European Medicines Agency

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ASSESSMENT REPORT
FOR
ABILIFY

International Nonproprietary Name:
aripiprazole

Procedure No. EMEA/H/C/471/II/0041

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

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1. Introduction

Acutely agitated patients with neuropsychiatric illness risk harming themselves or others. Psychomotor agitation is defined in the Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as "excessive motor activity associated with a feeling of inner tension."

Patients experiencing agitation may manifest a range of disturbed behaviours that interfere with their diagnosis and care (e.g. threatening behaviours, escalating or urgently distressing behaviours, or self-exhausting behaviour) requiring clinicians to use intramuscular antipsychotic medications to achieve immediate control of the agitation.

Treating patients during the first few hours of agitation is most important in emergency and critical care situations. Because such patients may be unable or unwilling to take oral antipsychotic drugs, it may be necessary to use an alternative route of administration to treat them.

Currently, a limited choice of rapid acting intramuscular (IM) formulations of antipsychotics is available for agitated patients with neuropsychiatric illness.

In this type II variation, the MAH applied for an extension of indication of Abilify 7.5mg/ml as follows (the new indication is underlined):

'Aripiprazole is indicated for 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.'

2. Non Clinical aspects

Environmental risk assessment (ERA)

The MAH predicted that based on available forecasts the approval of this formulation and use will not significantly increase the use of aripiprazole in the EU.

Overall, given the latest ERA submitted and related commitments made by MAH in the type II variation EMEA/H/C/471/II/39, the CHMP considered the available information to date, to be acceptable.

3 Clinical aspects

3.1 Clinical efficacy

The development program completed to support this extension of indication consisted of one randomised, double-blind study **(CN138013)** comparing the efficacy and safety of aripiprazole intramuscular (IM), lorazepam, or placebo in the treatment of acutely agitated patients diagnosed with Bipolar I Disorder, manic or mixed.

Study CN180013 was conducted in accordance with GCP as stated by the MAH.

METHODS

Study design

It is a randomised, double-blind, IM study comparing 2 fixed doses of aripiprazole (10 and 15 mg) and 1 dose of lorazepam (2mg) with placebo over 24 hours in patients with bipolar I disorder, manic or mixed and acute agitation with a PEC (positive and negative syndrome scale excited component): at least 2 components ≥4 and sum of 5 components ≥15 but ≤ 32.

Primary and Secondary Objectives

The primary objective was to compare the efficacy of IM aripiprazole versus placebo in the treatment of acutely agitated patients with a diagnosis of Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to 2 hours post first IM injection using the PEC scale.

Secondary objectives were:

- to compare the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with a diagnosis of Bipolar I Disorder, manic or mixed, as assessed by the Clinical Global Impressions Improvement Scale (CGI-I), Clinical Global Impressions Severity of Illness Scale (CGI-S), Agitation-Calmness Evaluation Scale (ACES), and Corrigan Agitated Behavior Scale (CABS).
- to compare the effects in this study of IM lorazepam, a known active therapy and standard of care in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed, versus placebo.
- to determine the safety and tolerability of IM aripiprazole in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to each specified observation time in the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (Barnes). Safety and tolerance was evaluated by reports of adverse events (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.

Efficacy Endpoints

The primary efficacy measure was mean change from baseline to 2 hours post first IM injection in PEC Score. Efficacy rating scales completed during this study included PEC, ACES, CGI-I, CGI-S, CABS, PANSS, and Y-MRS.

Sample size

The planned sample size of 260 evaluable patients (65 per treatment group) would yield 90% power to differentiate between placebo and at least 1 of the 2 aripiprazole treatment groups (10 mg or 15 mg), when the true difference in the mean changes from baseline in PEC score was 3.4. This assumed a standard deviation of 5.4 and a 2-sided test at the 0.025 level of significance (adjusted for 2 comparisons versus placebo to ensure an overall probability of type 1 error ≤ 0.05).

RESULTS

Baseline characteristics – Table 1

Table 1 - Key Baseline Scores: IM Placebo-Controlled Study (CN138013), Efficacy Sample (Randomized patients)

Measurement	Statistics	Placebo N=73	Lorazepam N=68	Aripiprazole N=150
PEC Score	Mean	17.92	18.41	18.46
	Median	17	17	18
	Min-Max	15-29	15-28	15-25
	SD	2.63	2.88	2.33
CGI-S Score	Mean	4.10	4.16	4.14
	Median	4	4	4
	Min-Max	3-5	3-6	2-5
	SD	0.56	0.61	0.62
ACES Score	Mean	2.38	2.40	2.34
	Median	2	2	2
	Min-Max	1-3	2-3	1-3
	SD	0.52	0.49	0.52
CABS Score	Mean	28.03	28.75	28.36
	Median	28	28	28
	Min-Max	19-38	21-39	19-42
	SD	4.80	3.98	4.52

Recruitment/Number analysed

Three hundred twenty-nine (329) patients were enrolled in the study and 301 patients were randomised to double-blind treatment: 75 to the placebo group, 70 to the lorazepam group, 78 to the 10-mg aripiprazole group, and 78 to the 15-mg aripiprazole group. Of the 301 patients randomised to treatment, 291 were included in the safety and efficacy Samples. Two hundred eighty-two (94%) of the 301 randomised patients completed the study.

