



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**

OPINION

18 February 2009

**ABILIFY 5 mg tablets, pack of 28 (CIP: 364 069-7)**

**ABILIFY 10 mg tablets, pack of 28 (CIP: 364 073-4) and pack of 98 (CIP: 565 796-3)**

**ABILIFY 15 mg tablets, pack of 28 (CIP: 364 078-6) and pack of 98 (CIP: 565 798-6)**

**ABILIFY 10 mg orodispersible tablets, pack of 28 (CIP: 369 214-5)**

**ABILIFY 15 mg orodispersible tablets, pack of 28 (CIP: 369 217-4)**

**Applicant: BRISTOL-MYERS SQUIBB**

aripiprazole

ATC code: N05AX12

List I

Date of marketing authorisation (MA):

ABILIFY 5 mg, 10 mg, 15 mg, and tablets: 04 June 2004 modified on 31 March 2008

ABILIFY 10 mg, 15 mg orodispersible tablets: 20 June 2005 modified on 31 March 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication "for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of new manic episodes in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment"

Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals:

Pack of 28

Inclusion on the List of Medicinal Products Approved for Use by Hospitals: Pack of 98

## 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Aripiprazole

### 1.2. Indications

"ABILIFY is indicated for the treatment of schizophrenia.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of new manic episodes in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment"

### 1.3. Dosage

Oral route.

Schizophrenia:

The recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule, without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes:

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

Recurrence prevention of manic episodes in Bipolar I Disorder:

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

Children and adolescents: there is no experience in children and adolescents aged under 18 years.

Hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. Dosing should be managed cautiously in these patients. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment.

Patients with renal impairment: no dosage adjustment is required for patients with renal impairment.

Elderly patients: the effectiveness of ABILIFY in the treatment of schizophrenia and bipolar I disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant.

Gender: no dosage adjustment is required for female patients as compared to male patients.

Smokers: no dosage adjustment is required for smokers according to the metabolism pathway of ABILIFY.

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is stopped, the aripiprazole dose should then be increased.

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is stopped, the aripiprazole dose should then be reduced to the recommended dose.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2008)

N : Nervous system  
N05 : Psycholeptics  
N05A : Antipsychotics  
N05AX : Other antipsychotics  
N05AX12 : Aripiprazole

### 2.2. Medicines with a similar therapeutic aim

Neuroleptics indicated in the treatment of acute psychotic states

Medicinal products indicated in the treatment of manic episodes:

Lithium salts	- TERALITHE, tablet, oral suspension - TERALITHE PR, tablet - NEUROLITHIUM, oral solution
Olanzapine	- ZYPREXA, coated tablet - ZYPREXA VELOTAB, orodispersible tablet.
Carbamazepine	- TEGRETOL, tablet and its generics - TEGRETOL PR, tablet and its generics
Risperidone	- RISPERDAL, tablet and its generics - RISPERDALORO, orodispersible tablet
Sodium divalproate	- DEPAKOTE, enteric-coated tablet (in patients with bipolar disorder in the case of contraindication or intolerance to lithium)

Medicinal products indicated for recurrence prevention in bipolar disorders:

Lithium salts	- TERALITHE, tablet, oral suspension - TERALITHE PR, tablet - NEUROLITHIUM, oral solution
Olanzapine	- ZYPREXA, coated tablet - ZYPREXA VELOTAB, orodispersible tablet. (in patients who have already responded to olanzapine treatment during a manic episode)
Valpromide	- DEPAMIDE, tablet (in the case of contraindication or intolerance to lithium and carbamazepine)
Carbamazepine	- TEGRETOL, tablet and its generics - TEGRETOL PR, tablet and its generics (in particular, in patients with relative resistance, contraindications or intolerance to lithium)

Sodium Divalproate - DEPAKOTE, enteric-coated tablet (continuation of treatment may be considered after the manic episode in patients who responded to acute treatment of this episode)

### 3 ANALYSIS OF AVAILABLE DATA

#### 3.1. Efficacy

##### 3.1.1. Treatment of acute manic episodes

Six placebo-controlled comparative studies of short-term efficacy have been performed in this indication, including two with a second active treatment arm.

