EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/488885/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abilify

International non-proprietary name: ARIPIPRAZOLE

Procedure No. EMEA/H/C/000471/II/0084

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Europe Ltd submitted to the European Medicines Agency on 5 July 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Abilify	aripiprazole	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of section 4.4 of the Summary of Product Characteristics (SmPC) to add information on the risk of suicidality in paediatric patients based on the results of the epidemiological study CN138598.

The requested variation proposed amendments to the Summary of Product Characteristics.

Rapporteur: Bruno Sepodes

1.2. Steps taken for the assessment

Submission date:	5 July 2012
Start of procedure:	22 July 2012
Rapporteur's preliminary assessment report circulated on:	24 August 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	14 November 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	9 January 2013
Rapporteur's updated assessment report on the MAH's responses circulated on:	14 January 2013
Follow on Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
MAH's responses submitted to the CHMP on:	21 March 2013
Rapporteur's preliminary assessment report on the MAH's responses to the Follow on Request for supplementary information circulated on:	8 April 2013
Rapporteur's updated assessment report on the MAH's responses to the Follow on Request for supplementary information circulated on:	17 April 2013
CHMP opinion:	25 April 2013

2. Scientific discussion

2.1. Introduction

Aripiprazole, a dihydrocarbostyril (quinolinone) derivative, is an antipsychotic agent. Aripiprazole (Abilify) was authorised in the European Union (EU) on 4 June 2004. Aripiprazole tablets, orodispersible tablets and oral solution are currently approved in the EU for the treatment of schizophrenia in adults with recommended starting dose of 10 mg or 15 mg/day and target dose of 15 mg/day administered on a once-a-day schedule irrespective of meals. These formulations are also 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.

Abilify tablets, orodispersible tablets and oral solution are also approved in the EU for the treatment of schizophrenia in adolescents 15 years and older. The recommended dose in this patient group is 10 mg/day administered on a once-a-day schedule irrespective of 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.

In December 2012, the CHMP recommended a variation to the marketing authorisation to add the following paediatric indication: "treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older".

Aripiprazole intramuscular (7.5mg/ml, solution for injection) is specifically indicated for the treatment of the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

This variation refers to an update of section 4.4 of the Summary of Product Characteristics (SmPC) to add information on the risk of suicidality in paediatric patients based on the results of the epidemiological study CN138598.

Study CN138598 was submitted in accordance with Article 46 of the Paediatric Regulation 1901/2006.

2.2. Clinical Safety aspects

As part of the variation to extend the indication of schizophrenia to adolescents aged 15 years and older, the MAH made the following commitment (FUM 50):

Follow-up Measures:

Area	Description	Due Date
Clinical	*From procedure EMEA/H/C/000471/II/0048:* to provide a protocol for an epidemiologic cohort study to assess suicide in all identified patients under the age of 18 years using aripiprazole. The study will be conducted once final protocol is agreed by the CHMP.	**March 2010**

In January 2011, the protocol was agreed by the CHMP.

Within this variation application, the MAH submitted the final results of study CN138598.

The main objective of Study CN138598 was to determine the combined incidence of suicidal events (attempted or completed suicides) in patients less than 18 years of age after first exposure to an atypical antipsychotic (i.e., in an inception cohort; no evidence of previous exposure to antipsychotics). Within this cohort, the event rates for aripiprazole users were compared to event rates for users of all other atypical antipsychotics.

2.2.1. Methods – analysis of data submitted

Three study sites were included in this study: (1) HealthCore Inc., (2) Kaiser Permanente Health Plan, and (3) Henry Ford Health System. Each study site had access to detailed automated patient level data (including cause of death data) and served as the source of the base population for 2 previous MAH-sponsored observational studies of suicide events in adult patients.

While the electronic format of data from each site chosen was not identical, the principal investigators of this study had experience compiling data from these multiple sources and had developed site-specific algorithms needed to construct a single, uniform analytic dataset.