Primary Efficacy Endpoint – PEC (PANSS Excitement Component) score

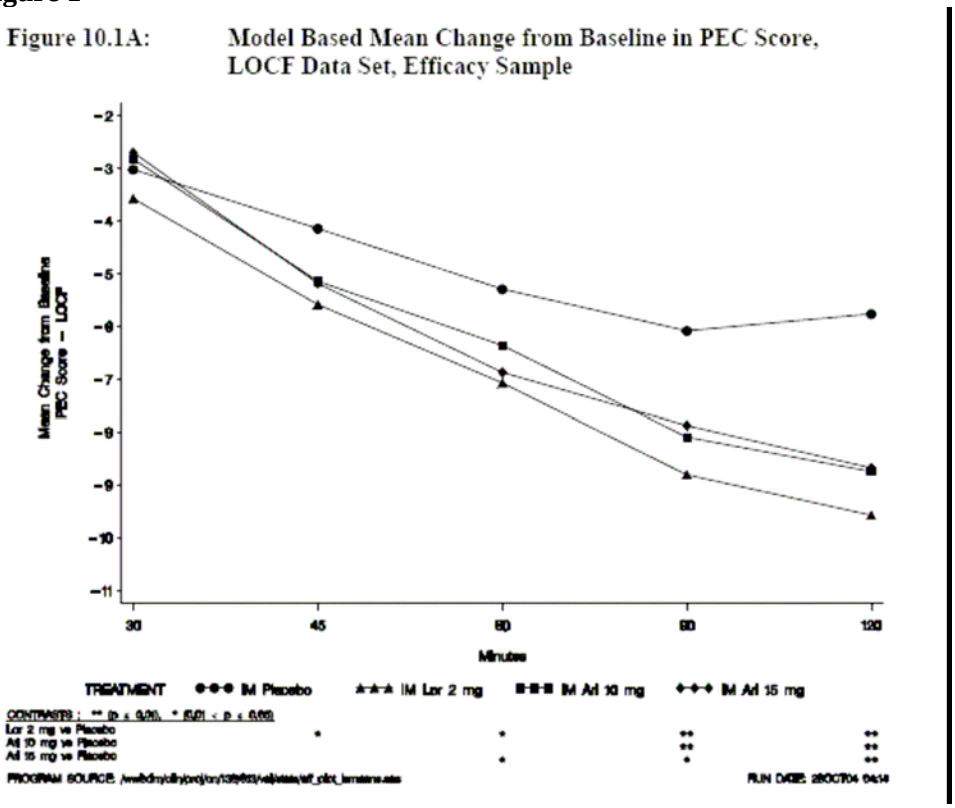
Results are presented in Table 2 and Figure 1.

Table 2: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score: IM Placebo-Controlled Study CN138013, LOCF Data Set, Efficacy Samples

		PEC Score			
Study/ Treatment	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Bipolar I Disorder CN138013					
Placebo	73	18.04	-5.76	--	--
Aripiprazole 10 mg	75	18.84	-8.74	-2.99 (-4.53, -1.44)	<0.001
Aripiprazole 15 mg	75	18.25	-8.67	-2.91 (-4.44, -1.38)	<0.001
Lorazepam 2 mg	68	18.47	-9.57	-3.81 (-5.38, -2.24)	<0.001

Aripiprazole 10-mg and 15-mg (both $p < 0.001$) were statistically superior to placebo in the primary efficacy measure. Statistical separation from placebo (ie, $p \leq 0.05$) was demonstrated as early as 60 minutes ($p = 0.028$) for the 15-mg aripiprazole group and as early as 90 minutes ($p = 0.008$) for the 10mg aripiprazole group (see Figure 1).

Figure 1



Lorazepam was statistically superior to placebo in the primary efficacy measure ($p < 0.001$) and demonstrated statistical separation from placebo as early as 45 minutes ($p = 0.040$).

Subgroup analysis -non sedated patients

Results are presented in Tables 3 and 4.

