HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

6 November 2013

ABILIFY 1 mg/ml, oral solution

150 ml vial (CIP: 3400937329798)

ABILIFY 5 mg, tablet

B/28 (CIP: 3400936406971)

ABILIFY 10 mg, tablet

B/28 (CIP: 3400936407343)

ABILIFY 15 mg, tablet

B/28 (CIP: 3400936407862)

ABILIFY 10 mg, orodispersible tablet

B/28 (CIP: 3400936921450)

ABILIFY 15 mg, orodispersible tablet

B/28 (CIP: 3400936921740)

Applicant: OTSUKA PHARMACEUTICAL FRANCE SAS

INN	aripiprazole
ATC code (2013)	N05AX12 (antipsychotics)
Reason for the review	**Extension of indication**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older."**

Actual Benefit	**The actual benefit of the proprietary medicinal product ABILIFY is substantial in the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.**
Improvement in Actual Benefit	**ABILIFY provides a minor improvement in actual benefit (level IV) in the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	ABILIFY 5 mg, 10 mg, 15 mg, tablet: 04/06/2004 ABILIFY 10 mg, 15 mg, orodispersible tablet: 20/06/2005 ABILIFY 1mg/ml, oral solution: 28/10/2005 Extension of indication in the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: 24/01/2013
Prescribing and dispensing conditions / special status	List I

ATC Classification	N	: Central nervous system
	N05	: Psycholeptics
	N05A	: Antipsychotics
	N05AX	: Other antipsychotics
	N05AX12:	: Aripiprazole

02 BACKGROUND

The company is applying for the inclusion of the ABILIFY proprietary medicinal products on the National Health Insurance and hospital use lists in the extension of indication in the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

03 THERAPEUTIC INDICATIONS

ABILIFY is indicated:
"for the treatment of schizophrenia in adults and in adolescents aged 15 years and older";
"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";
"for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older".

04 DOSAGE

For the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:
"The recommended dose is 10 mg/day administered on a once-a-day schedule during or without regard to meals.
Treatment should be initiated in a dose of 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, then titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg.
The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks.

Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including extrapyramidal symptoms (EPS), somnolence, fatigue and weight gain."

05 THERAPEUTIC NEED

Bipolar I disorder in adolescents is a recognised disease entity defined by the occurrence of one or more manic episodes or mixed episodes[1]. A manic episode of a bipolar disorder in adolescents is difficult to diagnose because of its variety of clinical presentations and may be atypical when compared with the symptoms in adults. Combination with other psychiatric or developmental disorders, particularly attention deficit hyperactivity disorder [ADHD], behavioural disorders and anxiety disorders, also complicates the diagnosis. Bipolar disorder is a severe disorder which has a major impact on the life of the patient and his friends and relatives. The major risk incurred is suicide.

Pharmacological treatments of manic episodes in bipolar disorder (lithium salts, anticonvulsants, antipsychotics) have been little studied in adolescents[2].

No medicinal product has Marketing Authorisation in France in adolescents in this indication.

06 CLINICALLY RELEVANT COMPARATORS

The pharmacological treatments used off-label in adolescents in the treatment of manic episodes in bipolar disorder are identical to the treatments in adults: lithium salts, entiepilepticsand antipsychotics.

Conclusion:

ABILIFY is the only antipsychotic with an indication in the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older.

[1] Cohen D et al. [Bipolar episodes in adolescents: diagnostic issues and follow-up in adulthood]. Encephale. 2009 Dec;35 Suppl 6:S224-30

[2] Bailly D. et Mouren MC. Drug prescribing in child and adolescent psychiatry. Ed. Masson. 2007.

07 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion	8 December 2004 (inclusion on the list of medicines reimbursed by National Health Insurance and inclusion for hospital use)
Indications	Treatment of schizophrenia
AB	Substantial
IAB	IAB III in terms of safety versus HALDOL IAB IIV in terms of safety versus ZYPREXA
Study requested	The Transparency Committee asks the company to carry out a practical randomised study of ABILIFY versus the atypical neuroleptics olanzapine and risperidone in order to assess, under real conditions of long-term use: - the compliance of patients on ABILIFY compared with that of patients on atypical neuroleptics. - the value of ABILIFY on morbidity in terms of safety in particular and in terms of the experience of the patient or his friends and relatives, versus atypical neuroleptics.