All patients less than 18 years of age who received at least one prescription for a typical or atypical antipsychotic from 1 November 2002 through to 31 December 2009 were identified. The first atypical antipsychotic prescription filled during the study period was considered as the index prescription. Although only atypical antipsychotics were evaluated in this study, patients exposed to typical or atypical antipsychotics before the index date were excluded to identify new users (inception cohort) not previously exposed to any antipsychotic. Any patient not continuously enrolled in the database/health plan for at least 90 days before the index date was excluded from the study population. The study population was further limited to individuals with no previous prescription filled for any antipsychotic any time before the index date (all available historical data were used to exclude patients with previous antipsychotic exposure). All patients identified using this approach formed the base population for the inception cohort and were considered previously unexposed.

The endpoint for this study was the combined incidence of suicidal events (i.e., attempted or completed suicide) recorded through the end of the follow-up period (31 December 2009). All health system encounters associated with serious suicide attempts (defined as hospitalization or emergency department encounter associated with a suicide attempt) were collected, and follow up continued for patients who attempted suicide until one of the censoring events occurred e.g. death from suicide, disenrollment from the database/health plan, death from any cause (other than suicide), attaining 18 years of age, or end of the study period.

Statistical Analysis

Descriptive statistics, including means and percentages, were calculated according to demographics and clinical characteristics. Rates of suicide events were calculated as number of events among current users divided by current use person-time. Cox proportional hazard models were used to compare rate of suicide events (i.e., attempted or completed suicides combined) in current users of aripiprazole to the rate of current users of all other atypical antipsychotics. Adjusted Hazard Ratios (HRs) controlled for the following variables: age, gender, previous suicide attempt, indication for antipsychotic use, comorbidity, health care encounters, study site, history of antipsychotic use, exposure to pharmacotherapy and year of index prescription.

In this population, a validation substudy was also conducted, using a medical record review on a sample of charts (n=386) to determine the validity of claims-based diagnosis codes to ascertain indication for antipsychotic use in paediatric/adolescent patients. Schizophrenia, bipolar disorder and autism were included in the validation substudy. Descriptive analyses were performed to compare

claims data with data obtained from the medical record. A sensitivity/specificity analysis was performed for each of the behavioural diagnoses that were indicated for use according to the Product Information.

2.2.2. Results

Demographic and Clinical Characteristics

These data are presented in Table 1.

Table 1: Distribution of Demographic and Clinical Characteristics (N=36,587):

Demographic/Characteristic	N (%)
Sex	
Male	22,448 (61.4)
Female	14,139 (38.6)
Age (mean (SD)[*])	12.9 (3.7)
Health System Encounters[†] (mean (SD)[*])	
Inpatient	0.2 (0.6)
Emergency Department	0.3 (0.8)
Outpatient	5 (6.8)
Indication	
Bipolar Disorder	10,219 (27.9)
Schizophrenia	1,016 (2.8)
Autism	2,741 (7.5)
Multiple Indications (Bipolar, Schizophrenia, and/or Autism)	106 (0.3)
Pharmacotherapy Exposure	
Analgesics	14,246 (38.9)
Anxiolytics	8,958 (24.5)
Opioids	10,520 (28.8)
Stimulants	17,676 (48.3)
Antiretrovirals	24 (0.1)
Corticosteroids	7,624 (20.8)
Antidepressants	22,718 (62.1)

Table 1(cont.): Distribution of Demographic and Clinical Characteristics (N=36,587):

Demographic/Characteristic	N (%)
Comorbidity	
Anxiety Disorders	9,331 (25.5)
ADHD[‡]	13,484 (36.9)
Cancer	148 (0.4)
Depression	25,527 (69.8)
Eating Disorder	889 (2.4)
Epilepsy	1,929 (5.3)
HIV/AIDS	4 (0.0)
Personality Disorder	1,205 (3.3)
Multiple Sclerosis	4 (0.0)
Chronic Pain	9,678 (26.5)
Psoriasis	20 (0.1)
Stroke	56 (0.2)
Substance Abuse	3,717 (10.2)
Previous Suicide Attempt	457 (1.2)

Source: Table 3 of the CN138598 CSR

[*]—SD = standard deviation.

