HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

ABILIFY 1 mg/ml, oral solution, 150 ml
(CIP code: 373 297-9)

ABILIFY 5 mg, tablets
B/28 (CIP code: 364 069-7)

ABILIFY 10 mg, tablets
B/28 (CIP code: 364 073-4)

ABILIFY 15 mgs, tablets
B/28 (CIP code: 364 078-6)

ABILIFY 10 mg, orodispersible tablets
B/28 (CIP code: 369 214-5)

ABILIFY 15 mg, orodispersible tablets
B/28 (CIP code: 369 217-4)

Applicant: OTSUKA PHARMACEUTICAL FRANCE SAS

aripiprazole
ATC code: N05AX12

List I

Date of Marketing Authorisation (centralised procedure):

ABILIFY 1 mg/ml, oral solution: 28 October 2005, 7 November 2005, 7 September 2006, 28 November 2006, 5 June 2007, 31 March 2008, 25 August 2008, 21 April 2009, 8 June 2009, 21 August 2009 (extension to adolescents with schizophrenia), 5 November 2009

ABILIFY 5 mg, 10 mg, 15 mg, tablets and 10 mg and 15 mg, orodispersible tablets: 4 June 2004, 30 March 2005, 7 November 2005, 7 September 2006, 28 November 2006, 5 June 2007, 31 March 2008, 25 August 2008, 21 April 2009, 8 June 2009, 21 August 2009 (extension to adolescents with schizophrenia), 5 November 2009

Reason for request: Inclusion on list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication “Treatment of schizophrenia in adolescents aged 15 years and older”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Aripiprazole

1.2. Indications

“ABILIFY is indicated for the treatment of schizophrenia in adults and in **adolescents 15 years and older**.

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

1.3. Dosage

"Adults:

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 (see section 5.1). 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.

Paediatric population:

Schizophrenia in adolescents 15 years and older: The recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg.
When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).
ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.
ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).
ABILIFY tablets are for oral use.

Patients with 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. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: No dosage adjustment is required in patients with renal impairment.

Elderly: 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 (see section 4.4).
Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).
Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:
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 withdrawn from the combination therapy, 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 withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose."

1.4. Pharmacodynamics

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2004)

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

2.2. Medicines in the same therapeutic category
None

2.3. Medicines with a similar therapeutic aim
Schizophrenia in adolescents over 15 years of age:

- Amisulpride - SOLIAN and its generics (contraindicated in children under 15 years of age)
- Loxapine - LOXAPAC (indicated in adults and children from 15 years of age, contraindicated in children under 15 years of age)

3. ANALYSIS OF AVAILABLE DATA

3.1. Data on efficacy and adverse effects

A randomised, double-blind superiority study[1] (Study 31-03-239) compared the efficacy and safety of aripiprazole with those of placebo in the treatment of acute psychosis in patients of 13 to 17 years of age presenting schizophrenia according to DSM-IV[2] criteria, confirmed with the K-SADS-PL[3] questionnaire. The study was carried out in 101 centres (USA, Europe, South America, Asia, the Caribbean, and South Africa).

At the time of inclusion, the patients could be hospitalised or monitored on an outpatient basis foran acute psychotic episode with a total PANSS[4] score ≥ 70.
The primary efficacy endpoint was the change in the total PANSS score compared to baseline.
Among the secondary endpoints, the PANSS positive and negative symptoms scores, the CGAS[5] and CGI-S[6] scores, and the percentage responder rates[7] were evaluated.

Three hundred and two patients with a mean age of 15.5 years were randomised to three groups for a treatment period of 6 weeks: placebo (n = 100), aripiprazole 10 mg/day (n = 100), aripiprazole 30 mg/day (n = 102). The doses were increased at 2-day intervals in a titration phase (2, 5, 10, 15, 20, and 30 mg). After 25 days' treatment, the doses could be reduced to 5 mg/day in the 10 mg/day group and 15 mg/day in the 30 mg/day group. The proportion of patients who were previously treated with an antipsychotic was 48% and the proportion of these who received an atypical antipsychotic was 41%.

The initial mean PANSS scores were 94.5 for the total score, 22.8 for the positive symptoms, and 25.3 for the negative symptoms. The initial mean CGI-S score was 4.6. The mean dosages of aripiprazole were 9.8 and 28.9 mg/day.

1 Findling RL, Robb A, Nyilas M, *et al*. A Multiple-Centre Randomized, Double-Blind, Placebo-Controlled Study of Oral Aripiprazole for Treatment of Adolescents With Schizophrenia. Am J Psychiatry, 2008;165:1369-72.