##### As monotherapy: aripiprazole versus placebo

- Study CN 138 007

This randomised, double-blind study compared aripiprazole 15 mg (n=131) and 30 mg (n=136) with placebo (n=134) for 3 weeks in patients with bipolar I disorder according to DSM IV<sup>1</sup> criteria, admitted to hospital for acute manic or mixed episodes. Patients had to have a YMRS score<sup>2</sup>  $\geq$  20 during randomisation.

The mean baseline YMRS score was 28 in the three treatment groups. This study did not demonstrate a difference between groups for the primary endpoint: change in YMRS score from baseline to 3 weeks.

Adverse events observed with a frequency  $\geq$  10% and a higher incidence than in the placebo group were: headaches, nausea, agitation, constipation, asthenia, akathisia, anxiety, vertigo, vomiting and pain in the extremities.

Seven percent of the patients discontinued treatment because of adverse effects in the placebo group, 15% in the aripiprazole 15 mg group and 7% in the aripiprazole 30 mg group.

Extrapyramidal symptoms were observed in 14% of the patients in the placebo group, 28% of the patients in the aripiprazole 15 mg group and 24% of the patients in the aripiprazole 30 mg group.

- Studies CN 138 009<sup>3</sup> (n=262) and CN 138 074<sup>4</sup> (n=272)

These randomised, double-blind studies compared aripiprazole 15 to 30 mg/day with placebo in patients with a bipolar I diagnosis according to the DSM IV criteria and admitted to hospital for acute manic or mixed episodes.

Patients had to have a YMRS score  $\geq$  20 at randomisation. The starting dose of aripiprazole was 30 mg/day and a reduction to 15 mg/day was authorised during treatment.

The primary efficacy endpoint was the change in the YMRS score from baseline to 3 weeks of treatment.

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<sup>1</sup> Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Bipolar I disorder is mainly characterised by the occurrence of one or several manic or mixed episodes. Subjects have also often presented one or more major depressive episodes.

<sup>2</sup> YMRS: Young Mania Rating Scale (Young et al. 1978) – 11-item mania severity scale, global score from 0 to 60.

<sup>3</sup> A Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Aripiprazole in Patients With Acute Bipolar Mania. Keck P., Marcus R., Tourkodimitris S. et al. Am J Psychiatry 2003; 160:1651-1658.

<sup>4</sup> Aripiprazole in the treatment of acute maniac or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. Sachs G., Sanchez R., Marcus R., Stock E., et al. Journal of psychopharmacology 2006 British Association for Psychopharmacology.

In study CN 138 009, the double-blind treatment was stopped in non-responders (change in CGI-BP score between 4 (no improvement) and 7 (major deterioration) at the end of week 2; these patients could receive aripiprazole open-label during week 3. The change in the CGI-BP<sup>5</sup> score and the responder rate at 3 weeks were secondary endpoints.

Results at 3 weeks:

	Study CN 138 009		Study CN 138 074	
	Placebo n=132	Aripiprazole n=130	Placebo n=135	Aripiprazole n=137
Baseline YMRS	29.7 (n=122)	28.2 (n=123)	28.5 (n=132)	28.8 (n=136)
Change in YMRS	-3.4	-8.2*	-7.19	-12.52*
Baseline CGI-BP	4.7 (n=122)	4.6 (n=124)	4.71 (n=129)	4.69 (n=135)
Change in CGI-BP	-0.4	-1.0*	-1.12	-1.59*
Responder rate**	23/122 19%	49/123 40%*	42/132 32%	72/136 53%*

LOCF method, \* p<0.01 versus placebo, \*\* Reduction in YMRS score ≥ 50% relative to baseline

In study CN 138 009, 31% of the patients completed the 3-week double-blind period: 28 patients (21%) in the placebo group, 54 patients (42%) in the aripiprazole group. Eleven percent of patients discontinued treatment for adverse events (vs 10% with placebo), 10% stopped for lack of efficacy (vs 12% with placebo).

The adverse events reported in the aripiprazole group with a frequency ≥ 10% and at least twice the frequency observed with placebo were: nausea, dyspepsia, drowsiness, vomiting, constipation, accidental injury, akathisia. The incidence of extrapyramidal symptoms was 27% in the aripiprazole group (versus 11% in the placebo group): akathisia (11% vs 2%), tremors (6% vs 3%).

