICAL TRIALS

Schizophrenia

The efficacy of ABILIFY™ in the treatment of schizophrenia was evaluated in six short-term (4- and 6-week), placebo-controlled trials of inpatients, four of which also included an active control group consisting of either risperidone (one trial) or haloperidol (three trials). Studies were not powered to allow for a comparison of ABILIFY™ and the active comparators. Efficacy was also documented in two long-term trials, one of 52 weeks duration, which compared ABILIFY™ to haloperidol and one of 26 weeks duration, which compared ABILIFY™ to placebo. Patients in these trials met DSM-III/IV criteria for schizophrenia or schizo-affective disorder.

Several instruments were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The BPRS Psychosis Cluster (Core Score), a subset of the BPRS that can also be derived from the PANSS, is used to assess actively psychotic patients. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

Four short-term, fixed-dose trials were well controlled and powered to statistically demonstrate the efficacy of ABILIFY™ over placebo. The results of these trials are described below.

Trial 1) In a 4-week, placebo-controlled trial (n=414) involving administration of 2 fixed doses of ABILIFY™ (15 or 30 mg/day) and haloperidol (10 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder, ABILIFY™ 15 mg/day was superior to placebo with clinically meaningful changes in PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement, and PANSS-derived BPRS-core scores. The 30-mg dose was superior to placebo for all parameters except PANSS negative subscale.

Trial 2) In a 4-week, placebo controlled trial (n=404) involving administration of 2 fixed doses of ABILIFY™ (20 or 30 mg/day) and risperidone (6 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder, both doses of ABILIFY™ were superior to placebo with clinically meaningful changes in the PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement and PANSS-derived BPRS-core scores.

Trial 3) In a 6-week, placebo-controlled trial (n=420) involving administration of 3 fixed doses of ABILIFY™ (10, 15, or 20 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, all ABILIFY™ dose groups were superior to placebo with clinically meaningful changes in the PANSS total score, the PANSS positive and negative subscales, the CGI severity and improvement scales, and the PANSS-derived BPRS core score.

Trial 4) In a 6-week trial (n=367) comparing three fixed doses of ABILIFY™ (2, 5 or 10mg/day) to placebo, in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia, the 10-mg

dose of ABILIFY^{TM} was superior to placebo in the PANSS total score, the primary outcome measure of the study. In addition, the 10mg dose was also superior to placebo in the PANSS positive subscale and the CGI severity score. Although the 5-mg dose of ABILIFY^{TM} did not reach significance in the PANSS total score or the PANSS positive subscale, it was superior to placebo in the PANSS negative subscale and the CGI severity scale. The 2-mg dose did not reach significance in any of these outcome measures.

Two initial placebo-controlled trials were conducted to explore the efficacy of ABILIFY^{TM} . The first one (Trial 5) was a placebo-controlled, 4-week ascending dose trial of ABILIFY^{TM} (5 to 30 mg/day) in 103 patients diagnosed with schizophrenia according to the DSM-III-R criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. In this trial, ABILIFY^{TM} differentiated from placebo in the PANSS total score, the PANSS positive subscale, and the CGI severity scale. The second one (Trial 6) was a placebo-controlled, 4-week, fixed-dose trial of ABILIFY^{TM} (2, 10, or 30 mg/day) in 272 patients diagnosed with schizophrenia according to the DSM-IV criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. Statistical significance was reached only for the 30-mg dose on the PANSS total score, the PANSS positive subscale, and the CGI severity and improvement scales.

Thus, the efficacy of 10-mg, 15-mg, 20-mg and 30-mg was established in two studies for each dose. Among these doses there was no evidence that the higher dose groups offered any advantage over the lowest dose group. Broad efficacy was established across a variety of endpoints with an onset of action as early as Week 1 for positive symptoms at doses of 15 mg and higher.

Table 1 summarizes the results across all six trials.

Table 1: Key Efficacy Results in Short-Term, Placebo-Controlled Trials

	PANSS Total Score	PANSS Positive Subscale Score	PANSS Negative Subscale Score	PANSS-Derived BPRS Core Score	CGI-Severity Score	CGI Improve-ment Score
Trial/ Treatment	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**	**Mean Change**
Trial 1						
Placebo	-2.9	-0.6	-1.2	-1.1	-0.1	4.3
Ari 15 mg	-15.5**	-4.2**	-3.6**	-3.1**	-0.6**	3.5**
Ari 30 mg	-11.4**	-3.8**	-2.3	-3.0**	-0.4**	3.8*
Trial 2						
Placebo	-5.0	-1.8	-0.8	-1.7	-0.2	4.0
Ari 20 mg	-14.5**	-4.9**	-3.4**	-3.5**	-0.5*	3.4**
Ari 30 mg	-13.9**	-3.9*	-3.4**	-3.3*	-0.6**	3.3**
Trial 3						
Placebo	-2.3	-1.1	0.1	-1.4	-0.2	4.0
Ari 10 mg	-15.0**	-5.0**	-3.5**	-3.9**	-0.7**	3.3**
Ari 15 mg	-11.7**	-3.8**	-2.6**	-2.9*	-0.5*	3.4**
Ari 20 mg	-14.4**	-4.5**	-3.3**	-3.6**	-0.6**	3.3**
Trial 4						
Placebo	-5.3	-2.3	-1.3	-2.3	-0.3	3.6
Ari 2 mg	-8.2	-2.4	-2.0	-2.3	-0.3	3.6
Ari 5 mg	-10.6	-3.4	-2.9*	-3.2	-0.6*	3.2
Ari 10 mg	-11.3*	-4.2*	-2.7	-3.4	-0.6*	3.2
Trial 5						
Placebo	-1.5	-0.1	-0.9	-2.4	0.0	4.0
Ari 5-30 mg	-13.5**	-3.0*	-3.6	-8.6*	-0.6**	3.5*
Trial 6						
Placebo	-3.0	-0.97	-1.31	-1.48	-2.8	3.9
Ari 2 mg	-8.0	-1.96	-2.05	-1.95	-0.30	3.7
Ari 10 mg	-8.6	-2.10	-2.48	-1.79	-0.30	3.5
Ari 30 mg	-13.7**	-3.89*	-3.11	-2.97	-0.60*	3.1**

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$) significantly different from placebo.

NOTE: Results in boxes indicate the protocol-specified primary efficacy measures.