Date of opinion	18 February 2009, (inclusion in an extension of indication)
Extension of indication	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
AB	Substantial
IAB	IAB V in the treatment of patients with bipolar I disorder
Study requested	Not applicable

Date of opinion	21 July 2010 (inclusion in an extension of indication)
Extension of indication	Treatment of schizophrenia in adolescents aged 15 years and older
AB	Substantial
IAB	Given the absence of any comparison with an active comparator and the inadequate assessment period, IAB V in the treatment of schizophrenia in adolescents for a treatment period of at least 6 months, pending the availability of controlled data.
Studies requested	Not applicable

Date of opinion	14 March 2012 (reassessment)
Indication	Treatment of schizophrenia in adults
AB	Substantial
IAB	ASMR III in the treatment of schizophrenia
Studies requested	Not applicable

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company's dossier is based on two studies:
- a randomised, double-blind, controlled study (31-03-240) versus placebo which assessed the efficacy and safety of aripiprazole 10 and 30 mg over 30 weeks in 296 children and adolescents aged 10 to 17 years with bipolar I disorder;
- an open study (31-03-241) that assessed the safety of aripiprazole in 239 adolescents with schizophrenia and 86 children and adolescents with bipolar disorder. The assessment of the efficacy of aripiprazole was a secondary endpoint.

Only study 31-03-240 will be presented here. The results of study 31-03-241 will be presented in the safety section.

8.1.1 Study 31-03-240[3]

8.1.1.1 Methodology

Study 31-03-240 is a randomised, double-blind, placebo-controlled study lasting 30 weeks.

In this study, the efficacy and safety of two fixed doses of aripiprazole (10 and 30 mg) were compared with placebo in children and adolescents aged 10 to 17 years with a diagnosis of a manic episode of bipolar I disorder.

The subjects included were children and adolescents aged between 10 and 17 years with a diagnosis of bipolar I disorder (DSM-IV criterion) and a score of ≥ 20 on the YMRS[4] mania scale on inclusion. The diagnosis of bipolar disorder had to be confirmed by a second clinician on the K-SADS-PL scale[5]. The presence of behavioural or psychiatric comorbidities was permitted: attention deficit hyperactivity disorder (ADHD), behavioural disorder, oppositional defiant disorder and anxiety disorder (with the exception of post-traumatic stress syndrome and obsessive-compulsive disorder).

Patients were randomised to three groups:
- aripiprazole 10 mg;
- aripiprazole 30 mg;
- placebo.

The study had two phases:
- an acute titration phase of 4 weeks;
- a maintenance phase of 26 weeks.

The primary efficacy endpoint was the mean change in the YMRS score at 4 weeks.

[3] Findling RL et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2009 Oct;70(10):1441-51

[4] The YMRS (Young Mania Rating Scale) allows the severity of a manic episode to be assessed (score > 20) in patients with bipolar disorder. The score obtained ranges from 0 (no manic symptoms) to 60 (maximum score).

[5] The K-SADS-PL (Kiddie-Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version) is a semi-structured diagnostic interview which is intended to assess current and past psychopathic episodes in children and adolescents according to the DSM-IV criteria.

The secondary endpoints included, in particular, the assessment of the severity of the manic symptoms on the CGI-BP scale[6], the assessment of the percentage of responder patients (response was defined as a reduction of ≥ 50% in the total YMRS score by comparison with that on inclusion) and the percentage of patients in remission (defined as a total YMRS score of ≤ 12 and a CGI-BP severity score for mania of ≤ 2).

As part of the Marketing Authorisation procedure, a post-hoc analysis was made for the age groups 10-12 years and 13-17 years, plus an analysis of the results at 12 weeks (maximum duration of treatment authorised by the Marketing Authorisation).

