

Formulary Monograph

Aripiprazole for Extended-Release Injectable Suspension (Aripiprazole Long-acting Antipsychotic Injection [LAI]; ABILIFY MAINTENA™)

Classification: Atypical antipsychotics (AHFS 28:16.08.04)

Indications

Abilify Maintena's NDA was approved 02-28-2013 showing that it is indicated for the *treatment of schizophrenia*. (Abilify Maintena Product Label §1)

Contraindications

Known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole. (Abilify Maintena Product Label §4)

Dosing

- Document prior tolerability and efficacy to oral aripiprazole prior to initiating aripiprazole LAI
- Recommended starting and maintenance dose is 400 mg administered monthly (≥ 26 days) as a single injection
- Overlap 14 consecutive days of concurrent oral antipsychotic (aripiprazole 10–20 mg) or current oral antipsychotic at same dose
- Some patients may benefit from a reduction to a 300 mg maintenance dose to improve tolerability
- Dosage adjustments are required for late doses or missed doses ([Table 22](#)), and for patients who are CYP2D6 genotypic poor metabolizers and for patients taking that are taking ≥ 14 days of CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers ([Table 21](#))
- See [instructions](#) for use for reconstitution and administration procedures (Abilify Maintena Product Label §2)

Medicinal Chemistry and Pharmaceutics

Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy]-3,4-dihydrocarbostyryl. The polymorphic monohydrate is used in the commercial products. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$ and its molecular weight is 466.40 daltons. The labeled strengths are calculated based on the anhydrous form (aripiprazole).

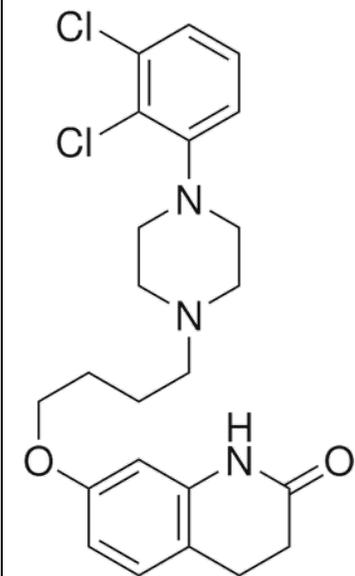
Inactive ingredients include carboxymethyl cellulose sodium, mannitol, sodium phosphate monobasic monohydrate and sodium hydroxide. (Abilify Maintena Product Label, §11)

Clinical Pharmacology

Mechanism of Action

The mechanism of action of aripiprazole, like all antipsychotics, in the treatment of schizophrenia is unknown.

*Illustration 1:
Aripiprazole Structure*



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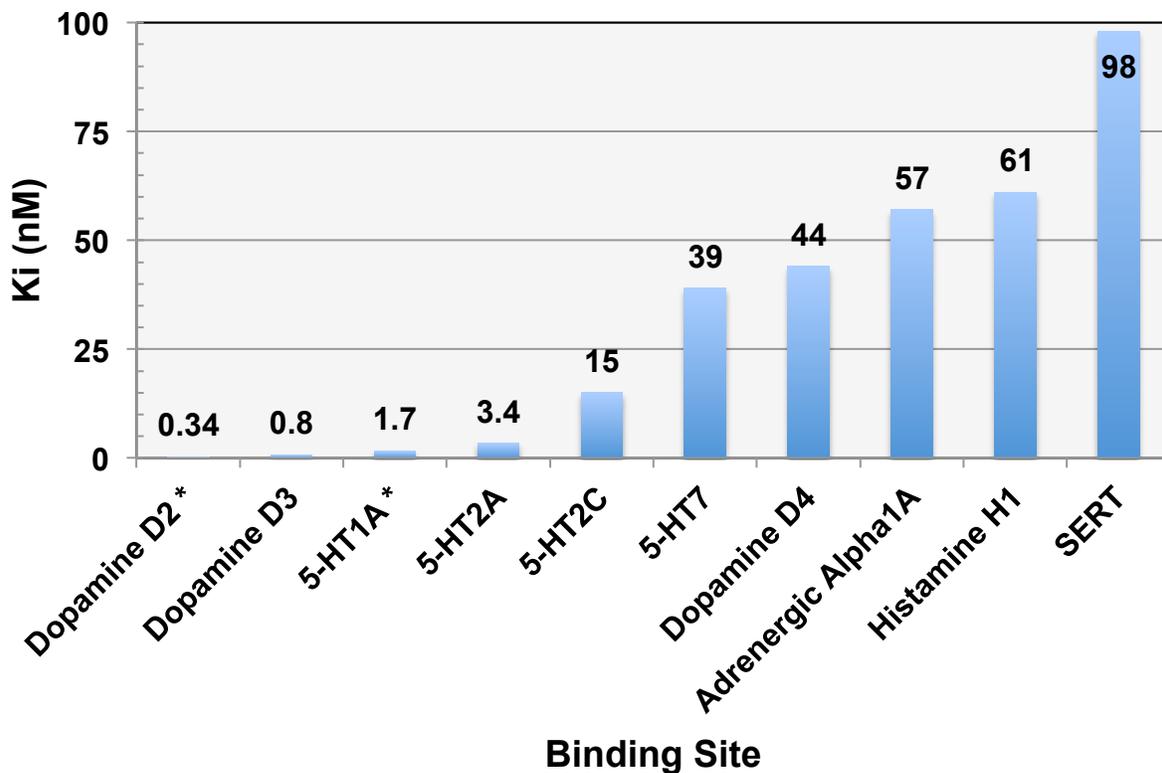
However, the efficacy of aripiprazole is believed to be mediated through a combination of partial agonist activity at D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D₂, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other adverse reactions of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic α₁ receptors). (Abilify Maintena Product Label §12.1)

Pharmacodynamics

The binding coefficients for the most highly bound receptors for aripiprazole are shown in Illustration 2. (Ki values from: Abilify Maintena Product Label §12.2) Lower Ki values indicate *stronger* binding.