Ari = aripiprazole

A 52-week, haloperidol-controlled, long-term, maintenance trial (n=1294) was conducted in patients with acute relapse of chronic schizophrenia. In this trial involving the administration of ABILIFY™ 30mg/day and haloperidol 10mg/day, with a one time option to decrease ABILIFY™ to 20mg/day and haloperidol to 7mg/day, ABILIFY™ was at least comparable to haloperidol in time-to-failure to maintain response in responders. Based on patients who responded at any time during the 52-week study (610/853, 72% in the ABILIFY™ group and 298/430, 69% in the haloperidol group), there was a 12% lower risk of subsequent failure with ABILIFY™ relative to haloperidol (relative risk: 0.881, 95% CI: 0.645 - 1.204). ABILIFY™ was comparable to haloperidol in time-to-failure to maintain response in all randomized patients. Patients in the ABILIFY™ group had a 14% lower risk of failure compared with the haloperidol group (relative risk: 0.858, 95% CI: 0.721, 1.021). ABILIFY™ was statistically superior to haloperidol in the analysis of the proportion of patients on treatment and in response at Weeks 8, 26, and 52 (prespecified key time points). At Week 52, 40% of ABILIFY™ patients were still on-study and in response compared to 27% of haloperidol patients ($p<0.001$). ABILIFY™-treated patients had a statistically significant lower risk (31%) of discontinuations due to lack of efficacy or adverse event relative to haloperidol treated patients (relative risk 0.692; 95% CI: 0.573 - 0.837). There were no significant differences between ABILIFY™ and haloperidol groups in terms of change from baseline PANSS total scores, PANSS positive subscores, CGI-severity or improvement scores. ABILIFY™ did result in a significantly greater improvement in the PANSS negative subscores at weeks 26 & 52 and the MADRS total score at Weeks 8, 26, and 52. [Mean change PANSS negative subscale score (week 26: p=0.029; 95% CI: -1.52 , -0.08) (week 52: p=0.011; 95% CI: -1.73, -0.23). Mean change MADRS total score (week 8: p=0.027; 95% CI: -1.74, -0.11) (week 26: p=0.22; 95% CI :-1.95, -0.15) (week 52: p= 0.031; 95% CI: -1.97, -0.09).]

To further demonstrate the maintenance effects of ABILIFY™, a double-blind study was conducted in chronic, symptomatically stable schizophrenic patients (n=310) randomised to ABILIFY™ 15mg or placebo and followed for 26 weeks. Patients were observed for "impending psychotic relapse", defined as CGI-improvement score ≥5 (minimally worse) or scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days or ≥20% increase in the PANSS Total Score. Patients in the placebo group experienced a higher relapse rate and/or relapsed sooner than those in the ABILIFY™ group. From 4 weeks onwards there were noticeably more relapses in the placebo group than the ABILIFY™ group. Kaplan Meier estimates showed that the estimated probability of not experiencing relapse prior to week 26 was 39% in the placebo group versus 63% in the ABILIFY™ group [relative risk ABILIFY™: placebo = 0.50 (95% CI=0.35, 0.71, p≤0.01)]. The number of relapses was significantly lower in the ABILIFY™ group compared to placebo (34% vs 57%, RR=0.59, 95% CI: 0.45, 0.75, p≤0.01).

No trials have been conducted in patients with first episode schizophrenia or treatment-resistant schizophrenia. Thus, efficacy in these groups of patients has not been established.

Bipolar I Disorder

Acute manic and mixed episodes

Adults

Monotherapy

The efficacy of ABILIFY in the treatment of acute manic episodes was established in four 3-week, placebo-controlled trials in hospitalized adult patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These studies included adult patients with or without psychotic features and two of the studies also included adult patients with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behaviour, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression – Bipolar (CGI-BP) Scale.

In the four positive, 3 week, placebo-controlled trials (n=268; n=248; n= 480; n= 485) which evaluated ABILIFY in a range of 15 mg to 30mg, once daily (with a starting dose of 15 mg/day in two studies and 30 mg/day in two studies). ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint.In the two studies with a starting dose of 30mg/day, 86% and 85% of patients were on 30mg/day at endpoint.

Combination therapy with lithium or valproate

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabiliser monotherapy phase in adult patients who met DSM-IV criteria for Bipolar 1 Disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Adult patients were initiated on open-label lithium (0.6mEq/L to 1.0 mEq/L) or valproate (50µg/mL to 125µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score $\geq$ 16 and $\leq$25% improvement on the Y-MRS total score) to lithium or valproate were randomized to

receive either aripiprazole (15mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6mEq/L to 1.0 mEq/L or 50µg/mL to 125µg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients co-administered valproate and 62% of the patients coadministered lithium were on 15mg/day at the 6-week endpoint.

Maintenance of manic and mixed episodes

Monotherapy Maintenance of Effect

Two short term studies in adult patients with an acute manic or mixed episode included assessment of maintenance of effect to 12 weeks. Patients in the haloperidol active-comparator study commenced on placebo, haloperidol (5mg daily with an option to increase up to 15 mg daily), or aripiprazole (15mg daily with an option to increase up to 30 mg daily). At Week 3 patients initially randomized to placebo were switched to aripiprazole. There were 274 (56.5%) patients completed the 12-week double-blind phase of the study, 56.9% given aripiprazole, 57.6% given haloperidol and 54.9% who were initially randomized to placebo and then switched to aripiprazole. The placebo-aripiprazole patients were not included in the maintenance of effect analyses. The mean change from baseline in Y-MRS total scores at Week 12 for patients given 12 weeks of continuous aripiprazole was -17.16 compared with -17.84 for haloperidol. An increase in the proportion of patients with a reduction in Y-MRS total score of at least 50% from baseline (50% responder rates) for both aripiprazole and haloperidol was apparent between Weeks 3 and 12 (from 47.0% to 72.3% for aripiprazole and from 49.7% to 73.9% for haloperidol).

The other 12-week study included lithium as the active comparator. Adult patients in this study commenced on placebo, lithium (900 mg daily with an option to increase up to 1200 mg daily at Day 4 and 1500 mg daily at Day 7), or aripiprazole (15 mg daily with an option to increase to 30 mg daily). At Week 3 patients initially randomized to placebo were switched to aripiprazole. There were 143 (29.8%) patients who completed the 12-week double-blind phase of the study: 27.1% given aripiprazole, 33.8% given lithium, and 28.5% who were initially randomized to placebo and then switched blindly to aripiprazole. The placebo-aripiprazole patients were not included in the maintenance of effect analyses. The mean change from baseline in Y-MRS total scores at Week 12 for patients given 12 weeks of continuous aripiprazole was -14.41 compared with -12.71 for lithium. An increase in the proportion of patients with a reduction in Y-MRS total score of at least 50% from baseline (50% responder rates) for both aripiprazole and lithium was apparent between Weeks 3 and 12 (from 46.8% to 56.5% for aripiprazole and from 45.8% to 49.0% for lithium).

A placebo-controlled, randomised withdrawal study was conducted in adult patients who had experienced a recent acute manic or mixed episode. This study had an initial stabilisation phase where all patients received aripiprazole for 6 to 18 weeks. Patients continued in this phase until symptoms were stable for at least 6 weeks. They were then randomised to aripiprazole or placebo for a 26 week maintenance phase.