Table 3: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score Excluding Patients with Scores of 8 (Deep Sleep) or 9 (Unarousable) on ACES During the First 2 Hours: IM Placebo-Controlled Studies (CN138013), LOCF Data Set, Efficacy Sample

Study	Medication	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138013	Placebo	68	17.91	-5.10	--	--
Bipolar 1	Aripiprazole 10mg	70	18.76	-8.44	-3.34 (-4.96,-1.71)	<0.001
Disorder	Aripiprazole 15mg	62	18.19	-7.72	-2.62 (-4.29,-0.95)	0.002
	Lorazepam 2mg	55	18.31	-8.70	-3.60 (-5.33,-1.88)	<0.001

Table 4: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score Excluding Patients with Sedation/Somnolence Related AEs During the First 2 Hours: IM Placebo-Controlled Studies (CN138013), LOCF Data Set, Efficacy Sample

Study	Medication	N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138013	Placebo	69	18.00	-5.47	--	--
Bipolar 1	Aripiprazole 10mg	70	18.69	-8.59	-3.12 (-4.77,-1.48)	<0.001
Disorder	Aripiprazole 15mg	66	18.24	-8.20	-2.73 (-4.39,-1.07)	0.001
	Lorazepam 2mg	59	18.44	-9.09	-3.62 (-5.34,-1.91)	<0.001

For the subgroup of non sedated patients (defined on the basis of the ACES Score), statistically significant differences versus placebo in the primary efficacy measure were observed in favour of the 10-mg and 15-mg aripiprazole groups, as well as for the lorazepam group.

Secondary endpoints and other efficacy measures

Aripiprazole 10-mg and 15-mg were statistically superior to placebo on all secondary efficacy measures at 2 hours post first IM injection (LOCF data set, see Table 5).

Table 5

Summary of Efficacy Results at 2 Hours, LOCF Data Set, Efficacy Sample

Variable	Treatment Group: IM Placebo	IM Lor 2 mg	IM Ari 10 mg	IM Ari 15 mg
PRIMARY EFFICACY ENDPOINT				
PEC Score	N = 73	N = 68	N = 75	N = 75
Mean Baseline	18.04	18.47	18.84 *	18.25
(95% CI)	(17.50, 18.58)	(17.91, 19.03)	(18.30, 19.37)	(17.71, 18.78)
Mean Change at 2 Hours	-5.76	-9.57 **	-8.74 **	-8.67 **
(95% CI)	(-6.89, -4.62)	(-10.74, -8.40)	(-9.87, -7.62)	(-9.79, -7.55)
SECONDARY EFFICACY ENDPOINTS				
CGI-Improvement Score	N = 73	N = 68	N = 75	N = 75
Mean at 2 Hours	3.05	2.10 **	2.17 **	2.33 **
(S.E.)	(0.13)	(0.12)	(0.13)	(0.15)
CGI-Severity Score	N = 73	N = 68	N = 75	N = 75
Mean Baseline	4.12	4.16	4.24	4.09
(95% CI)	(3.99, 4.25)	(4.03, 4.30)	(4.11, 4.37)	(3.95, 4.22)
Mean Change at 2 Hours	-0.94	-1.61 **	-1.48 **	-1.34 *
(95% CI)	(-1.17, -0.70)	(-1.85, -1.36)	(-1.72, -1.25)	(-1.57, -1.10)
ACES Score	N = 73	N = 68	N = 75	N = 75
Mean Baseline	2.38	2.38	2.28	2.41
(95% CI)	(2.28, 2.49)	(2.27, 2.49)	(2.17, 2.38)	(2.30, 2.52)
Mean Change at 2 Hours	1.00	2.34 **	1.87 **	2.32 **
(95% CI)	(0.58, 1.42)	(1.90, 2.77)	(1.45, 2.29)	(1.91, 2.74)
CABS Score	N = 73	N = 68	N = 75	N = 75
Mean Baseline	28.38	28.96	29.36	28.00
(95% CI)	(27.43, 29.34)	(27.98, 29.95)	(28.42, 30.31)	(27.05, 28.94)
Mean Change at 2 Hours	-6.37	-10.35 **	-9.60 **	-9.08 **
(95% CI)	(-7.63, -5.11)	(-11.66, -9.05)	(-10.86, -8.34)	(-10.34, -7.83)
PEC Response Rate (a)	N = 73	N = 68	N = 75	N = 75
Number (%) at 2 Hours	27(37%)	47(69%) **	52(69%) **	47(63%) **
(S.E.%)	(5.7%)	(5.7%)	(5.4%)	(5.6%)

The mean CGI-I Score, and the mean change from baseline in the CGI-S, ACES, and CABS Score showed statistically significant comparisons versus placebo in favour of the 10-mg and 15-mg aripiprazole groups. Furthermore, statistically significantly higher rates of PEC response were observed for 10-mg and 15-mg aripiprazole than for placebo. Lorazepam was statistically superior to placebo on these secondary outcome measures.