[†]—Mean number of encounters three months before index date.

[‡]—ADHD = attention deficit hyperactivity disorder.

Table 2 summarises the distribution of covariates by antipsychotic exposure in the overall population. For each antipsychotic category, the data apply to patients ever-exposed to that agent.

Table 2: Distribution of Demographic and Clinical Characteristics Stratified by Antipsychotic Exposure (N=36,587):

Demographic/Characteristic	Aripiprazole (N=11,624) N (%)	Other Atypical Antipsychotics (N=29,459) N (%)	Multiple Antipsychotics (N=4,970) N (%)
Sex			
Male	6,536 (56.2)	18,573 (63.0)	3,013 (60.6)
Female	5,088 (43.8)	10,886 (37.0)	1,957 (39.4)
Age (mean (SD)*)	13.1 (3.5)	12.7 (3.8)	12.5 (3.7)
Health System Encounters† (mean (SD)*)			
Inpatient	0.2 (0.6)	0.2 (0.6)	0.3 (0.6)
Emergency Department	0.3 (0.8)	0.3 (0.9)	0.4 (0.9)
Outpatient	6 (7.0)	5 (6.7)	6 (7.1)
Indication			
Bipolar Disorder	3,942 (33.9)	8,000 (27.2)	2,054 (41.3)
Schizophrenia	300 (2.6)	749 (2.5)	272 (5.5)
Autism	829 (7.1)	2354 (8.0)	509 (10.2)
Multiple Indications (Bipolar, Schizophrenia and/or Autism)	51 (0.4)	92 (0.3)	37 (0.7)
Pharmacotherapy Exposure			
Analgesics	4,615 (39.7)	11,547 (39.2)	2,129 (42.8)
Anxiolytics	3,198 (27.5)	7,380 (25.1)	1,789 (36.0)
Opioids	3,419 (29.4)	8,609 (29.2)	1,655 (33.3)
Stimulants	5,750 (49.5)	14,502 (49.2)	2,559 (51.5)
Antiretrovirals	12 (0.1)	17 (0.1)	8 (0.2)
Corticosteroids	2,501 (21.5)	6,230 (21.1)	1,179 (23.7)
Antidepressants	7,867 (67.7)	18,286 (62.1)	3,712 (74.7)

Table 2 (cont.): Distribution of Demographic and Clinical Characteristics Stratified by Antipsychotic Exposure (N=36,587):

Demographic/Characteristic	Aripiprazole (N=11,624) N (%)	Other Atypical Antipsychotics (N=29,459) N (%)	Multiple Antipsychotics (N=4,970) N (%)
Comorbidity			
Anxiety Disorders	3,380 (29.1)	7,529 (25.6)	1,742 (35.1)
ADHD[‡]	4,501 (38.7)	11,065 (37.6)	2,107 (42.4)
Cancer	30 (0.3)	133 (0.5)	15 (0.3)
Depression	8,824 (75.9)	20,411 (69.3)	4,016 (80.8)
Eating Disorder	348 (3.0)	665 (2.3)	127 (2.6)
Epilepsy	657 (5.7)	1,664 (5.6)	463 (9.3)
HIV/AIDS	1 (0.0)	3 (0.0)	0 (0.0)
Personality Disorder	526 (4.5)	963 (3.3)	322 (6.5)
Multiple Sclerosis	0 (0.0)	4 (0.0)	0 (0.0)
Chronic Pain	3,397 (29.2)	7,774 (26.4)	1,635 (32.9)
Psoriasis	7 (0.1)	16 (0.1)	4 (0.1)
Stroke	18 (0.2)	46 (0.2)	6 (0.1)
Substance Abuse	1,225 (10.5)	3,026 (10.3)	656 (13.2)
Previous Suicide Attempt	139 (1.2)	367 (1.2)	52 (1.0)

Source: Table 4 of the CN138598 CSR

[*]—SD = standard deviation.