8.1.1.2 Results

A total of 296 patients were randomised at 59 centres in the United States.
After 4 weeks, 237 patients (80%) were present in the study: aripiprazole 10 mg arm (84/98), aripiprazole 30 mg arm (77/99), placebo arm (76/99).
A total of 68 patients (23 %) finished the study (week 30): aripiprazole 10 mg arm (34/98), aripiprazole 30 mg arm (22/99), placebo arm (12/99).

a) Patient characteristics

The patient characteristics are shown in Table 1.
Nearly 63% of the patients included were between 13 and 17 years of age, the age group corresponding to the indication of the Marketing Authorisation.

Table 1: Characteristics of the randomised patients

	Aripiprazole 10 mg (n=98)	**Aripiprazole 30 mg (n=99)**	**Placebo (n=99)**
Mean age ± SD (years)	13.7 ± 2.2	13.3 ± 2.3	13.3 ± 2.1
Age groups, n (%)			
10-11 years	18 (18.4)	26 (26.3)	21 (21.2)
12-17 years	80 (81.6)	73 (73.7)	78 (78.8)
Male, n (%)	52 (53.1)	51 (51.5)	56 (56.6)
Mean duration of the bipolar disorder ± SD* (years)	1.3 ± 2.2	1.3 ± 2.5	1.4 ± 1.9
Mean total YMRS score on inclusion ± SD*	29.8 ± 6.5	29.5 ± 6.3	30.7 ± 6.8
Types of episodes, n (%)			
Mixed	43 (43.9)	39 (39.4)	43 (43.4)
Manic	41 (41.8)	40 (40.4)	38 (38.4)
Unknown	14 (14.3)	20 (20.2)	18 (18.2)
Psychotic symptoms, n (%)			
Yes	7 (7.1)	4 (4.0)	3 (3.0)
No	58 (59.2)	58 (58.6)	64 (64.7)
Unknown	33 (33.7)	37 (37.4)	32 (32.3)
ADHD or history of it, n (%)			
Yes	48 (49.0)	50 (50.5)	55 (55.6)
No	34 (34.7)	25 (25.3)	18 (18.2)
Unknown	16 (16.3)	24 (24.2)	26 (26.3)
Oppositional defiant disorders, n (%)			
Yes	28 (28.6)	34 (34.3)	31 (31.3)
No	48 (49.0)	39 (39.4)	41 (41.4)
Unknown	22 (22.5)	26 (26.3)	27 (27.3)

* SD = Standard deviation

[6] The CGI-BP (Clinical Global Impression) 7-point scale is used for investigator assessment of the severity of the bipolar symptoms (mania, depression, global bipolar disorder) ranging from “normal” to “extremely ill”.

b) Efficacy results

- Change in the YMRS score

After 4 weeks, the mean YMRS score was significantly reduced in the 10 and 30 mg aripiprazole arms versus the placebo arm (aripiprazole 10 mg versus placebo: - 5.99; 95% CI [- 8.49 to - 3.50]; aripiprazole 30 mg versus placebo: - 8.26; 95% CI [- 10.7 to - 5.77]).
The change in the YMRS score at 4 weeks and 12 weeks for the 13-17 year-olds (post-hoc analysis requested by the European Medicines Agency) is shown in Table 2. At 4 and 12 weeks, aripiprazole was more effective than placebo on the change in the YMRS score in the 13-17 year-olds.

Table 2: Mean change in the total YMRS score at 4 and 12 weeks in the 13-17 year-olds

YMRS score	Aripiprazole 10 mg		Aripiprazole 30 mg		Placebo	
	N	Mean change	N	Mean change	N	Mean change
Inclusion	65	29.0	59	30.3	58	31.9
Week 4	65	-13.9*	59	-16.8**	58	-10.1
Week 12	65	-15.6*	59	-16.8**	58	-9.7

* p<0.05 vs. placebo ** p<0.001 vs. placebo

- Other efficacy endpoints

CGI-BP bipolar disorder severity scores:

After 4 weeks, aripiprazole in a dose of 10 and 30 mg was more effective than placebo on the CGI-BP bipolar disorder severity scores (aripiprazole 10 mg versus placebo: - 0.83; 95% CI [- 1.16 to – 0.51]; aripiprazole 30 mg versus placebo: - 1.18; 95% CI [- 1.51 to – 0.86]).
The results for the 13-17 year-olds are given in Table 3.