2 DSM-IV: Diagnostic and Statistical Manual of Mental Disorders

3 Kaufman J, Birmaher B, Breslau D, Rao U, Ryan N : Kiddie-SADS-Present and Lifetime Version (K-SADS-PL). Pittsburgh, University of Pittsburgh, School of Medicine, Oct 1996 (http://www.wpic.pitt.edu/ksads-pl.pdf).

4 PANSS: Positive And Negative Syndrome Scale (score from 30 to 210). Three subscales: Positive symptom subscale (7 items), Negative symptom subscale (7 items), General psychopathology subscale (16 items). The severity of each symptom is graded 1 to 7.

5 Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlias, S. (1983). A Children's Global Assessment Scale (CGAS). Arch. Gen. Psychiatry, 1983;40:1228-31. Score 1 à 100.

6 Clinical Global Impressions - Severity: score 0 to 7

7 Decrease ≥ 30% in total PANSS score

Mean changes in scores compared to baseline:

Endpoint	Placebo n = 98	Aripiprazole 10 mg n = 99	Aripiprazole 30 mg n = 97
Total PANSS score	-21.2	-26.7*	-28.6**
Difference vs PL [95% CI]	-	-5.46 [-10.7 ; -0.21]	-7.40 [-12.7 ; -2.13]
Positive symptoms	-5.6	-7.6*	-8.1**
Negative symptoms	-5.4	-6.9*	-6.6 ns
CGAS	9.8	14.7**	14.8**
CGI-S	-0.9	-1.2**	-1.3**

ITT analysis - LOCF,
* $p < 0.05$ versus placebo, ** $p < 0.01$ versus placebo

The percentage responder rates (PANSS score decrease ≥ 30%) were: 47.5% in the aripiprazole 10 mg/day group, 44.3% in the aripiprazole 30 mg/day group, and 35.7% in the placebo group.

A subgroup analysis of the PANSS scores in the adolescents between 15 and 17 years of age (74% of the patients evaluated) showed changes of -22 in the placebo group (n = 72), -26.8 in the aripiprazole 10 mg/day group (n = 77), and -28.8 in the aripiprazole 30 mg/day group (n = 70).

Forty-four patients (15%) discontinued the treatment before the end of the double-blind period: placebo (n = 10), aripiprazole 10 mg/day (n = 16), aripiprazole 30 mg/day (n = 18).
Seven patients (2%) discontinued the treatment because of lack of efficacy (6 patients on aripiprazole), 21 (7%) withdrew their consent (16 patients on aripiprazole), and 13 (4%) discontinued it because of an adverse event (11 patients on aripiprazole). The most frequent adverse event leading to discontinuation of the treatment were “psychotic disorder” (one patient in each group) and "schizophrenia" (3 patients in the aripiprazole group). One patient discontinued the treatment because of hypomania.
At least one adverse event was reported in 67% of the patients. The following adverse events were reported more frequently on aripiprazole: extrapyramidal disorders (placebo group 5%, aripiprazole 10 mg/day group 13%, aripiprazole 30 mg/day group 22%); signs of parkinsonism (7%, 15%, 30%), somnolence (6%, 11%, 22%), tremor (2%, 2%, 12%), and akathisia (5%, 5%, 12%). No information regarding use of anticholinergics was reported.

The mean serum levels of prolactin decreased: low mean serum prolactin levels (< 3 ng/ml in women, < 2 ng/ml in men) were observed in 8% of the placebo patient group, 34% of the patients on aripiprazole 10 mg/day group, and 26% of the patients on aripiprazole 30 mg/day group.
Weight loss of 0.8 kg and weight gain of 0.2 kg were observed on placebo and on aripiprazole 30 mg/day groups respectively. The percentages of patients experiencing clinically significant (≥ 5%) weight gain were 9% for aripiprazole 30 mg/day group, 11% for aripiprazole 10 mg/day group, and 2% for placebo group.
Glucose and lipid parameters didn’t show clinically relevant differences between treatment arms.

<u>26-week open follow-up (Study 31-03-241)</u>

Patients who completed the randomised double-blind period of study 31-03-239 or who dropped out of the extension phase of a study carried out in children and adolescents with type I bipolar disorder (study 31-03-240) could take part in an extension phase of at least 26

weeks in which aripiprazole was used at flexible doses (2 to 30 mg/day) on an open label basis.