[†]—Mean number of encounters three months before index date.

[‡]—ADHD = attention deficit hyperactivity disorder.

Number and Rate of Suicide Events

The rate of suicide events according to current use of atypical antipsychotics and statistical results are shown in Tables 3 and 4, respectively.

Table 3: Number and Rate of Suicide Events in Antipsychotic Current Use Among Children Less Than 18 Years of Age:

Current Use	Number of Children	Number of Events	Person-time (years)	Rate (per 1,000 person-years) (95% CI)[*]
Aripiprazole	11,624	57	6,004	9.49 (7.19–12.30)
Atypical Antipsychotic	29,459	147	17,434	8.43 (7.12–9.91)
Multiple	4,970	15	793	18.92 (10.59–31.20)
Total	36,587	219	24,231	9.04 (7.88–10.32)

Source: Table 5 of the CN138598 CSR

[*]—CI = confidence interval.

Table 4: Crude and Adjusted Hazard Ratios Comparing Rate of Suicide Events in Aripiprazole Current Use Versus Other Atypical Antipsychotic Current Use Among Children Less Than 18 Years of Age:

Current Use	Crude HR[*] (95% CI)[†]	Adjusted[‡] HR[*] (95% CI)[†]
Aripiprazole	1.17 (0.86–1.59)	0.94 (0.68–1.28)
Atypicals Other Than Aripiprazole	1.00 (referent)	1.00 (referent)

Source: Table 6 of the CN138598 CSR

[*]—HR = hazard ratio.

[†]—CI = confidence interval.

[‡]—Adjusted for age, study site, sex, year of index prescription, history of antipsychotic use, exposure to other pharmacotherapy, presence of comorbidity, indication, suicide attempt before index date and number of health care encounters.

Validation - Substudy Results

Results from the substudy evaluating the indication for antipsychotic use demonstrated that, in a subset of this paediatric population (n=386), automated data accurately identified patients with bipolar disorder and schizophrenia. Hyperkinetic syndrome of childhood or ADHD (claims-based diagnoses: 35.2%; chart-based diagnoses: 28.2%), disturbance of emotions specific to childhood adolescence (claims-based diagnoses: 21.5%; chart-based diagnoses: 15.5%) and anxiety, dissociative, and somatoform disorders (claims-based diagnoses: 19.4%; chart-based diagnoses: 9.6%) were frequently coded behavioural diagnoses in this population.

However, the accuracy of identifying precise indication beyond the schizophrenia and bipolar disorder conditions was limited. The sensitivity for bipolar disorder was 81.3% and the specificity was 89.5%. The sensitivity for schizophrenia was 100.0%, and the specificity was 99.0%. The sensitivity for autism was 40.9%, and the specificity was 97.5%.

2.2.3. Additional Analyses

At the CHMP request, the MAH provided additional analyses per paediatric subgroups (schizophrenia and Bipolar Disorder as defined by ICD9 diagnosis codes), taking into account other factors such as the comorbidities and concomitant medication. Furthermore, an analysis related to the occurrence of suicide within the first 28 days following the initiation of treatment in the entire study population was performed by the MAH. Results are presented below.

Schizophrenia population

Results of the subgroup analysis in paediatric patients with schizophrenia are presented in Tables 5-8.