Table 3: Mean change in the CGI-BP score (mania) at 4 and 12 weeks in the 13-17 year-olds

CGI-BP score (mania)	Aripiprazole 10 mg		Aripiprazole 30 mg		Placebo	
	N	Mean change	N	Mean change	N	Mean change
Inclusion	65	4.6	59	4.6	58	4.9
Week 4	65	-1.7*	59	-2.1**	58	-1.0
Week 12	65	-1.9*	59	-2.2**	58	-1.1

* p<0.05 versus placebo ** p<0.001 versus placebo

Percentages of responder patients and patients in remission:

After 4 weeks:
- the percentage of responders was higher in the aripiprazole arm than in the placebo arm: 26% in the placebo arm, 45% in the aripiprazole 10 mg arm (p = 0.0074 versus placebo) and 64% in the 30 mg arm (p < 0.001);
- remission was achieved in 5% of the patients in the placebo arm, 25% of the patients in the aripiprazole 10 mg arm (p = 0.0002 versus placebo) and 47% of the patients in the 30 mg arm (p < 0.001).

The percentage of responder patients and patients in remission was not analysed specifically for the 13-17 years age group.

Efficacy in the subgroup of patients with or without psychiatric comorbidity:

The change in the YMRS score was analysed in the subgroups of patients with or without behavioural comorbidity, particularly ADHD. The subgroups of patients analysed were too small to allow robust statistical analysis. In patients without ADHD, no difference in efficacy was seen between the aripiprazole arm and the placebo arm in the change in the YMRS score (see Table 4). The theories put forward by the company are lack of statistical power and a greater response to the placebo in this group of patients.

Table 4: Mean change in the YMRS score at 4 and 12 weeks as a function of the presence or absence of ADHD in 13-17 year-olds

YMRS score	Aripiprazole 10 mg		Aripiprazole 30 mg		Placebo	
	N	Mean change versus the value on inclusion	N	Mean change versus the value on inclusion	N	Mean change versus the value on inclusion
With ADHD						
Week 4	23	-15.06*	23	-16.20*	26	-9.55
Week 12	23	-16.95*	23	-17.08*	26	-8.32
Without ADHD						
Week 4	31	-12.54	22	-14.16	17	-10.88
Week 12	31	-15.45	22	-12.55	17	-10.58

* p<0.05 versus placebo

08.2 Adverse effects

8.2.1 Data from clinical studies 31-03-240 and 31-03-241

8.2.1.1 Study 31-03-240

In the aripiprazole 10 mg arm, the most commonly reported adverse effects (incidence ≥ 5%) were somnolence (24.5%), headaches (20.4%), fatigue (18.4%), nausea and vomiting (13.3%) and extrapyramidal symptoms (12.2%).
In the aripiprazole 30 mg arm, the most commonly reported adverse effects were extrapyramidal symptoms (28.3%), somnolence (27.3%), headaches (23.2%), nausea (14.1%) and akathisia (13.1%).
The adverse effects in the population of 13-17 year-olds are described in Table 5.

Table 5: Adverse effects with an incidence of ≥ 5% in those aged 13-17 years (study 31-03-240)

AEs reported, n (%)	Aripiprazole 10 mg (n=66)	Aripiprazole 30 mg (n=59)	Placebo (n=58)
Blurred vision	7 (10.6)	4 (6.8)	0
Abdominal pain	6 (9.1)	2 (3.4)	2 (3.4)
Diarrhoea	4 (6.1)	3 (5.1)	0
Nausea	8 (12.1)	8 (13.6)	5 (8.6)
Salivary hypersecretion	2 (3.0)	5 (8.5)	0
Stomach pains	1 (1.5)	4 (6.8)	0
Vomiting	7 (10.6)	4 (6.8)	6 (10.3)
Fatigue	12 (18.2)	8 (13.6)	2 (3.4)
Viral gastroenteritis	1 (1.5)	3 (5.1)	0
Infection of the upper airways	3 (4.5)	1 (1.7)	2 (3.4)
Elevation of the serum levels of CPK*	1 (1.5)	4 (6.8)	0
Weight gain	5 (7.6)	2 (3.4)	1 (1.7)
Loss of appetite	6 (9.1)	1 (1.7)	3 (5.2)
Increased appetite	3 (4,5)	3 (5.1)	2 (3.4)
Akathisia	8 (12.1)	12 (20.3)	1 (1.7)
Dizziness	7 (10.6)	4 (6.8)	1 (1.7)
Dystonia	1 (1.5)	5 (8.5)	0
Extrapyramidal disorders	6 (9.1)	17 (28.8)	1 (1.7)
Headaches	14 (21.2)	13 (22.0)	14 (24.1)
Somnolence	19 (28.8)	16 (27.1)	3 (5.2)