The number of patients included in the follow-up study who took part in study 31-03-239 was 239/302 patients (80%). The mean dosage was 17 mg/day. 76% of the patients were followed up for 26 weeks. 33% of the patients were from the placebo group.
After 26 weeks of treatment, 178 patients (74%) were evaluated: 59/80 patients (74%) from the aripiprazole 10 mg/day group, 59/77 patients from the aripiprazole 30 mg/day group, and 60/77 from the placebo group. The initial PANSS scores (last evaluation in study 31-03-239) were: 62 in the aripiprazole 10 mg/day group, 63 in the aripiprazole 30 mg/day group, and 72 in the placebo group. The mean changes in total PANSS scores at 26 weeks compared to inclusion in this open label follow-up were: -14.6 (placebo group), -9.5 (aripiprazole 10 mg/day group), and -9.2 (aripiprazole 30 mg/day group).

The number of patients who discontinued the treatment prematurely was 58/239 patients (24%): withdrawal of consent 11.7%, lost to follow-up 2.9%, discontinued treatment because of adverse events 2.5%.

At least one adverse event was reported in 69% of the patients. The most frequently reported adverse events were: extrapyramidal disorders (19.2%), akathisia (8.4%), somnolence (13.8%), insomnia (9.2%), weight gain (7.9%), headache (7.1%), nausea (6.7%), tremor (6.3%).
Extrapyramidal symptoms related with the treatment were observed in 26.3% of the adolescents.
Suicidal ideation was reported in one patient. One treatment-unrelated death was reported.
The percentage of patients who experienced clinically significant (≥ 7%) weight gain was 24.5%.

3.2. Conclusion

The randomised double-blind study 31-03-239 compared the efficacy and safety of the aripiprazole tablet versus placebo over a short treatment period (6 weeks) in patients of 13 to 17 years of age diagnosed as schizophrenic and presenting an acute psychotic episode.

The mean changes in the total PANSS scores on aripiprazole were -26.7 (10 mg/day) and -28.6 (30 mg/day) and were different from the mean change observed on placebo
(-21). The responder rates were: 47.5% in the aripiprazole 10 mg/day group, 44.3% in the aripiprazole 30 mg/day group, and 35.7% in the placebo group. The difference in efficacy in comparison with placebo can be considered as modest.
Extrapyramidal symptoms (13 to 22%) and signs of parkinsonism (15 to 30%) were common on aripiprazole. Weight gain (> 5%) was reported in 9 and 11% of the patients (versus 2% on placebo group). Low serum prolactin levels were found in 26 to 34% of the adolescents treated with aripiprazole (versus 8% on placebo).

After 26 weeks of treatment, the percentage of schizophrenic children and adolescent who carried out the 31-03-239 study was 59% (178/302). . The changes in the total PANSS scores were -5.23 and -6.21 in the patients previously on aripiprazole 10 and 30 mg/day versus -10.7 in the patients treated with placebo.
Extrapyramidal symptoms were observed in 26% of the adolescents. Clinically significant
(> 7%) weight gain was observed in 24.5% of the patients.
The absence of an active comparator and the open label designof the study make these results hard to interpret.

In view of the limited data on the efficacy and safety of the product, the CHMP restricted the indication to adolescents over 15 years of age. The company promised to carry out a post-

MA study to evaluate the efficacy and safety of the treatment over a treatment period of at least 6 months.

ABILIFY 1 mg/ml, oral solution, was not evaluated.

No controlled randomised study versus an active treatment was submitted.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The key features of schizophrenia are the presence of a set of what are called positive (delusional ideas, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour) or negative (blunted affect, alogia, loss of will) signs and symptoms associated with clear social or activity-related dysfunction.
The course of schizophrenia varies, some patients experiencing exacerbations and remissions, while others are chronically affected. Some patients seem to show a relatively stable course, while others experience progressive worsening associated with severe disability. The disorder has particularly deleterious effects on the development and psychosocial adjustment of adolescents. The risks of suicide or accidental death are stressed.

These medicinal products are symptomatic treatments.

The short-term (6 weeks) efficacy/adverse effects ratio for these medicinal products is moderate. The long-term (at least 6 months) efficacy/adverse effects ratio remains to be determined.

There are alternatives to these medicinal products.

Public health benefit:

The public health burden of schizophrenic psychoses is substantial, given their frequency and severity. The burden represented by schizophrenic psychoses in adolescents of 15 years of age or over is small, given the size of the population concerned.

It is an established priority in the public health needs to improve the management of chronic delusional psychoses and schizophrenia in particular (GTNDO[1] priority).