In study CN 138 074. 53% of the patients completed the 3-week double-blind period: 70 patients (52%) in the placebo group, 75 patients (55%) in the aripiprazole group. In the aripiprazole group, nine percent of patients discontinued treatment because of adverse events (vs 7.5% with placebo) and 9% stopped for lack of efficacy (vs 21% with placebo).

The adverse events reported in the aripiprazole group with a frequency ≥10% and at least twice the frequency observed with placebo were: dyspepsia, constipation, akathisia, pain in the extremities. The incidence of extrapyramidal symptoms was 25% in the aripiprazole group (versus 13% in the placebo group).

- Studies CN 138 135 (n=480) and CN 138 162 (n=485)

These randomised, double-blind, placebo-controlled studies evaluated the efficacy of aripiprazole monotherapy in the treatment of manic or mixed episodes in hospitalised patients with bipolar 1 disorder (DSM-IV-TR). These studies had a second active treatment arm.

After a screening period, patients had to have a YMRS score ≥ 20, an increase relative to the baseline score of < 25% and a MADRS score ≤ 17<sup>6</sup>. Aripiprazole was administered at the starting dosage of 15 mg/day; an increase to 30 mg/day was authorised.

The primary endpoint was the change in the YMRS score from baseline to week 3.

In study CN 138 135 the mean baseline YMRS score was 29 and the mean baseline CGI-BP score was 4.6. Twenty-three percent of randomised patients had had a previous psychotic episode. The lithium starting dose was 900 mg/day; an increase in the dosage to 1500 mg/day was authorised.

<sup>5</sup> Clinical Global Impression scale for use in Bipolar illness. Psychiatry Res 1997;73:159-171.

<sup>6</sup> A new depression scale designed to be sensitive to change. Montgomery SA, Asberg M.Br J Psychiatry 1979; 134:382-389. MADRS (Montgomery-Asberg Depression Rating Scale): 10 items scored on a scale of from 0 to 6 to measure the course of depressive symptoms.

In study CN 138 162 the mean baseline YMRS score was 28 and the mean baseline CGI-BP score was 4.5. Ten percent of randomised patients had had a previous psychotic episode. Haloperidol was administered at the dosage of 5 mg/day; an increase in the dosage to 15 mg/day was authorised.

Results at 3 and 12 weeks of treatment:

	Study CN 138 135			Study CN 138 162		
	Placebo n=163	Lithium n=155	Aripiprazole n=154	Placebo n=152	Haloperidol n=161	Aripiprazole n=166
YMRS week 3	-9.01	-12.03**	-12.64**	-9.70	-12.83**	-11.98*
<i>Responder rate</i>	34.4%	45.8%*	46.8%*	38.2%	49.7% ns	47.0% ns
YMRS week 12	-	-12.71	-14.48	-	-17.84	-17.16
<i>Responder rate</i>	-	49.0%	56.5%	-	73.9%	72.3%
CGI-BP week 3	-1.06 n=162	-1.34* n=154	-1.48** n=153	-1.17 n=151	-1.56**	-1.44*
CGI-BP week 12	-	-1.53 n=154	-1.70 n=153	-	-2.19	-2.11

\* p≤0.05 versus placebo, \*\* p≤0.01 versus placebo

In study CN 138 135, fourteen percent of patients stopped treatment at 3 weeks because of adverse events in the aripiprazole group, 12% in the lithium group and 10% in the placebo group.

The adverse events (AE) most frequently reported in the aripiprazole group (frequency ≥ 5% and at least twice that observed in the placebo group) were: sedation 12% (vs 5%), akathisia 11% (vs 3%), agitation 8% (vs 3%), fatigue 8% (vs 1%), dry mouth 7% (vs 2%), pain in the extremities 6% (vs 2%) and musculoskeletal rigidity 5% (vs 1%); the most commonly reported AE with lithium were tremors (10% vs 5%).

The incidence of extrapyramidal symptoms was 23% in the aripiprazole group versus 12% in the placebo group and 15% in the lithium group.