* creatinine phosphokinase

Details of the weight gain:

No significant difference was observed between the aripiprazole arm and the placebo arm at the end of the acute phase (week 4): the mean weight gain was 0.82 kg in the aripiprazole 10 mg arm, 1.08 kg in the aripiprazole 30 mg arm versus 0.56 kg in the placebo arm (p=0.3488 and p=0.1276 versus placebo).
At week 12 and until the end of the study (week 30), the mean weight gain was significantly larger in the aripiprazole arm than in the placebo arm: 3.20 kg in the aripiprazole 10 mg arm, 2.85 kg in the aripiprazole 30 mg arm versus 0.98 kg in the placebo arm (p=0.0002 and p=0.0019 versus placebo).
At the end of the study, clinically significant weight gain (≥ 7% of the weight on inclusion) was observed in 35.8% (34/95) of the patients in the aripiprazole 10 mg arm, 29.2% (28/96) of the patients in the aripiprazole 30 mg arm and 9.8% (9/92) of the patients in the placebo arm.

8.2.1.2 Study 31-03-241

Study 31-03-241 is an open study the aim of which was to assess the safety of aripiprazole in adolescents with schizophrenia and in children and adolescents with bipolar disorders who have manic or mixed episodes.
A total of 86 children and adolescents between 10 and 17 years of age with bipolar disorder received treatment with aripiprazole in a mean dose of between 4.9 and 17.7 mg/day. Of these, 57 (66%) completed the 26 weeks of the study.
The most commonly reported adverse effects were headaches (16.3%), nausea (10.5%) and somnolence (10.5%).
A clinically significant weight gain (≥ 7% of the weight on inclusion) was observed in 44% of the children and adolescents aged 10 to 17 years.

8.2.2 Post-marketing surveillance data

The estimated number of patients exposed to aripiprazole from its market launch to 31 March 2012 is 13,004,432, i.e. 6,502,216 patient-years.
No safety signal likely to alter the global safety profile of aripiprazole was identified during the period covered by the last pharmacovigilance report (July 2011 to July 2012).

08.3 Summary & discussion

Aripiprazole 10 mg or 30 mg was compared with placebo in a 30-week study performed in 296 children and adolescents aged 10 to 17 years (study 31-03-240) with a manic episode of bipolar disorder. A second study (study 31-03-241) assessed the safety of aripiprazole in 86 children and adolescents with bipolar disorder.

In study 31-03-240, after 4 weeks the reduction in the YMRS score (scale for rating the severity of a manic episode; score between 0 and 60) was significantly greater in the aripiprazole 10 and 30 mg groups than in the placebo group (difference between aripiprazole 10 mg versus placebo: - 5.99; 95% CI [- 8.49 to – 3.50]; aripiprazole 30 mg versus placebo: - 8.26; 95% CI [- 10.7 to – 5.77]). These results were confirmed at 12 weeks.

The adverse effects reported in studies 31-03-240 and 31-03-241 were similar to those reported in the adult population: somnolence, headaches, extrapyramidal symptoms, fatigue and akathisia. The extension of treatment after 30 weeks was associated with a weight gain of ≥ 7% versus the weight on inclusion in nearly 30% of the patients in study 31-03-240 and in 44% of the patients in study 31-03-241.

The indication of the Marketing Authorisation was restricted to adolescents aged 13 to 17 years, since the risk/benefit ratio in younger children was considered unfavourable in view of the risk of extrapyramidal symptoms, somnolence and weight gain.