Table 5. Distribution of Demographic Characteristics and Health Encounters in Subpopulation of Paediatric Patients with ICD-9 Codes Indicative of Schizophrenia (N=1,163)

	N (%)
Sex	
Male	821 (70.6)
Female	342 (29.4)
Age (mean (SD)*)	13.7 (4.0)
Health system encounters† (mean (SD)*)	
Inpatient	0.4 (0.6)
Emergency department	0.5 (1.0)
Outpatient	6 (7.2)
†—Mean number of encounters three months before index date *—S.D. = standard deviation	

Table 6. Distribution of Comorbidity and Concomitant Medication Use Among Paediatric Patients

	Total Study Population of Pediatric Psychiatric Patients† (N= 36,587)	Subpopulation of Pediatric Patients with ICD-9 Codes Indicative of Schizophrenia (N=1,163)
Concomitant Medications (N, %)		
Analgesics	14,246 (38.9)	456 (39.2)
Anxiolytics	8,958 (24.5)	363 (31.2)
Opioids	10,520 (28.8)	336 (28.9)
Stimulants	17,676 (48.3)	398 (34.2)
Antiretrovirals	24 (0.1)	0 (0.0)
Corticosteroids	7,624 (20.8)	237 (20.4)
Antidepressants	22,718 (62.1)	704 (60.5)
Comorbidity (N, %)		
Anxiety disorders	9,331 (25.5)	369 (31.7)
Attention Deficit Hyperactivity Disorder	13,484 (36.9)	346 (29.8)
Cancer	148 (0.4)	4 (0.3)
Depression	25,527 (69.8)	811 (69.7)
Eating disorder	889 (2.4)	22 (1.9)
Epilepsy	1,929 (5.3)	104 (8.9)
HIV/AIDS	4 (0.0)	0 (0.0)
Personality disorder	1,205 (3.3)	80 (6.9)
Multiple sclerosis	4 (0.0)	0 (0.0)
Chronic pain	9,678 (26.5)	319 (27.4)
Psoriasis	20 (0.1)	1 (0.1)
Stroke	56 (0.2)	6 (0.5)
Substance abuse	3,717 (10.2)	188 (16.2)
Previous suicide attempt	457 (1.2)	17 (1.5)
†— Data as presented in the CN138-598 final study report		

Table 7. Distribution of Antipsychotic Exposure, Number of Suicide Events, Person-Time Exposed, Rate of Suicide Events and 95% Confidence Intervals Among Patients with ICD-9 Codes Indicative of Schizophrenia

Drug Exposure (Current Use)	Number of Individuals	Number Events	Person-Time (Years)	Rate per 1,000 person-years (95% CI†)
Age < 18 years				
Aripiprazole	417	5	249	20.08 (6.52,46.86)
Other Atypicals	1,000	8	689	11.61 (5.01, 22.88)
Multiple	368	1	86	11.63 (0.29, 64.79)
Total	1,163	14	1,024	13.67 (7.47, 22.94)
Age ≥ 15 years				
Aripiprazole	237	4	102	39.22 (10.69, 100.41)
Other Atypicals	570	5	272	18.38 (5.97, 42.90)
Multiple	245	1	49	20.41 (0.52, 113.71)
Total	674	10	423	23.64 (11.34, 43.48)

†CI= confidence interval

Table 8. Crude and Adjusted Hazard Ratios Comparing Suicide Events in Paediatric Patients with ICD-9 Codes Indicative of Schizophrenia Exposed to Current Use of Aripiprazole to Current Use of Other Atypical Antipsychotic Agents

Analysis Group	Crude (95 % CI †)	Adjusted* (95% CI)	Adjusted** (95% CI)
Patients with ICD-9 Codes Indicative of Schizophrenia **< 18 years of age** (N=1,163)	1.90 (0.62, 5.83)	1.14 (0.33, 3.90)	1.23 (0.37, 4.09)
Patients with ICD-9 Codes Indicative of Schizophrenia **≥ 15 years of age** (N=674)	2.19 (0.59, 8.19)	1.24 (0.27, 5.68)	1.41 (0.32, 6.14)

* Adjusted for age, study site, sex, year of index prescription, history of antipsychotic use, exposure to other pharmacotherapy, presence of comorbidity, indication, suicide attempt before index date, and number of health care encounters

** Adjusted **only** for covariates with estimable regression coefficients

† CI= confidence interval

Bipolar Disorder population

Results of the subgroup analysis in paediatric patients with schizophrenia are presented in Tables 9-12.