567 patients entered the stabilisation phase, of these 361 (64%) did not proceed further due mostly to adverse events (22%), lack of efficacy (12%) and withdrawal of consent (12%). Of the 206 patients who completed the stabilisation phase 161 were randomised to placebo (n=83) or aripiprazole (n=78). 94 (58%) of patients discontinued the maintenance phase, the most frequent reason for discontinuation was lack of efficacy (placebo 43%; aripiprazole 24%). The placebo group relapsed sooner than the aripiprazole group. In the maintenance phase the hazard ratio for recurrence for aripiprazole was 0.523 (95% CI: 0.300; 0.913; p =0.020).

There is insufficient data to know whether ABILIFY is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender, however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

INDICATIONS

ABILIFY^{TM} is indicated for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy.

Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate;

Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy.

CONTRAINDICATIONS

ABILIFY^{TM} is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients (see **DESCRIPTION**).

For specific information about the contraindications of mood stabilisers refer to the CONTRAINDICATIONS section of the prescribing information for these products when combination with lithium or valproate is indicated.

PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In three placebo-controlled trials of ABILIFY ^{TM} in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, occurred in 1.3% (8/595) of ABILIFY ^{TM} -treated patients compared with 0.6% (2/343) of placebo-treated patients during the 10-week double-blind period or within 30 days of the last dose for those who discontinued the study during the double-blind phase. The all cause mortality rate in the same trials over the same period was 3.5% (21/595) in ABILIFY ^{TM} -treated patients and 1.7% (6/343) in the placebo group.

ABILIFY^{TM} is not approved for the treatment of patients with dementia-related psychosis.

General

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and Bipolar I Disorder and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY^{TM} should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Tardive Dyskinesia

The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY^{TM}, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs including ABILIFY^{TM}. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine kinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ABILIFY^{TM} must be discontinued.

Seizure

In short-term, placebo controlled trials, seizures occurred in 0.1% (3/2467) of adult patients treated with aripiprazole.

As with other antipsychotic drugs, ABILIFY^{TM} should be used cautiously in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (2 flexible dose and 1 fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also **PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Use in Patients with Concomitant Illness***: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease*.)

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents including ABILIFY^{TM}. In clinical trials with ABILIFY^{TM}, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with ABILIFY^{TM} and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY^{TM}, should be observed for signs and symptoms of hyperglycaemia

(such as polydipsia, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.

Cardiovascular Adverse Events

Potentially due to its α_1-adrenergic receptor antagonism, ABILIFY^{TM} may be associated with orthostatic hypotension.

The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%).

Orthostatic hypotension occurred in 0.8% (112/13543) of oral aripiprazole-treated patients during clinical trials.

As with other atypical antipsychotics, ABILIFY^{TM} should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before treatment with ABILIFY^{TM} and preventive measures undertaken.

Body Temperature Regulation

Disruption of the body's ability to increase or reduce core body temperature has been attributed to antipsychotic agents, including ABILIFY^{TM}. Appropriate care is advised when prescribing ABILIFY^{TM} for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. ABILIFY^{TM} and other antipsychotic drugs should be used cautiously in patients at risk of aspiration pneumonia (e.g. elderly patients).

Akathisia

Class effect: The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Leukopenia, Neutropenia and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leucopenia/neutropenia have been reported temporally related to antipsychotic agents, including Abilify. Agranulocytosis has also been reported.

Possible risk factors for leucopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leucopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leucopenia/neutropenia should have their complete blood cell (CBC) monitored frequently during the first few months of therapy and discontinuation of Abilify should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < $1000/mm^3$) should discontinue Abilify and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment

Abilify, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral Abilify (11%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients on oral Abilify in short-term, placebo-controlled trials.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with Abilify does not affect them adversely.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

Use in Patients with Concomitant Illness

Clinical experience with ABILIFY™ in patients with certain concomitant systemic illnesses is limited. (See **PHARMACOLOGY**: ***Renal Impairment*** and ***Hepatic Impairment***).

ABILIFY™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥5% and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%] and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%].

The safety and efficacy of ABILIFY™ in the treatment of patients with psychosis associated with dementia have not been established. ABILIFY™ is not indicated for the treatment of psychosis associated with Alzheimer's disease. (See also **PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.**)

Use in Patients with Phenylketonuria

Phenylalanine is a component of aspartame. Each ABILIFY™ orally disintegrating tablet (ODT) contains the following amounts: 10 mg – 1.12 mg phenylalanine, 15 mg – 1.68 mg phenylalanine, 20 mg – 2.25 mg phenylalanine and 30 mg – 3.37 mg phenylalanine.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. (See **PRECAUTIONS Interactions and DOSAGE AND ADMINISTRATION – Concomitant Medication)**

Carcinogenicity and Mutagenicity

Carcinogenicity: Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and Fischer (F344) rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). SD rats were dosed orally by gavage for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 18 times the MRHD based on mg/m^2). There was no evidence of tumorigenesis in male mice

or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (< 0.1 times MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times MRHD based on mg/m^2). In male rats, the incidence of benign and combined benign/malignant phaeochromocytomas were also increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. Hyperprolactinaemia was observed in female mice in a 13-week dietary study at doses associated with mammary gland and pituitary tumours, but not in female rats in 4- and 13-week dietary studies at doses associated with mammary gland tumours. Hyperprolactinaemia was observed in female rats after 5 and 13 weeks of oral administration at doses up to that associated with adrenocortical tumours, but serum prolactin was decreased at this dose in male rats. The relationship between tumourigenic findings with aripiprazole and prolactin is unclear and the relevance for human risk of prolactin-mediated endocrine tumours is unknown. The adrenocortical response in female rats is considered a consequence of increased adrenocortical cell proliferation secondary to chronic drug-related adrenocortical cytotoxicity; the no-effect exposure (plasma AUC) was about fold 7 clinical exposure at the MRHD

Mutagenicity: Aripiprazole was tested in a standard range of assays for gene mutation, chromosomal damage, and DNA damage and repair. Aripiprazole was non-genotoxic in the *in vitro* bacterial reverse-mutation assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, *in vitro* bacterial DNA repair assay, and the unscheduled DNA synthesis assay in rat hepatocytes. However, aripiprazole and its minor metabolite 2,3-DCPP were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells in both the presence and absence of metabolic activation. A positive response for aripiprazole in 1 of 6 *in vivo* mouse micronucleus tests was attributed to drug-induced hypothermia.