At 12 weeks, the percentage of treatment discontinuations for adverse effects was 20% in the aripiprazole group and 18% in the lithium group. The effects observed with a frequency ≥ 10% in the aripiprazole group were: headaches, nausea, sedation, akathisia, constipation in the aripiprazole group; nausea, headaches, constipation and tremors in the lithium group.

A reduction in blood prolactin levels was observed at 3 weeks with aripiprazole compared to placebo. At 12 weeks, the reduction in prolactin levels was -7 in the aripiprazole group and -2 in the lithium group.

In study CN 138 162, Ten percent of patients stopped aripiprazole treatment at 3 weeks because of adverse effects, 7% in the haloperidol group and 11% in the placebo group: mania (4.8% with aripiprazole vs 6.5% with placebo), extrapyramidal symptoms with haloperidol (2%).

At 3 weeks of treatment, the most frequent adverse effects with aripiprazole (frequency ≥ 5% and at least twice that observed with placebo) were extrapyramidal symptoms: 20% in the aripiprazole group (versus 6% in the placebo group and 44% for the haloperidol group).

At 12 weeks, 15% of patients had discontinued treatment because of adverse effects in the aripiprazole group and 11% in the haloperidol group. The most frequent adverse effects (≥ 10%) were akathisia and insomnia in the aripiprazole group, akathisia and extrapyramidal symptoms in the haloperidol group.

A reduction in blood prolactin levels was observed at 3 weeks with aripiprazole compared to placebo. At week 12, a reduction in prolactin levels (- 13.39) was observed in the aripiprazole group (+6.65 with haloperidol).

An increase in CPK was observed after 3 weeks of treatment in 9% of patients in the aripiprazole group, 1.4% of patients in the haloperidol group and 5% of patients in the placebo group. At week 12, high CPK values were observed in 11% of patients on aripiprazole (vs 3% of patients with haloperidol).

### **In combination with a mood stabilizer : aripiprazole versus placebo**

Study CN 138 134 was a randomised, double-blind trial versus placebo in patients with bipolar I disorder according to DSM IV criteria.

Three hundred and eighty four patients partially non-responsive to valproate or lithium monotherapy during a 2-week period before trial entry (YMRS score  $\geq 16$  and reduction in the score  $\leq 25\%$ ) were randomised to a 6-week double-blind treatment period: aripiprazole 15 to 30 mg/day (n=253) or placebo (n=131) in combination with divalproate or lithium.

The study primary endpoint, the reduction in the YMRS score at week 6 was higher in the aripiprazole group (- 13.3) than in the placebo group (- 10.7); difference -2.62. 95% CI: [-4.29.-0.95]. The reduction in the total CGI-BP score was higher in the aripiprazole group (- 1.89) than in the placebo group (-1.56); difference -0.33. 95% CI: [-0.60.-0.07].

The reduction in the YMRS score observed at week 6 with valproate/aripiprazole was -14 versus -10.7 with valproate/placebo. The reduction in this score was -12.4 with lithium/aripiprazole versus -10.8 with lithium/placebo.

Twelve percent of patients stopped treatment because of adverse effects in the aripiprazole group (versus 6% in the placebo group): 5% of patients (vs 1%) stopped because of akathisia with aripiprazole.

The most frequently reported adverse effect with aripiprazole ( $\geq 10\%$ ) with an incidence at least twice that with placebo was akathisia (19% vs 5%). The incidence of extrapyramidal symptoms was 28% in the aripiprazole group (versus 14% for the placebo group).

In the aripiprazole group, QTc prolongation was observed at week 6 in 11 patients (5%) vs 3 patients (2.5%) in the placebo group.

### **3.1.2. Prevention of mood disorder recurrences**

Study CN 138 010<sup>7,8</sup> was a randomised, double-blind comparison of the efficacy and safety of aripiprazole versus placebo for recurrence prevention in patients with a bipolar I disorder according to DSM-IV criteria.

Included patients:

- had just taken part in a 3-week study comparing aripiprazole with placebo in acute mania
- or had presented a manic or mixed episode requiring hospitalisation during the previous 3 months.

The 567 included patients were treated by aripiprazole (15 to 30 mg/day) during a 6 to 18 week open-label period.