Table 9. Distribution of Demographic Characteristics and Health Encounters in Subpopulation of Paediatric Patients with ICD-9 Codes Indicative of Bipolar Disorder (N=10,695)

	N (%)
Sex	
Male	5,617 (52.5)
Female	5,078 (47.5)
Age (mean (SD)*)	13.7 (3.4)
Health system encounters† (mean (SD)*)	
Inpatient	0.3 (0.7)
Emergency department	0.4 (1.0)
Outpatient	6.0 (6.3)

†—Mean number of encounters three months before index date
*—S.D. = standard deviation

Table 10. Distribution of Comorbidity and Concomitant Medication Use Among Paediatric Patients

	Total Study Population of Pediatric Psychiatric Patients† (N= 36,587)	Subpopulation of Pediatric Patients with ICD-9 Codes Indicative of Bipolar Disorder (N=10,695)
Concomitant Medications (N, %)		
Analgesics	14,246 (38.9)	4,907 (45.9)
Anxiolytics	8,958 (24.5)	3,035 (28.4)
Opioids	10,520 (28.8)	3,498 (32.7)
Stimulants	17,676 (48.3)	5,040 (47.1)
Antiretrovirals	24 (0.1)	12 (0.1)
Corticosteroids	7,624 (20.8)	2,362 (22.1)
Antidepressants	22,718 (62.1)	7,382 (69.0)
Comorbidity (N, %)		
Anxiety disorders	9,331 (25.5)	3,206 (30.0)
Attention Deficit Hyperactivity Disorder	13,484 (36.9)	4,333 (40.5)
Cancer	148 (0.4)	16 (0.1)
Depression	25,527 (69.8)	8,394 (78.5)
Eating disorder	889 (2.4)	276 (2.6)
Epilepsy	1,929 (5.3)	655 (6.1)
HIV/AIDS	4 (0.0)	4 (0.0)
Personality disorder	1,205 (3.3)	721 (6.7)
Multiple sclerosis	4 (0.0)	0 (0.0)
Chronic pain	9,678 (26.5)	3,576 (33.4)
Psoriasis	20 (0.1)	12 (0.1)
Stroke	56 (0.2)	10 (0.1)
Substance abuse	3,717 (10.2)	1,905 (17.8)
Previous suicide attempt	457 (1.2)	233 (2.2)

†— Data as presented in the CN138-598 final study report

Table 11. Distribution of Antipsychotic Exposure, Number of Suicide Events, Person-Time Exposed, Rate of Suicide Events and 95% Confidence Intervals Among Patients with ICD-9 Codes Indicative of Bipolar Disorder

Drug Exposure (Current Use)	Number of Individuals	Number Events	Person-Time (Years)	Rate per 1,000 person-years (95% CI†)
Age < 18 years				
Aripiprazole	4,270	40	2,511	15.93 (11.38, 21.69)
Other Atypicals	8,487	89	5,616	15.85 (12.73, 19.50)
Multiple	2,252	9	406	22.17 (10.14, 42.08)
Total	10,695	138	8,533	16.17 (13.59, 19.11)
Age ≥ 15 years				
Aripiprazole	2,031	24	813	29.52 (18.91, 43.92)
Other Atypicals	4,308	55	1,771	31.06 (23.40, 40.42)
Multiple	908	5	112	44.64 (14.50, 104.18)
Total	5,576	84	2,696	31.16 (24.85, 38.57)
†CI= confidence interval				

Table 12. Crude and Adjusted Hazard Ratios Comparing Suicide Events in Paediatric Patients with ICD-9 Codes Indicative of Bipolar Disorder Exposed to Current Use of Aripiprazole to Current Use of Other Atypical Antipsychotic Agents