Impairment of Fertility

Aripiprazole had no effect on fertility in female rats treated orally with 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD based on mg/m^2) for 2 weeks prior to mating through gestation day 7. Drug-related effects (persistent dioestrus and increased mating time pre-implantation losses, and corpora lutea) observed at all doses were considered the result of perturbed oestrous cyclicity secondary to drug-mediated hyperprolactinaemia.

Aripiprazole had no effect on fertility in male rats treated with PO doses of 20, 40, and 60 mg/kg/day (6, 12, and 18 times the MRHD based on mg/m^2) for 9 weeks prior to mating through mating. Disturbances of spermatogenesis were seen at 60 mg/kg/day and prostatic atrophy was seen at 40 and 60 mg/kg/day.

Use in Pregnancy (Category B3)

Congenital anomalies have been reported; however, a causal relationship with aripiprazole could not be established. In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects, in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on a mg/m^2 basis) of aripiprazole during the period of organogenesis. At 30 mg/kg, treatment was associated with slightly prolonged gestation, and a slight delay in foetal development as evidenced by decreased foetal weight, undescended testes, and delayed skeletal ossification. There were no adverse effects on embryofoetal or pup survival. Delivered offspring had increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other doses were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the foetuses exposed to 30 mg/kg). Postnatally, decreased pup weight (persisting into adulthood) was seen at 30 mg/kg, delayed vaginal opening was seen at 10 and 30 mg/kg, and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live foetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Maternal toxicity was seen at 30 mg/kg, which was similar to doses eliciting embryotoxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 8, 24, and 81 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption, and increased abortions were seen at 100 mg/kg. Treatment caused increased foetal mortality (100 mg/kg), decreased foetal weight (30 mg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 100 mg/kg) and minor skeletal variations (100 mg/kg).

Rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on a mg/m^2 basis) of aripiprazole from late gestation through weaning. At 30 mg/kg, maternal toxicity, slightly prolonged gestation, an increase in stillbirths, poor postnatal care/nursing, and decreases in pup weight (persisting into adulthood) and survival were seen.

There are no adequate and well-controlled studies of ABILIFY^{TM} in pregnant women. It is not known whether ABILIFY^{TM} can cause harm when administered to pregnant women or can affect reproductive capacity. ABILIFY^{TM} should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Patients should be advised to notify their doctors if they become pregnant or intend to become pregnant.

Use in Lactation

Aripiprazole and/or its metabolites have been found in the milk of lactating rats. It is not known whether aripiprazole or its metabolites are excreted in human milk. Patients should be advised not to breast-feed if they are taking ABILIFY™.

Use in Labor and Delivery

The effect of aripiprazole on labor and delivery has not been studied.

Animal Toxicology

Choleliths (gallsand and/or gallstones) were observed in the bile of monkeys given aripiprazole orally for 4 – 52 weeks at doses of 25 –125 mg/kg/day (1 – 3 times the MRHD based on plasma AUC and 15 –76 times the MRHD based on mg/m^2) and were attributed to precipitation of sulfate conjugates of hydroxy metabolites, which exceeded their solubility limits in bile. Human biliary concentrations of these sulfate conjugates after repeated daily administration of the MRHD are substantially lower (0.2 – 14% of their *in vitro* solubility limits).

Bilateral retinal degeneration was observed in albino rats given oral aripiprazole for 6 months or two years at exposures of 6-13 times the clinical exposure at the MRHD (based on plasma AUC). The exposure at the NOEL dose was 3 times that at the MRHD. A subsequent 18-month study reported this finding in albino but not pigmented rats, possibly due to lack of photoprotective ocular melanin in the albino rats, although it is unknown whether pigmentation prevented or merely delayed retinal degeneration in the pigmented rats.. The clinical relevance of this finding is uncertain.

Use in Children

The safety and efficacy of ABILIFY in patients less than 18 years of age have not been established.

Use in the Elderly

Placebo-controlled studies of ABILIFY™ in schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 13,543 patients treated with oral ABILIFY™ in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1073 patients were diagnosed with Dementia of the Alzheimer's Type.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis** and **Use in Patients with Concomitant Illness**). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. ABILIFY™ is not indicated for the treatment of psychosis associated with Alzheimer's disease.

Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Almost all of the use in the elderly was in clinical trials for an indication for which registration has not been requested. Placebo-controlled studies of aripiprazole injection in patients with agitation associated with schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There was no effect of age on the pharmacokinetics of a single, 15-mg dose of ABILIFY™. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Effects on Ability to Drive and to Use Machines

As with other antipsychotics, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that ABILIFY™ does not affect them adversely.

Interactions

CNS Drugs (including Alcohol)

Given the primary CNS effects of ABILIFY™, caution should be used when ABILIFY™ is taken in combination with other centrally acting drugs and alcohol.

Patients should be advised to avoid alcohol while taking ABILIFY™.

Coadministration of ***lithium*** titrated upwards from a starting dose of 900 mg until serum lithium concentrations near the upper end of the lithium therapeutic concentration range (1.0 – 1.4 mmol/L) were achieved and maintained for at least 5 days or until dose-limiting adverse events were observed and ***valproate*** (divalproex sodium) titrated upwards from a starting dose of 250 mg twice daily to achieve serum concentrations within the therapeutic range of 50 – 125 μg/mL for at least 14 days, with 30 mg ABILIFY™ once daily had no clinically significant effects on the pharmacokinetics of aripiprazole. Nor was there any clinically significant change in valproic acid or ***lithium*** pharmacokinetics when aripiprazole 30 mg once daily was administered concomitantly

for 7 days with either divalproex sodium 500 mg every 12 hours or controlled release lithium 450 mg every 12 hours.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Antihypertensive Agents

Due to its α_1-adrenergic receptor antagonist activity, ABILIFY^{TM} has the potential to enhance the effect of certain antihypertensive agents.

Medicines which cause QT prolongation or electrolyte imbalance

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Inhibitors and Inducers of CYP2D6 & CYP3A4

Aripiprazole is metabolized by multiple pathways primarily involving the CYP2D6 and CYP3A4 enzymes. In clinical studies with healthy subjects, potent inhibitors of CYP2D6 (***quinidine***) and 3A4 (***ketoconazole***) decreased oral clearance of aripiprazole by 52% and 38%, respectively. Other potent inhibitors of CYP3A4 and CYP2D6 may be expected to have similar effects. When concomitant administration of quinidine or ketoconazole with aripiprazole occurs, the aripiprazole dose should be halved. When the inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased. (See **DOSAGE & ADMINISTRATION – Concomitant Medication**)

No data are available for use of ABILIFY^{TM} with other inhibitors of CYP3A4 or CYP2D6. Examples of medicines or substances that have the potential to inhibit CYP3A4 or CYP2D6 include, but are not limited to, clarithromycin, erythromycin, itraconazole, fluconazole, ritonavir, indinavir, nefazodone, cyclosporin, amiodarone, cimetidine, fluoxetine, paroxetine and grapefruit juice.