One hundred and sixty-one patients with mean age of 40 years, with no mood disorder during this period (YMRS score  $\leq 10$  and MADRS score  $\leq 13$  for 6 consecutive weeks ) were randomised to two groups: placebo (n=83) or aripiprazole (15 to 30 mg/day, n=78), for a 26-week, double-blind period. Sixty-six of these patients (27 patients in the placebo group and 39 patients in the aripiprazole group) took part in the additional 74-week, double-blind extension period.

The starting dose of aripiprazole was 30 mg/day and a reduction in the dosage to 15 mg/day was authorised. The mean dosage of aripiprazole was 24 mg/day during the 26-week double-blind period.

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<sup>7</sup> A Randomized, Double Blind, Placebo-Controlled 26-Week Trial of Aripiprazole in Recently Manic patients with bipolar I disorder. Keck P. Calabrese J., Mc Quade R. et al. J Clin psychiatry 67:4. April 2006.

<sup>8</sup> Aripiprazole Monotherapy for Maintenance Therapy in Bipolar I Disorder: A 100-Week, Double Blind sstudy Versus Placebo. Keck P. Calabrese J., McIntyre et al. J Clin psychiatry 2007;68:1480-1491.

Twenty-two percent of patients in the placebo group and 38% of patients in the aripiprazole group had presented a mixed episode with 17% and 18% of "rapid-cycling" patients. During randomisation, the mean YMRS scores were 2.1 in the placebo group and 2.6 in the aripiprazole group. Mean MADRS scores were 4.5 and 3.9 respectively.

The primary efficacy endpoint at 26 weeks was the time to symptomatic relapse into any mood disorder (manic, depressive or mixed episodes) defined by:

- hospitalisation for a new mood disorder episode or
- a change in antipsychotic medication

The percentage of recurrent episodes of mania and depression was evaluated at 26 and 100 weeks.

Sixty-seven patients completed the 26-week double-blind period (28 patients on placebo, 39 patients on aripiprazole).

### Results:

At 26 weeks, the time to recurrence was longer in the aripiprazole group than with placebo (HR=0.52 95% CI: [0.30-0.91]) as was the time to recurrence of mania (HR=0.31 95% CI: [0.12-0.77]). There was no difference in the time to recurrence of depression in the two groups (HR=0.83 95% CI: [0.35-2.01]) at 26 weeks.

At 100 weeks, the time to recurrence was higher in the aripiprazole group than in the placebo group (HR=0.53 95% CI: [0.32-0.87]).

Number of patients (%) presenting a recurrence:

Type of recurrence	26 weeks		100 weeks	
	Placebo (n=83)	Aripiprazole (n=77)	Placebo (n=83)	Aripiprazole (n=77)
Mood disorder	36 (43)	19 (25)*	43 (52)	25 (32)*
Mania	19 (23)	6 (8)**	(28)	(12)*
Depression	11 (13)	9 (12)	(16)	(14)
Mixed	5 (6)	4 (5)	(6)	(5)
Unknown	1 (1)	0 (0)	(2)	(1)

\* p ≤ 0.05 versus placebo, \*\* p ≤ 0.01 versus placebo

At 26 weeks, the mean changes in the YMRS scores were 7.5 in the placebo group and 3.4 in the aripiprazole group; the mean changes in MADRS scores were 6.4 and 5.1 respectively.

Secondary endpoints at 26 weeks:

Endpoint	Baseline score Placebo group	Baseline score Aripiprazole group	Change Placebo group	Change Aripiprazole group
YMRS	2.06	2.55	7.50	3.42**
MADRS	4.51	3.87	6.43	5.11 ns
Total PANSS	36.41	35.85	9.13	5.22 ns
Total CGI-BP	1.41	1.42	1.28	0.74*

\*  $p \leq 0.05$  versus placebo, \*\*  $p \leq 0.01$  versus placebo

During this period, 55/83 patients (66%) in the placebo group and 39/78 patients (50%) in the aripiprazole group prematurely stopped treatment.

There were 43% discontinuations for lack of efficacy in the placebo group vs 24% in the aripiprazole group. One patient stopped treatment because of an adverse event in the placebo group and 5 patients (6%) in the aripiprazole group.