Statistically significantly higher rates in terms of CGI response were observed for all active treatment groups at all timepoints. Patients in the 10-mg and 15-mg aripiprazole groups were more likely to respond and/or to respond sooner in terms of PEC response than patients in the placebo group during the 2-hour period post first IM injection.

Furthermore, patients in the placebo group were more likely to require and/or require sooner a second or third injection than patients in the 10-mg and 15-mg aripiprazole groups, as well as in the lorazepam group (see Table 6).

Table 6: Number and Percentage of Patients Who Received Study Medication by Number of Injections: IM Placebo-Controlled Study CN138013, Efficacy Sample

			Aripiprazole	
Injections	Placebo	Lorazepam 2mg	10mg	15mg
	N=73	N=68	N=75	N=75
Only One Injection	27(37)	44(65)	45(60)	52(69)
Only Two Injections	15(21)	18(26)	24(32)	16(21)
Three Injections(a)	31(42)	6(9)	6(8)	7(9)

(a) Third Injection for placebo was 10-mg aripiprazole

Aripiprazole 10-mg and 15-mg, as well as lorazepam, were statistically superior to placebo for the mean change in the PEC Score from predose (ie, immediately prior to second IM injection) to 2 hours post second IM injection.

For the subgroup of patients who were non responders to the first IM injection (defined as a patient who received a second injection within 4 hours of the first and who was not a PEC responder in the evaluation just prior to the second injection), statistically significant differences versus placebo were observed in the mean change from predose in favour of the 10-mg and 15-mg aripiprazole and lorazepam groups. In addition, aripiprazole 10-mg and lorazepam also showed superiority over placebo at the 60 minute time point. Following the third IM injection, 10-mg aripiprazole appeared to be similar in effect as lorazepam for the mean change in the PEC Score from baseline (ie, immediately prior to first IM injection).

DISCUSSION ON CLINICAL EFFICACY

The repeated measures analysis on the PEC Score through 2 hours post first IM injection showed improvement over time for all treatment groups. The improvement was statistically significantly greater for the 10-mg and 15-mg aripiprazole and lorazepam groups than placebo.

The PEC score has not been formally validated in bipolar patients with acute mania. However, results from all secondary efficacy measures are reassuring and support the primary efficacy analysis for study CN138013.

Overall, the CHMP recommended to reflect the results of this study in section 5.1 of the SPC. *'In one short-term (24-hour) placebo-controlled trial involving 291 patients with bipolar disorder presenting*

with agitation and disturbed behaviours, aripiprazole solution for injection was associated with statistically significant greater improvements in agitation/behavioural symptoms compared to placebo and was similar to the reference arm lorazepam. The observed mean improvement from baseline on the PANSS Excitement Component score at the primary 2-hour endpoint was 5.8 for placebo, 9.6 for lorazepam, and 8.7 for aripiprazole. In subpopulation analyses on patients with mixed episodes or on patients with severe agitation, a similar pattern of efficacy to the overall population was observed but statistical significance could not be established due to a reduced sample size.'

Furthermore, inclusion of the approved information for oral aripiprazole related to this indication has been made into section 5.1 of the SPC.

3.2 Clinical safety

Patient Exposure

The safety sample comprised 1214 patients: 795 patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder (CN138012, CN138050), 291 patients with a diagnosis of bipolar I disorder, manic or mixed (CN138013), and 128 patients with a diagnosis of dementia (additional safety study CN138131 conducted in elderly patients and provided by the applicant). A total of 660 patients received aripiprazole as initial treatment, 240 patients received haloperidol, 69 patients received lorazepam, and 245 patients received placebo. In addition, 62 placebo-treated patients received 10-mg aripiprazole as a third injection and 27 placebo-treated patients received 15-mg aripiprazole as a third injection. Therefore, from the 4 IM placebo-controlled Phase 2/3 studies a total of 749 patients received IM aripiprazole. This safety sample was already evaluated by CHMP at the time of the opinion for the extension of the marketing authorisation to IM aripiprazole (EMEA/H/C/471/II/15 and X/16).

Adverse events

Aside from those events that are associated with the method of administration (e.g. injection site pain), the profile of AEs reported with IM aripiprazole was generally similar to those observed with oral-tablet aripiprazole (Table 7).