Dose reduction of ABILIFY should be applied with concomitant administration of potent CYP3A4 inhibitors such as itraconazole, clarithromycin and HIV protease inhibitors, as similar effects to that seen in the clinical studies with ketaconazole may be expected. Dose reduction of ABILIFY should be applied with concomitant administration of potent CYP2D6 inhibitors such as fluoxetine and paroxetine as similar effects to that seen in the clinical studies with quinidine may be expected **(see DOSAGE & ADMINISTRATION – Concomitant Medications).**

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of ***carbamazepine*** (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg daily) resulted in an approximate 70% decrease in AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. Other potent inducers of CYP3A4 and CYP2D6 may be

expected to have similar effects. When a potent inducer like carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be increased. Other potent inducers of CYP3A4 include, but are not limited to, St Johns Wort, phenytoin, rifampicin, efavirenz, and nevirapine. Additional dose increases should be based on clinical evaluation. When the inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced. (See **DOSAGE & ADMINISTRATION – Dosage adjustment for patients taking CYP3A4 inducers**)

Inhibitors and Inducers of CYP1A1, CYP1A2, CYP2C9, and CYP2C19

Aripiprazole is not metabolized by CYP1A1, CYP1A2, CYP2C9, and CYP2C19 *in vitro*, suggesting that interactions with medications or other factors (e.g., smoking), which are inhibitors or inducers of these enzymes, are unlikely.

Effects of ABILIFY^{TM} on Substrates for CYP2D6, CYP2C9, CYP2C19, CYP3A4, & CYP1A2

Aripiprazole and dehydro-aripiprazole were weak inhibitors of CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism *in vitro* (IC_{50} values 2.4 –25 μM). Neither aripiprazole nor dehydro-aripiprazole inhibited CYP1A2 -mediated metabolism *in vitro* (IC_{50} value >50 – 66 μM).

In clinical studies, 10-30 mg/day doses of ABILIFY^{TM} had no significant effect on metabolism of substrates of CYP2D6 (***dextromethorphan***), CYP2C9 (***warfarin***), CYP2C19 (***omeprazole, warfarin***), and CYP3A4 (***dextromethorphan***). Thus, ABILIFY^{TM} is unlikely to cause clinically important drug interactions mediated by these enzymes.

Famotidine

There was no significant effect of the H_2 antagonist famotidine, a potent gastric acid blocker, on the pharmacokinetics of aripiprazole.

Food

ABILIFY^{TM} can be administered without regard to meals. Following administration of a 15-mg ABILIFY^{TM} tablet with a standard high-fat meal, the Cmax of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed Tmax by 3 hours for aripiprazole and 12 hours for the active metabolite.

ADVERSE REACTIONS

ABILIFY^{TM} has been evaluated for safety in 13543 patients who participated in multiple-dose clinical trials in Schizophrenia (including schizo-affective disorder), Bipolar I Disorder, Major Depressive Disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole and 749 patients with

exposure to aripirazole injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with ABILIFY^{TM} (monotherapy and in combination treatment with lithium or valproate) included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer- term exposure.

Adverse events during exposure were obtained by collecting voluntarily reported adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, MedDRA dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Oral Administration

Adult Patients with Schizophrenia

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which ABILIFY^{TM} was administered to acutely relapsed patients with schizophrenia in doses ranging from 2 to 30 mg/day, there was no difference in the incidence of discontinuation due to adverse events between ABILIFY^{TM}-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the ABILIFY^{TM} and placebo-treated patients.

Adult Patients with Bipolar I Disorder

Monotherapy

The following findings are based on a pool of 3-week, placebo-controlled, Bipolar I Disorder trials in which oral aripiprazole was administered at doses of 15mg/day or 30mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar I Disorder, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (11%) and placebo-treated (10%) patients. The types of adverse reactions that led to discontinuation were similar between aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of aripiprazole in patients with Bipolar I Disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in the following Table:

Table 2: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar I Disorder Treated with Oral Abilify Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	Aripiprazole	Placebo
	(n=917)	(n=753)
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Adverse Events Occurring at an Incidence of at Least 2% Among ABILIFY™-Treated Patients in Short-Term Placebo-Controlled Trials

Table 3 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in Schizophrenia and up to 3 weeks in Bipolar Mania), 2 or more of patients treated with ABILIFY™ (doses ≥2 mg/day) and

for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 3: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Abilify		
	Percentage of patients Reporting Reaction[a]	
System Organ Class Preferred Term	Aripiprazole (n=1843)	Placebo (n=1166)
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3

Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasm	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyradimal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2
[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.		

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Adult Patients with Adjunctive Therapy with Bipolar I Disorder

The following findings are based on a placebo-controlled trial of adult patients with Bipolar I Disorder in which aripiprazole was administered at doses of 15mg/day or 30mg/day in combination with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment

In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole compared with 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with adjunctive aripiprazole and lithium or valproate in patients with Bipolar I Disorder (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

Less Common Adverse Reactions in Adults with Adjunctive Therapy in Bipolar I Disorder

Table 4 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses of 15mg/day or 30mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 4: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of combination therapy with lithium or valproate in Patients with Bipolar I Disorder.

	Percentage of Patients Reporting Reaction [a]	
System Organ Class	**Aripiprazole + Lithium or Valproate**	**Placebo + Lithium or Valproate**
Preferred Term	**(n=253)**	**(n=130)**
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo

Dose-Related Adverse Events in Short-Term, Placebo-Controlled Trials in Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials comparing fixed doses (2, 10, 15, 20, and 30 mg/day) of ABILIFY™ to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (including sedation) [placebo, 7.1%; 10mg, 8.5%, 15 mg, 8.7 %; 20 mg, 7.5%; 30 mg, 12.6%].

Adverse Events Occurring in Long-Term Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for ABILIFY vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 5% (40/859). A similar profile was observed in a long-term study in Bipolar I Disorder.

Weight Gain

In placebo-controlled trials, there was a slight difference in mean weight change between ABILIFY™ and placebo patients (+0.7 kg vs –0.05 kg, respectively, in short-term studies; p≤0.01, and –1.3 kg vs –0.9 kg, respectively, in 26 week study; p=n.s.) and also a difference in the proportion of patients meeting the significant weight gain criterion of ≥7% of body weight (ABILIFY™ 8% compared to placebo 3% in short-term studies; p≤0.01; and ABILIFY™ 6% compared to placebo 4% in long-term studies; p = n.s.).