Analysis Group	Crude (95 % CI †)	Adjusted* (95% CI)	Adjusted** (95% CI)
Patients with ICD-9 Codes Indicative of Bipolar Disorder **< 18 years of age** (N=10,695)	1.06 (0.73, 1.54)	1.01 (0.69, 1.49)	1.01 (0.68, 1.48)
Patients with ICD-9 Codes Indicative of Bipolar Disorder **≥ 15 years of age** (N=5,576)	0.97 (0.60, 1.57)	1.02 (0.62, 1.68)	1.03 (0.62, 1.69)

* Adjusted for age, study site, sex, year of index prescription, history of antipsychotic use, exposure to other pharmacotherapy, presence of comorbidity, indication, suicide attempt before index date, and number of health care encounters

** Adjusted **only** for covariates with estimable regression coefficients

† CI= confidence interval

Entire study population

Data on the number and rate of suicide events during the first 28 days of initial exposure are presented in Tables 13 and 14.

Table 13. Number and Rate of Suicide Events in Antipsychotics Current Use Among Children Less than 18 years during the first 28 days of initial exposure

Drug Exposure (Current Use)	Number of Individuals	Number Events	Person-Time (Years)	Rate per 1,000 person-years (95%CI*)
Aripiprazole	8,420	2	613	3.26 (0.40,11.79)
Other Atypicals	27,947	37	2,016	18.35 (12.92,25.30)
Multiple	1,173	3	48	62.50 (12.89,182.65)
Total	36,587	42	2,677	15.69 (11.31,21.21)
*CI: confidence interval				

Table 14: Crude and Adjusted Hazard Ratios Comparing Rate of Suicide Events in Aripiprazole Current Use Versus Other Atypical Antipsychotic Current Use Among Children Less Than 18 Years of Age during the first 28 days of initial exposure

Drug Exposure (Current Use)	Crude Hazard Ratios (95% CI)	Adjusted Hazard Ratios* (95%CI)	Adjusted Hazard Ratios** (95%CI)
Aripiprazole	0.18 (0.04,0.74)	0.17 (0.04,0.72)	0.19 (0.05,0.81)
Atypicals other than aripiprazole	1.00 (referent)	1.00 (referent)	1.00 (referent)
*: Adjusted for age, study site, sex, year of index prescription, history of antipsychotic use, exposure to other pharmacotherapy, presence of comorbidity, indication, suicide attempt before index date, and number of death of health care encounters ** adjusted **only** for covariates with estimable regression coefficients			

2.2.4. Discussion

After reviewing the original analysis based on the overall population (see Table 1), the CHMP noted that only 2.8% of the patients studied had schizophrenia. Moreover, the mean age of paediatric patients was 12.9, and from the CHMP viewpoint, the risk of suicide is generally higher in older children. Therefore the CHMP considered that the presented results were not sufficient to evaluate the risk of suicide in the authorised paediatric indication, which at the time of the submission of this variation application, was limited to schizophrenia in adolescents aged 15 years and older. At the CHMP request, additional analyses were performed per paediatric subgroups (schizophrenia and Bipolar Disorder as defined by ICD9 diagnosis codes) and taking into account other factors such as comorbidities and concomitant medications. Furthermore, an analysis related to the occurrence of suicide within the first 28 days following the initiation of treatment was performed in the entire study population by the MAH. All these analyses were based with an age cut off of 15 years, since at the time of the responses to the CHMP request for supplementary information, the paediatric indication was limited to schizophrenia in adolescents aged 15 years and older.