Adverse events with a reported frequency in the aripiprazole group  $\geq 5\%$  and at least twice that in the placebo group were: tremors (9.1%), akathisia (6.5%), vaginitis (6.4%) and pain in the extremities (5.2%). Thirteen percent of patients in the placebo group and 8% of patients in the aripiprazole group reported a serious adverse event.

An increase in mean body weight of +0.5 kg was observed in the aripiprazole group (vs -1.7 kg in the placebo group). A weight gain  $\geq 7\%$  kg was observed in 13% of aripiprazole group patients (vs 0% for the placebo group).

Between weeks 26 and 100, 22/27 patients (81%) in the placebo group and 32/39 patients (82%) in the aripiprazole group stopped treatment prematurely.

Discontinuations for lack of efficacy were more frequent in the placebo group (26%) than in the aripiprazole group (13%).

### Conclusion

Survival curve analysis showed that the time to recurrence in the aripiprazole group was longer than the one observed in the placebo group; there was fewer recurrence of mania after 26 and 100 weeks of treatment in the aripiprazole group than in the placebo group. Thirty-eight percent of patients presented a mixed episode in the aripiprazole group (versus 22% in the placebo group). There was no difference in the number of recurrences of depression between the two groups.

### **3.2. Adverse events**

A total of 2,626 patients received aripiprazole during the trials performed in acute manic episodes of bipolar disorder; 1,895 patients received 3 weeks of treatment and 1,446 received 6 weeks, i.e. 547 patient-years of exposure.

During clinical studies performed in bipolar disorder, the dosage of aripiprazole was higher than 25 mg/day in 40% of patients.

The following adverse effects were observed in the aripiprazole groups with a frequency  $\geq 5\%$  and twice that reported for the placebo groups: akathisia, sedation, extrapyramidal symptoms, agitation, tremors and musculoskeletal rigidity. Mania and akathisia were the events that usually led to discontinuation of treatment.

The incidence of treatment discontinuations for adverse effects in the aripiprazole groups was 17.6%. The incidence of akathisia in the aripiprazole groups was higher for patients treated for a bipolar disorder (16%) than for patients treated for schizophrenia (7%). The incidence of treatment discontinuations for depression was 2.7%.

The incidence of weight gain in the aripiprazole groups increased with the duration of treatment.

A clinically relevant rise in CPK levels was observed in 43 patients of the 1,663 patients (2.6%) treated in bipolar disorder by aripiprazole.

The incidence of QT prolongation  $\geq$  30 msec in aripiprazole-treated groups of bipolar disorder patients was 7.9%.

### 3.3. Conclusion

Treatment by aripiprazole was compared to placebo over a 3-week period in patients with bipolar I disorder and presenting moderate to severe manic episodes. Aripiprazole was shown to be superior to placebo in 4 of the 5 studies presented. Changes in the YMRS score were from -8 to -13 in the aripiprazole groups (vs -3 to -10 in the placebo groups). Responder rates were: 40% in the aripiprazole group (vs 19% in the placebo group) in study CN 138 009. 53% (vs 32%) in study CN 138 074. 46.8% (vs 34.4%) in study CN 138 135. 47% (vs 38.2%) in study CN 138 162.

At 12 weeks, the changes in YMRS scores in the aripiprazole groups were -14 (vs -13 in the lithium group) and -17 (vs -18 in the haloperidol group).

A clinical improvement in the YMRS score at 6 weeks was observed in the mood regulator / aripiprazole combination group compared to the mood regulator / placebo group (- 13 vs -11).

Aripiprazole treatment was compared to placebo over a 26-week period for the prevention of recurrences of mood disorders in patients previously treated and stabilized with aripiprazole for manic or mixed episodes. Recurrences were fewer and occurred later with aripiprazole (25% with aripiprazole vs 43% with placebo) and mania recurrence rates were of 8% in the aripiprazole group versus 23% in the placebo group. The prevention of recurrences of mixed episodes was not demonstrated. No prevention of recurrences of depression was observed.

The mean number of mood disorder recurrences over a ten-year period was of 4; more comparative efficacy and longer-term safety (> 6 months) data are required.