In 3-week trials in adults with Bipolar I Disorder-with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1kg versus 0.0kg, respectively. The proportion of patients meeting a weight gain criterion of≥7% of body weight was aripiprazole (2%) compared to placebo (3%). In the 6-week trial in Bipoar I Disorder-with aripiprazole as adjunctive therapy with either lithium or valproate, the mean weight gain for aripiprazole and placebo patients was 0.6kg versus 0.2kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight with adjunctive aripiprazole was 3% compared to adjunctive placebo 4%.

In long-term, double-blind, active-comparator trials in schizophrenia, ABILIFY™ was associated with a higher incidence of significant weight gain (≥7% above baseline) compared with haloperidol (20% vs 13%, respectively; p≤0.01; 1.1 kg vs 0.4 kg , respectively; p=n.s.) but a

lower incidence of significant weight gain compared to olanzapine (ABILIFY™ 13% vs olanzapine 33%; p<0.001; -0.9 kg vs 3.4 kg; p<0.001 in a double-blind study).

Weight change results (see Table 5) from long-term, double-blind, controlled trials in schizophrenia showed that patients with high body mass index (BMI) (>27) were less likely to have significant weight gain on ABILIFY™ than those with low BMI (<23).

Table 5

Weight Change Results Categorised by BMI at Baseline in Double-Blind, Controlled Trials in Schizophrenia

Study		BMI <23	BMI 23-27	BMI >27
52-week Haloperidol Controlled	Mean Change from Baseline (kg)	2.6	1.4	-1.2
	% Patients with ≧7% increase of body weight relative to baseline	30%	19%	8%
26-week Olanzapine Controlled	Mean Change from Baseline (kg)	1.2	-0.4	-1.4
	% Patients with ≧7% increase of body weight relative to baseline	21%	7%	11%
26-week Placebo Controlled	Mean Change from Baseline (kg)	-0.5	-1.3	-2.1
	% Patients with ≧7% increase of body weight relative to baseline	7%	5%	6%

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia in adults, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 13% vs. 12 % for placebo. The incidence of akathisia-related events for aripiprazole-treated patients was 8% vs 5% for placebo-treated patients.

In the short-term, placebo-controlled trials in Bipolar I Disorder in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was 16% versus 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-treated patients was 13% versus 4% for placebo. In the 6-week,

placebo-controlled trial in Bipolar I Disorder for combination therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for patients treated with aripiprazole in combination with lithium or valproate was 15% versus 8% for patients treated with aripiprazole and placebo and the incidence of akathisia-related events for patients treated with aripiprazole in combination with lithium or valproate was 19% versus 5% for patients treated with aripiprazole and placebo.

Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05).

In the adult Bipolar I Disorder trials with monotherapy aripiprazole, The Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.50; placebo, -0.01 and aripiprazole, 0.21; placebo, -0.05). Changes in the Assessment of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the Bipolar I Disorder trials with aripiprazole in combination with either lithium or valproate, The Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and combination therapy placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessment of Involuntary Movement Scales were similar for adjunctive aripiprazole and combination therapy placebo.

In a long-term, double-blind, haloperidol-controlled study in schizophrenia, the incidence of haloperidol-treated patients showing at least one EPS-related adverse event, including dystonia, was significantly greater than that of the ABILIFY^{TM} group (57% vs 26%; $p<0.001$). In a long-term, double-blind, olanzapine-controlled study, the incidence of olanzapine-treated patients showing at least one EPS-related adverse event was comparable to ABILIFY^{TM}-treated patients (15% vs 15%, respectively; p= n.s.).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

ECG Changes

Between group comparisons for pooled, acute, placebo-controlled trials in patients with schizophrenia or Bipolar I Disorder-revealed no significant differences between oral ABILIFY^{TM} and placebo in the proportion of patients experiencing potentially important changes in ECG

parameters. In fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QTc interval. ABILIFY™ was associated with a median increase in heart rate of two beats per minute compared to no increase among placebo patients.

In a 26-week, placebo-controlled trial in schizophrenia, there were no significant differences between ABILIFY™ and placebo in the proportion of patients experiencing potentially important changes in ECG parameters.

Laboratory Test Abnormalities

A between group comparison for acute, 3 to 6-week, placebo-controlled trials in adults revealed no medically important differences between the ABILIFY™ and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, haematology, or urinalysis parameters. Similarly, there were no ABILIFY™/placebo differences in the incidence of discontinuations for changes in serum chemistry, haematology, or urinalysis in adult patients.

In a long-term (26-week), placebo-controlled trial, there were no statistically significant differences between the aripiprazole and placebo patients in the mean change from baseline in fasting glucose, triglyceride, LDL, and total cholesterol measurements.

Adverse Reactions Observed During the Premarketing Evaluation of oral ABILIFY™

The following is a list of MedRA terms that reflect adverse reactions reported by adult patients treated with oral aripiprazole at multiple doses≥ 2mg/day during any phase of a trial within a database of 13,543 adult patients. The listing does not show adverse events mentioned in Table 2, 3, and 4 or in other sections of this prescribing information. It is important to emphasise that although the events reported occurred with treatment they are not necessarily caused by it. The adverse reactions are classified by system organ class and are according to the following definitions: common adverse reactions are those occurring in at least 1/100 patients; uncommon adverse reactions are those occurring in at least 1/1000, but less than 1/100 patients; rare adverse reactions are those occurring in less than 1/1000 patients.

Blood and Lymphatic System Disorders: ***uncommon***: leukopenia, neutropenia, thrombocytopenia; ***rare*** – eosinophilia, lymphadenopathy

Cardiac Disorders: ***uncommon*** **–** bradycardia, palpitations; cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischaemia; ***rare*** **-** atrial flutter, supraventricular tachycardia, ventricular tachycardia.

Ear and Labyrinth Disorders: ***rare*** **-** ear canal erythema, hypoacusis, vertigo positional, tinnitus.

Endocrine Disorders: ***rare*** **-** early menarche.

Eye Disorders: ***uncommon*** **-** dry eye; photophobia, diplopia, eyelid oedema, photopsia; ***rare*** **-** eye redness, chromotopsia, conjunctivitis, eye disorder, eye movement disorder, gaze palsy, lacrimation increased.

Gastrointestinal Disorders: ***uncommon*** **-** diarrhoea, gastritis, dysphagia, gastroesophageal reflux disease, swollen tongue, oesophagitis, hypoaesthesia oral; ***rare*** **-** abdominal distension, abnormal faeces, eructation, faeces discoloured, constipation, gastrointestinal disorder, gastrointestinal pain, glossitis, lip dry, parotid gland enlargement, pruritus ani, tongue discolouration , pancreatitis.

General Disorders and Administration Site Conditions: ***common*** – asthenia, peripheral oedema, irritability, chest pain; ***uncommon*** – face oedema, angiodema, gait disturbance, adverse event, chills, discomfort, feeling abnormal, mobility decreased; ***rare*** **-** difficulty in walking, facial pain, swelling, malaise, thirst, chest discomfort, cyst, energy increased, feeling cold, generalised oedema, local swelling, oedema, tenderness, xerosis, hypothermia.