In schizophrenia patients aged 15 years and above, the studied population had a very high percentage of chronic pain and concomitant use of opiates, analgesics and corticosteroids (see Table 6). Presence of ADHD and use of stimulants were also very high, 29.8% and 34.2% respectively. These aspects may differently influence the risk of suicide. Similar findings were observed in the Bipolar Disorder population with frequent presence of comorbidities e.g. ADHD, anxiety disorders and chronic pain. Most suicidal events (4 out of 5) occurred in the schizophrenia population 15 years and above, with a rate per 1,000 person-years, almost double than with the other agents (see Table 7) and this was considered by the CHMP of concern in spite of the large and overlapping confidence intervals. Even the adjusted hazard ratios comparing suicidal events in paediatric patients with ICD-9 codes indicative of Bipolar Disorder exposed to current use of aripiprazole to current use of other atypical antipsychotic agents showed an increased risk compared to other antipsychotics (see Table 12), although the CIs still were highly overlapping. Hence, the CHMP was not in agreement with the MAH proposal to include a statement in section 4.4 of the SmPC regarding the results of this study, suggesting that there was no increased risk of suicidality with aripiprazole compared to other treatment. The CHMP considered that the results of the study were not sufficiently robust to make such conclusion. In addition, although there was no sizeable database at the time of this variation that can contribute to an adequate EU sample size to evaluate the risk of suicide in the paediatric population, the CHMP was of the opinion

that information in the SmPC should as far as possible relate to the intended (authorised) use, and no convincing arguments on the relevance of the available data to EU use had been provided by the MAH. On this basis, the MAH did not wish to pursue their initial proposed statement to reflect the results of this epidemiological study and hence did not provide further analyses taking into account paediatric patients with Bipolar Disorder aged 13 years and older and the launch dates of the antipsychotic agents, as requested by the CHMP. Subsequently, the MAH proposed to reflect in the SmPC that there are insufficient paediatric data to evaluate the risk of suicide with aripiprazole compared to other antipsychotics in younger patients (below 18 years of age). This proposal was considered acceptable by the CHMP and the MAH updated the Product Information in line with the final CHMP recommended wording (see 2.3).

Regarding temporal dispersion on suicide events rate on the first 4 weeks of use of aripiprazole in Bipolar Disorder patients only, the CHMP noted that suicide events occurring in the first 4 weeks were much more likely to occur with other atypical antipsychotics than with aripiprazole, with no CIs overlapping. The incidence rates (per 1,000 person-years) were respectively, 3.26 (0.40, 11.79) and 18.35 (12.92, 25.30) for aripiprazole and other atypical agents (see Table 13). The adjusted hazard ratios comparing suicide events in aripiprazole users versus other atypical agents users during the first 4 weeks were 0.17 (0.04-0.72) and 0.19 (0.05-0.81). Therefore the CHMP concluded that the risk of suicide events with aripiprazole appeared to have a different temporal pattern, with the risk being well more distributed over the time. Whilst acknowledging that the presented data were insufficient to evaluate the risk of suicide with aripiprazole compared to other antipsychotics in younger patients (below 18 years of age), the CHMP recommended to include in the SmPC that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole. This statement was agreed by the MAH (see 2.3).

2.3. Changes to the Product Information

The MAH initially proposed the following changes to the Product Information (PI).New text is underlined:

SmPC - Section 4.4

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among <u>adult</u> patients with schizophrenia or bipolar disorder<u>. Results of an epidemiological study in paediatric patients with any diagnosis suggested that there was no increased risk of suicidality with aripiprazole compared to other atypical antipsychotics.</u>

During the procedure, the CHMP requested amendments to the initially proposed PI, as discussed in detail above. The new text finally approved by the CHMP is as follows:

SmPC- Section 4.4

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

3. Overall conclusion and impact on the benefit/risk balance

On the basis of the submitted data, the CHMP concluded that the update of the Product Information regarding the results of the paediatric epidemiological study (CN 138598) was adequate. The CHMP considered that the changes do not affect the benefit risk profile of the product, which remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		Type
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of section 4.4 of the SmPC to add information on the risk of suicidality in paediatric patients based on the results of the epidemiological study CN138598.

The requested variation proposed amendments to the Summary of Product Characteristics.