On the basis of the available data and in view of the considerable placebo effect, the impact of ABILIFY in terms of morbidity is small. There is no guarantee that the results of the trial can be carried over into practice, particularly because of the limited duration of the study.

Consequently, it is not expected that the ABILIFY products will have an impact on public health in this extension of indication.

The actual benefit of these proprietary medicinal products in the extension of indication is substantial.

4.2. Improvement in actual benefit (IAB)

1 Groupe Technique National de Définition des Objectifs [National technical group for setting of public-health objectives] (DGS [Department of Health]-2003)

Given the absence of a comparison with an active comparator and the inadequate duration of evaluation, and pending the availability of controlled data over a treatment period of at least 6 months, ABILIFY does not provide an improvement in actual benefit in the management of schizophrenia in adolescents.

4.3. Therapeutic use[1,2,3]

Conventional and atypical neuroleptics have demonstrated their efficacy in the treatment of schizophrenia, especially with regard to the positive symptoms. Two-thirds to three-quarters of patients will suffer the psychological, neurological, vegetative, metabolic, and endocrinological adverse effects of these drugs.

In adults, atypical antipsychotics are not free from adverse effects, but they can be recommended as first-line treatment for early-stage schizophrenia, mainly because of the reduced risk of acute extrapyramidal adverse effects at the dosages in the Marketing Authorisation. Conventional antipsychotics continue to be indicated for patients who are stabilised and who do not experience major adverse effects.

In adolescents, only a comparison with an active treatment would make it possible to determine ABILIFY's place in the therapeutic strategy for schizophrenia in adolescents.

Antipsychotic monotherapy is to be preferred, administered orally if possible. In the case of stabilised patients, prescription of a long-acting form may be considered as part of polytherapy.

In a certain number of cases, particularly at the start of an acute psychotic episode, the presence of anxiety and/or agitation alongside the delusional ideas can lead practitioners to combine a drug with a sedative polarity (benzodiazepine or anxio-sedative antipsychotic) with an antidelusional antipsychotic.

A multidimensional approach is needed in patients suffering from schizophrenia. Drug treatments should be combined with individual or group psychotherapy, institutional or familial management, and social interventions.

4.4. Target population

In France, we do not have any studies of the (lifetime) prevalence of chronic delusional psychoses. In the world, the lifetime prevalences of these disorders reported in the general adult population are between 0.5% and 1.5%.
According to the Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] of the Ministry of Health (report dated 10.03.03), between 300,000 and 500,000 adults in France suffer from a chronic delusional psychosis, and 200,000 to 250,000 suffer from schizophrenia.

In young subjects, the occurrence of psychotic symptoms (delusional ideas, auditory hallucinations) poses diagnostic problems. Schizophrenia is hard to diagnose, having

1 Schizophrénies débutantes : diagnostic et modalités thérapeutiques - Conférence de consensus ANAES [Early-stage schizophrenia: diagnosis and methods of treatment - ANAES consensus conference], 23-24 January 2003.
2 Treatment of Schizophrenia 1999. The Journal of Clinical Psychiatry 1999; 60 (suppl 11):1-19.
3 Antipsychotic treatment in schizophrenia : atypical options and NICE guidance. European Psychiatry 2003;18:209-19.

numerous symptoms in common with affective psychoses (bipolar disorder in particular). Only 15% of these subjects will develop schizophrenia[1].

According to the INSERM group expert review of 2003[2], the number of 15-19-year-olds with schizophrenia or bipolar disorder in France is estimated at 19,839, or 0.5% of the population in this age group. According to the INSEE [French National Institute for Statistics and Economic Studies] data, the population of adolescents between 15 and 17 years of age is estimated at around 2.3 million. According to these data, and taking the prevalences of schizophrenia and bipolar disorder to be the same in this age group, the number of schizophrenic adolescents who might receive ABILIFY could be estimated at around 6000.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

The Committee stresses the need to make available ABILIFY 1 mg/ml oral solution, a dosage which allows initiation of the treatment in accordance with the SPC in the extension of indication.

4.5.1 Packaging

The packaging is appropriate for the prescription conditions in the extension of indication.

4.5.2 Reimbursement rate: 65%

1 Troubles mentaux - Dépistage et prévention chez l'enfant et l'adolescent [Mental disorders - detection and prevention in children and adolescents] - 2003

2 Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, et al. Declining transition rate in ultra high risk (Prodromal) services: Dilution or reduction of risk? Schizophr Bull 2007;33(3):673-81.