Hepatobiliary Disorders: ***rare*** **-** hepatitis , jaundice.

Immune System Disorders: ***rare*** **-** decreased immune responsiveness , hypersensitivity.

Infections and Infestations: ***rare*** **-** sinusitis, urinary tract infection, body tinea, gastroenteritis viral, herpes simplex, localized infection, lower respiratory tract infection, oral candidiasis, parotitis, gastroenteritis.

Injury, Poisoning, and Procedural Complications: ***common*** **-** fall; ***uncommon*** – self mutilation; ***rare –*** *heat stroke*, injury, muscle strain, clavicle fracture, femoral neck fracture, hip fracture, humerus fracture, mouth injury, open wound.

Investigations: ***common*** – weight decreased, creatinine phosphokinase increased; ***uncommon*** **-** weight increased, blood creatinine increased, heart rate increased, blood glucose increased, pyrexia, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood bilirubin increased, hepatic enzyme increased; ***rare*** **-** electrocardiogram abnormal, urine output increased, blood creatine phosphokinase abnormal, orthostatic hypotension, blood urine present, electrocardiogram PR prolongation, electrocardiogram T wave inversion, eosinophil count increased, head lag abnormal, heart rate irregular, physical examination, urine ketone body present, white blood cell count increased, blood lactate dehydrogenase increased, glycosylated haemoglobin increased, gamma-glutamyl transferase increased.

Metabolism and Nutrition Disorders: ***uncommon*** – hyperlipidaemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycaemia, hypokalaemia, hypoglycaemia, polydipsia; increased appetite, dehydration, hyponatraemia; ***rare*** **-** diabetic ketoacidosis, hyperuricaemia.

Musculoskeletal and Connective Tissue Disorders: ***uncommon*** **–**muscle rigidity, musculoskeletal rigidity, muscle tightness, muscle spasms, muscular weakness,mobility decreased; ***rare*** **-** bone pain, nuchal rigidity, sensation of heaviness, flank pain, jaw disorder, kyphosis, osteoarthritis , rhabdomyolysis.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): ***rare*** **-** oral neoplasm, skin papilloma.

Nervous System Disorders: ***common*** – coordination abnormal; ***uncommon*** – memory impairment, cerebrovascular accident, hypokinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia, drooling, cogwheel rigidity, dystonia, disturbance in attention, dizziness postural, dysarthria, paraesthesia, parkinsonism, psychomotor hyperactivity, hypoaesthesia, speech disorder, tardive dyskinesia; ***rare*** **-** burning sensation, convulsion, depressed level of consciousness, dysgeusia, akinaesthesia, ataxia, bradykinesia, coma, dysphasia, facial palsy, judgement impaired, loss of consciousness, migraine, neuroleptic malignant syndrome, paraesthesia circumoral, sleep phase rhythm disturbance, Grand Mal convulsion, choreoathetosis, unresponsive to verbal stimuli.

Psychiatric Disorders: ***common*** – suicidal ideation; ***uncommon*** **–** aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation, depression, confusional state, nightmare, mania, abnormal dreams, hallucination auditory, nervousness, hallucination, apathy, thinking abnormal, bruxism; ***rare*** **–** catatonia, sleep walking, bradyphrenia, delirium, depressed mood, disorientation, euphoric mood, logorrhea, mental status changes, mood altered, panic attack, sleep disorder, blunted affect, cognitive deterioration, delusional perception, insomnia, eating disorder, emotional distress, impulsive behaviour, asthenia, mood swings, psychomotor retardation, somatoform disorder.

Renal and Urinary Disorders: ***uncommon*** – nocturia, polyuria, pollakiuria, incontinence, urinary retention; ***rare*** **-** proteinuria, bladder discomfort, chromaturia, enuresis, micturition urgency, oliguria, urethral discharge, urinary hesitation.

Reproductive System and Breast Disorders: ***uncommon*** – erectile dysfunction, amenorrhea[f], breast pain, menstruation irregular[f]; ***rare*** **-** genital pruritus female[f], vulvovaginal discomfort[f], pelvic pain, breast discharge, sexual dysfunction, gynaecomastia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: ***common*** – nasal congestion, dyspnea, pneumonia aspiration; ***uncommon*** **-** hiccups, epistaxis; ***rare*** **-** dry throat, rhinorrhoea, sinus congestion, hoarseness, nasal dryness, painful respiration, paranasal sinus hypersecretion.

Skin and Subcutaneous Tissue Disorders: ***common*** – rash (including erythematous, exfoliative, generalised, macular, maculopapular, popular rash, acneiform, allergic contact, exfoliative seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ***uncommon*** **-** pruritus, photosensitivity reaction, alopecia, urticaria; ***rare*** **-** decubitus ulcer, face oedema, pemphigus, psoriasis, dry skin.

Social Circumstances: ***rare*** **-** smoker.

Vascular Disorders: ***common*** **–** hypertension; ***uncommon*** **–** hypotension, hot flush, ***rare*** **-** flushing, hyperaemia.

[f] (female) indicates incidence based on gender total

POSTMARKETING EXPERIENCE

The following adverse reactions have been identified during postapproval use of Abilify. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angiodema, laryngospasm, pruritis/urticaria, or oropharyngeal spasm), and blood glucose fluctuation. Very rare occurrences of increased AST and increased ALT have been reported.

DRUG ABUSE AND DEPENDENCE

ABILIFY™ has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In self-administration studies in rats and monkeys, ABILIFY™ demonstrated marginal to no abuse potential. In physical dependence studies in rats and monkeys, modest withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse and such patients should be observed closely for signs of ABILIFY™ misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behaviour).

DOSAGE AND ADMINISTRATION

Recommended Dosage

Schizophrenia

Adults

The recommended starting dose for ABILIFY™ tablets and orally disintergrating tablets is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Doses in the range of 10 to 30 mg/day have been effective in clinical trials. Daily dosage may be adjusted on the basis of individual clinical status within the range of 10-30 mg daily. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state. There is no evidence that doses higher than 15 mg/day are more effective than the recommended starting dose of 10-15mg .

The maintenance dose for ABILIFY™ tablets or orally disintegrating tablets is 15 mg/day.

Bipolar I Disorder

Acute Treatment

Adults

The recommended starting and target dose of Abilify tablets or orally disintegrating tablets is 15mg as monotherapy or as combination therapy with lithium or valproate given once a day, without regard to meals. The dose can be increased to 30mg/day based on clinical response. The safety of doses above 30mg/day has not been evaluated in clinical trials.