Table 7

Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 1% of Patients in the Aripiprazole Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Safety Sample

System Organ Class/ Preferred Terma	Number (%) Patients			
	Placebo N = 220	Haloperidol N = 240	Lorazepam N = 69	Aripiprazole N = 501
Cardiac Disorders				
Tachycardia	1 (0.45)	2 (0.83)	1 (1.45)	8 (1.60)
Gastrointestinal Disorders				
Nausea	7 (3.18)	3 (1.25)	0	46 (9.18)
Vomiting	2 (0.91)	2 (0.83)	0	17 (3.39)
Dyspepsia	1 (0.45)	0	0	7 (1.40)
Dry Mouth	1 (0.45)	5 (2.08)	1 (1.45)	6 (1.20)
General Disorders and Administration Site Conditions				
Fatigue	3 (1.36)	6 (2.50)	2 (2.90)	11 (2.20)
Injection Site Pain	4 (1.82)	2 (0.83)	0	9 (1.80)
Injection Site Burning	2 (0.91)	0	1 (1.45)	7 (1.40)
Investigations				
Blood Pressure Increased	1 (0.45)	3 (1.25)	1 (1.45)	6 (1.20)
Musculoskeletal and Connective Tissue Disorders				

Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 1% of Patients in the Aripiprazole Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Safety Sample

	Number (%) Patients			
Musculoskeletal Stiffness	1 (0.45)	4 (1.67)	0	6 (1.20)
Nervous System Disorder				
Headache	16 (7.27)	17 (7.08)	3 (4.35)	62 (12.38)
Dizziness	10 (4.55)	11 (4.58)	7 (10.14)	40 (7.98)
Somnolence	8 (3.64)	13 (5.42)	5 (7.25)	34 (6.79)
Sedation	5 (2.27)	7 (2.92)	8 (11.59)	14 (2.79)
Akathisia	0	12 (5.00)	0	10 (2.00)
Psychiatric Disorder				
Insomnia	14 (6.36)	23 (9.58)	1 (1.45)	28 (5.59)
Agitation	6 (2.73)	9 (3.75)	0	14 (2.79)

Deaths and other serious adverse events

There were 2 reports of death in patients who received study medication in the IM Phase 2/3 clinical program. These were not considered related to study treatment.

There were no SAEs reported in Studies CN138016 and CN138017. One SAE was reported in the Study CN138132: a 40-year old black female, experienced Grade 3 neutropenia that began on Day 27 after aripiprazole 15-mg treatment and lasted for 91 days.

Thirty-two of the 1214 patients in the IM safety Sample (CN138012, CN138050, CN138013, CN138131) experienced SAEs. One SAE for a patient in the placebo group occurred after the third injection, which was 15-mg aripiprazole. Most events were related to patients' underlying psychiatric diseases, and only one report event of dystonia with 6.5 mg haloperidol was considered by the investigators to be related to study medication.

Other safety findings

In the pooled schizophrenia studies (CN138012, CN138050), a higher incidence of increased fasting serum glucose in aripiprazole- and haloperidol-treated patients than placebo-treated patients following injection with study medication was reported.

When QT intervals were evaluated uncorrected and using other correction methods (QTcB, QTcN, and QTcF), there were no clinically meaningful differences across treatment groups.

Discontinuation due to adverse events

Eight of the 1214 patients discontinued from the studies because of an AE during the IM phase. Five aripiprazole-treated patients discontinued and only 1 of these patients (10-mg) discontinued due to possible drug related events (agitation and musculoskeletal stiffness). None of the 89 placebo-treated patients who received a third IM injection, which was either 10-mg or 15-mg aripiprazole, discontinued from the studies because of an AE.

DISCUSSION ON CLINICAL SAFETY

The safety profile of aripiprazole using the IM formulation was similar to that of the oral-tablet formulation. Based on data collected to date the IM formulation appears favourable. There was only a small number of SAEs, and very few AEs led to discontinuation. There were no important clinical concerns regarding laboratory, vital sign, or ECG findings. Section 4.8 of the SPC has been updated to reflect the safety information, already approved for oral aripiprazole at the time of the type II variation EMEA/H/C/471/II/39.

4. Risk Management Plan

Reference is made to the Risk Management Plan version 3.0 submitted in the type II variation EMEA/H/C/471/II/39, which was considered acceptable by CHMP.

5. Overall conclusions and benefit/risk assessment

Based on the CHMP review of safety and efficacy, the CHMP considers that the benefit-risk for Abilify 7.5 mg/ml solution for injection in the rapid control of agitation and disturbed behaviours in patients with manic episodes in Bipolar I disorder, when oral therapy is not appropriate, is favourable and recommended the variation to the marketing authorisation.