A European risk management plan has been set up for the monitoring of the safety of ABILIFY in its extension of indication.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Bipolar disorders are characterised by a propensity towards recurrent episodes of altered mood. Different clinical forms may be distinguished according to the characteristics of the mood disorder episodes and their progression in time, making this disease very heterogeneous. Comorbidities may worsen the prognosis.

Bipolar disorders may cause a marked deterioration in quality of life and cause social disability. The main risk is suicide.

These proprietary products provide curative treatment for moderate to severe manic episodes in bipolar 1 disorder.

These products are indicated for the prevention of mood disorder recurrences in bipolar 1 disorder in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

The efficacy/adverse effects ratio of these products is high.

Alternative medicines are available.

Public health benefit:

Bipolar disorders represent a high public health burden taking into account their frequency and their seriousness.

There is a public health need in particular for the prevention of recurrences during bipolar disorders.

Available data (efficacy versus placebo as monotherapy or combination therapy, insufficient comparative data) suggest that this medicine will not have an impact on morbidity, mortality or quality of life in the treatment of acute manic episodes or in the prevention of their recurrences.

ABILIFY should not therefore address an identified public health need. Consequently, ABILIFY is not expected to benefit public health in these indications.

The actual benefit of these products in this indication is substantial.

#### **4.2. Improvement in actual benefit**

ABILIFY does not provide an improvement in actual benefit (IAB V) in the management of patients with bipolar I disorder.

#### **4.3. Therapeutic use<sup>9,10,11</sup>**

The treatment of acute manic episodes is mainly based on two classes of psychotropic drugs: mood regulators (lithium, carbamazepine and sodium divalproate\*) and atypical and conventional antipsychotics.

The choice of treatment must take into account the clinical setting, patient preferences and the physician's experience.

The prescription of prophylactic treatment is justified in bipolar disorder to prevent the recurrences of the disorder that characterise this condition. It is currently acceptable for this treatment to be instituted from the onset of the first manic episode.

Lithium is used in the first-line treatment. Carbamazepine and valpromide are alternative medications, in particular for rapid-cycling, lithium-resistant or lithium-intolerant subjects.

Olanzapine and aripiprazole are indicated in patients who have already responded to these treatments during manic episodes. The prescription of these two antipsychotics under real-life conditions must take into account the fact that they have no proven efficacy for the prevention of the characterised major depressive episodes that form part of this disease. Their prolonged prescription for recurrence prevention must take into account the fact that no assessment of the long-term efficacy/safety ratio of these drugs has been made in this indication.

In addition to pharmacotherapy, patients and their close contacts must be given educational and psychological support.

Compliance with certain dietary and lifestyle rules contributes to a favourable outcome: these include regular sleep, avoiding periods of overwork and controlling intake of alcohol and psychostimulants.

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<sup>9</sup> Hirschfeld RMA et al. Practice guideline for the treatment of patients with bipolar disorder (second edition), April 2002 and Hirschfeld RMA et al. Guideline watch: Practice guideline for the treatment of patients with bipolar disorder (second edition), November 2005 viewed on 16/05/2008 at [http://www.psychiatryonline.com/pracGuide/pracGuideTopic\\_8.aspx](http://www.psychiatryonline.com/pracGuide/pracGuideTopic_8.aspx)

<sup>10</sup> NICE 2006. Bipolar disorder. The management of bipolar disorder in adults, children and adolescents in primary and secondary care. Viewed on 16/05/2008 at <http://www.nice.org.uk/CG38#documents>

<sup>11</sup> Yatham LN et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. *Bipolar Disorders* 2006; 8: 721–739.

\* indicated in the case of a contraindication or intolerance to lithium.

Management of stressful life events is based on the temporary stepping up of psychological support. Certain patients may benefit from the implementation of more highly structured psychotherapy.

#### **4.4. Target Population**

As the prevalence of bipolar I disorder is between 0.4 and 1.6 percent in the general population<sup>12</sup>, the target population of ABILIFY may be estimated to be approximately 200,000 to 700,000 patients. The target population of patients who may benefit from aripiprazole for the prevention of recurrent episodes of mania during bipolar I disorder remains to be determined.

#### **4.5. Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the extension of indication.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%

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<sup>12</sup> Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).