Maintenance Therapy

Adults

Patients responding to aripiprazole for an acute or mixed episode may be continued on monotherapy aripiprazole at 15 mg or 30 mg daily for a further 9 weeks. Maintenance of effect has not been demonstrated beyond 26 weeks (see CLINICAL TRIALS).

Patients given aripiprazole for an acute manic or mixed episode may be continued on monotherapy at the same dose. Adjustments of daily dosage, including dose reductions should be considered on the basis of clinical status.

Renal impairment

No dosage adjustment is required in adult patients with renal impairment. (See also **DOSAGE & ADMINISTRATION Paediatric**).

Hepatic impairment

No dosage adjustment is required for adult patients with hepatic impairment (Child-Pugh Class A, B or C). (See also **DOSAGE & ADMINISTRATION Paediatric**).

Elderly

No dosage adjustment is required for patients ≥65 years of age.

Gender

No dosage adjustment is required for female adult patients relative to male adult patients. (See also **DOSAGE & ADMINISTRATION Paediatric**).

Concomitant Medications

Dosage adjustment for patients taking ABILIFY™ concomitantly with potential CYP3A4 inhibitors: When concomitant administration of a potent CYP3A4 inhibitor such as ketoconazole, itraconazole, clarithromycin and HIV protease inhibitors with ABILIFY™ occurs, the ABILIFY™ dose should be decreased. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the ABILIFY™ dose should then be increased.

Dosage adjustment for patients taking ABILIFY™ concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with ABILIFY™ occurs, the ABILIFY™ dose should be halved. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the ABILIFY™ dose should then be increased.

Dosage adjustment for patients taking ABILIFY™ concomitantly with multiple medications that inhibit CYP3A4 and CYP2D6: Although no clinical studies have been conducted in which ABILIFY™ was taken together with multiple drugs that inhibit CYP3A4 and CYP2D6, consideration should be given to reducing the daily dose of ABILIFY™ in individual circumstances.

Dosage adjustment for patients taking ABILIFY™ concomitantly with potential CYP3A4 inducers: When a potent CYP3A4 inducer such as carbamazepine is added to ABILIFY™ therapy, the ABILIFY™ dose should be increased. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the ABILIFY™ dose should then be reduced.

Smoking Status

No dosage adjustment is required for smoking patients relative to non-smoking patients.

Switching from Other Antipsychotics

Data was prospectively and systematically collected to address the safety of switching from other antipsychotics to ABILIFY™ (30mg/day). These data indicate that any of the following methods can be used safely for switching patients to ABILIFY™ from another antipsychotic monotherapy:

- immediate discontinuation of the patient's current antipsychotic regimen and immediate initiation of ABILIFY™;
- immediate initiation of ABILIFY™ while tapering off the current antipsychotic regimen over a 2-week period;
- upward titration of ABILIFY™ over a 2-week period and simultaneous tapering off of the patient's current antipsychotic regimen over the same 2-week period.

Special Instructions for Use and Handling of Orally Disintegrating Tablets

Do not open the blister until you are ready to administer ABILIFY™ ODT.

Remove a blister square containing a tablet from the blister card using the perforated tear lines. One corner of the square is shaded where it is easy to separate the top foil from the bottom. Using this corner, peel back the foil to expose the tablet. Do not try to push the ABILIFY™ ODT through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place it on the tongue. Tablet disintegration occurs rapidly (median is approximately 1 minute) in saliva.

Alternatively, the Abilify™ ODT can be placed in a glass containing water, dispersed in the water, and the resulting suspension drunk. As some particles from the tablet may be left in the glass, more water should be added to the glass, swirled and the contents drunk. Rinsing should be repeated until all the solid particles are consumed.

Abilify ™orally disintegrating tablets are fragile and should not be broken or cut.

OVERDOSAGE

Human Experience

In clinical studies, and postmarketing experience accidental or intentional acute overdosage of aripiprazole alone was identified in adult patients with estimated doses up to 1260 mg with no fatalities. The potentially medically important signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 1260 mg included lethargy, blood pressure

increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported include somnolence, and transient loss of consciousness. In the patients who were evaluated in hospital settings, there were no reported observations indicating a clinically significant adverse change in vital signs, laboratory assessments, or ECG.

Management of Overdosage

No specific information is available on the treatment of overdose with ABILIFY^{TM}. The possibility of multiple drug involvement should be considered. Therefore cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

***Charcoal*:** In the event of an overdose of ABILIFY^{TM}, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. In a single-dose study in which 15 mg of aripiprazole was administered to fully compliant, fully conscious, healthy, male volunteers and followed by activated charcoal (50 g), administered one hour after ABILIFY^{TM}, aripiprazole AUC and Cmax was decreased by 51 and 41%, respectively, compared to historic controls, suggesting that charcoal may be effective for overdose management.

***Haemodialysis*:** Although there is no information on the effect of haemodialysis in treating an overdose with ABILIFY^{TM}, haemodialysis is unlikely to be useful in overdose management, since aripiprazole is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

The Poisons Information Centre, telephone number 131126, should be contacted for advice on management.

PRESENTATION

ABILIFY^{TM} (aripiprazole) is available as:

Tablets

*2 mg green, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with “A-006” and “2” and scored on the other side;

5 mg blue, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with “A-007” and “5”;

10 mg pink, modified rectangular, shallow convex, bevel-edged, tablets, marked on one side with "A-008" and "10";

15 mg yellow, round, shallow convex, bevel-edged, tablets, marked on one side with "A-009" and "15";

20 mg white to pale yellowish white, round, shallow convex, bevel-edged, tablets, marked on one side with "A-010" and "20";

30 mg pink, round, shallow convex, bevel-edged, tablets, marked on one side with "A-011" and "30".

ABILIFY^{TM} tablets are packed in aluminium blisters in cartons.

*Orally Disintegrating Tablets (see Special Instructions for Use and Handling of Orally Disintegrating Tablets)

*10 mg pink, round, flat faced, bevel-edged tablets with scattered specks on the surface, marked on one side with "A" over "640"and "10" on the other side;

*15 mg yellow, round, flat faced, bevel-edged tablets with scattered specks on the surface, marked on one side with "A" over "641"and "15" on the other side;

*20 mg white, round, flat faced, bevel-edged tablets with scattered specks on the surface, marked on one side with "A" over "642"and "20" on the other side;

*30 mg pink, round, flat faced, bevel-edged tablets with scattered specks on the surface, marked on one side with "A" over "643"and "30" on the other side;

*ABILIFY^{TM} orally disintegrating tablets are packed in aluminium blisters in cartons.

***This presentation is not currently marketed in Australia.**

STORAGE

Tablets & Orally Disintegrating Tablets

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Bristol-Myers Squibb Australia Pty. Ltd.

556 Princes Highway

Noble Park

Victoria 3174

Australia

POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

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