Study 31-03-240 was performed in the United States which raised the question of the extrapolation of its results to the European population during the Marketing Authorisation procedure[7], given the differences in diagnostic and treatment practice between the United States and Europe. In this context, the demographic characteristics of study 31-03-240 were compared with those of two studies performed in Spain and in Italy in children and adolescents with bipolar I disorders. The severity of the disorder and the age of onset of the disease were comparable in the three studies. The European Medicines Agency therefore considered that these data were sufficient to allow the extrapolation of the results of study 31-03-240 to the population of European patients.

[7] EMA/62007/2013 Abilify assessment report; 13 December 2012. www.ema.europa.eu.

09 THERAPEUTIC USE[2,8]

A well-founded diagnosis is essential before the initiation of drug treatment, and is made on the basis of a range of arguments: clinical picture and the analysis of physical signs, developmental history and family history of mood disorders.
Drug treatment must be incorporated in an overall treatment strategy which includes psychological, educational and social measures aimed at the adolescent and his friends and family.
The medicines available (off-label) to adolescents for manic episodes in bipolar disorders are the same as for adults: lithium salts, certain entiepilepticsand certain antipsychotics.
ABILIFY is the only antipsychotic with an indication in the treatment of manic episodes in bipolar I disorders in adolescents aged 13 years and older.

ABILIFY is a treatment option in the management of moderate to severe manic episodes in bipolar disorders in adolescents from age 13 years.
ABILIFY does not have Marketing Authorisation in the prevention of recurrences of bipolar disorder in adolescents from age 13 years.

[8] National Institute for Health and Clinical Excellence. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Nice clinical guideline 38; June 2006.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Bipolar I disorder is characterised by the occurrence of one or more manic episodes or mixed episodes. Bipolar disorder in adolescents may lead to substantial impairment of personal relationships and of the ability to fit in at school and at work. The major risk incurred is suicide.

◗ The efficacy/adverse effects ratio of ABILIFY in this indication is high.

◗ ABILIFY is a symptomatic treatment for moderate to severe manic episodes in bipolar I disorders in adolescents from age 13 years.

◗ There is no treatment alternative to ABILIFY which has Marketing Authorisation in this age group.

◗ The public health burden of bipolar disorder is substantial, given its frequency and severity. The burden of these disorders in adolescents aged 13 years and older is considered to be small, given the limited number of patients concerned.

Improving the management of bipolar disorders is a public health need which is an established priority (French Public Health Law of 2004), including in adolescents.

In view of the clinical trials available (non-comparative studies or versus placebo only), this medicinal product is not expected to have any impact on morbidity, mortality or quality of life in the treatment of acute manic episodes versus the current management of these adolescents.

No impact on the organisation of healthcare is expected (no demonstration of a reduction in hospital admissions in particular).

The ABILIFY products therefore would not be able to provide a response to the identified need.

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

Taking account of these points, the Committee considers that the actual benefit of ABILIFY is substantial in the treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorders in adolescents aged 13 years and older.
ABILIFY does not have Marketing Authorisation in the prevention of recurrences of bipolar disorder in adolescents.

010.2 Improvement in actual benefit (IAB)

ABILIFY provides a minor improvement in actual benefit (level IV) in the treatment of moderate to severe manic episodes in Bipolar I Disorders in adolescents aged 13 years and older.

010.3 Target population

The target population of ABILIFY is made up of adolescents aged 13 years and older with bipolar I disorders who are therefore likely to have a manic episode.
The prevalence of bipolar I disorder in adolescents is estimated to be 0.1%[9,10] or, in France, about 4000 adolescents aged 13 to 17 years.[11]

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indication "treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorders in adolescents aged 13 years and older".

- **Reimbursement rate: 65%**

- **Packaging**

Appropriate for the prescription conditions.

[9] Lewinsohn PM et al. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry. 1995 Apr;34(4):454-63.
[10] Kim-Cohen J et al. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry. 2003 Jul; 60(7): 709-17.
[11] 4,024,312 adolescents aged 13 to 17 years as at 1 January 2013 (www.insee.fr)