These data clearly show that the aripiprazole's most potent receptor binding sites are for D₂, D₃, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}. The binding to 5-HT₇, D₄, α₁, H₁, and SERT (serotonin transporter) are all likely to be significantly less important in their clinical effects.

Illustration 2: Aripiprazole Receptor Binding



Aripiprazole binds as partial agonist
Data from Abilify Maintena Product Label §12.2

The *apparent* clinical significance of the various receptors on adverse effects are summarized in Table 1.

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Table 1: Summary of Receptors and Associated Adverse Effects

Receptor Activity	Adverse Effect					
	Weight Gain	Glucose Intolerance	Sedation	Extra-pyramidal Symptoms	Prolactin Elevation	Anti-cholinergic Symptoms
Serotonin 5-HT _{2C} Antagonism	✓	✓				
Serotonin 5-HT _{1A}	✓					
Histamine H ₁ Antagonism	✓	✓	✓			
Dopamine D ₂ Antagonism	✓			✓	✓	
Muscarinic M ₁ Antagonism						✓
Muscarinic M ₃ Antagonism		✓				

Based upon: Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Molecular Psychiatry* 2008;13:27–35.

[Full Text <<http://www.nature.com.libproxy.uthscsa.edu/mp/journal/v13/n1/pdf/4002066a.pdf>>]

Pharmacokinetics

Absorption

Aripiprazole absorption from intramuscular injection (15–400 mg) into the systemic circulation is slow and prolonged following intramuscular injection due to low solubility of aripiprazole and the crystal structure of aripiprazole monohydrate. The physiochemical properties of the aripiprazole LAI formulation makes it unlikely that dose dumping (as seen with fluphenazine decanoate and olanzapine pamoate) into the systemic circulation would occur. No evidence of dose dumping was observed in the aripiprazole LAI clinical trials.

Following a single intramuscular dose, the plasma concentrations of aripiprazole gradually rise to reach maximum plasma concentrations at a median T_{max} of 5-7 days. More than dose-proportional increase in AUC was observed after single dose administration in the range of 15-400 mg.

Median T_{max} times were 7–24 days for aripiprazole and 7–25 days for dehydro-aripiprazole. Mean T_½ was 11-34 days for aripiprazole and 12-40 days for dehydro-aripiprazole, aripiprazole's active equipotent metabolite.

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Table 2: Pharmacokinetic (PK) Parameters (mean (SD)) of aripiprazole (Ara) and dehydro-aripiprazole (DeA) after single gluteal administration of IM depot formulation

Parameter	Aripiprazole LAI Single Dose Administered											
	15 mg		50 mg		100 mg		200 mg		300 mg		400 mg	
	Ara (n=2)	DeA (n=1)	Ara (n=2)	DeA (n=2)	Ara (n=4)	DeA (n=4)	Ara (n=3)	DeA (n=3)	Ara (n=3)	DeA (n=3)	Ara (n=3)	DeA (n=3)
T_{max} (day) *	7.5 (4-10)	11 (-)	9.5 (4-15)	13 (11-15)	24.0 (4-25)	24.5 (11-34)	7.0 (4-7)	7.0 (7-11)	7.0 (4-11)	15.0 (11-54)	22 (4-22)	22 (8-34)
C_{max} (ng/ml)	4.8 (3.1)	2.37 (-)	10.6 (2.2)	2.57 (1.3)	44.5 (29.4)	11.2 (5.8)	67.3 (24.2)	19.9 (8.0)	86.0 (20.6)	21.7 (8.6)	92.1 (82.0)	33.2 (13.6)
AUC_{0-inf} (hr×µg/mL)	4.5 (0.07)	1.5 (-)	12.7 (2.4)	3.9 (0.08)	41.7 (15.8)	12.3 (2.8)	71.0 (19.9)	27.8 (8.5)	115 (23)	35.6 (10.1)	80.4 (82.8)	31.3 (17.3)
T_½ (day)	27.4 (19.1)	12.5 (-)	34.3 (10.3)	40.2 (11.7)	19.5 (8.5)	30.5 (22.6)	18.9 (3.6)	17.4 (3.3)	24.9 (10.8)	32.9 (24.5)	10.5 (3.9)	12.1 (3.8)

* T_{max} (Time to Maximum Concentration) is shown as Median (Range)
Based upon data in NDA 202971 Clin Pharm Review, Tables 5, 6; P 19–20

After multiple dose administration of 200 mg, 300 mg, and 400 mg of intramuscular injections, T_{max} were reached in 5–7 days (same as single dose).

Mean aripiprazole T_½ apparent terminal was 30–47 days; T_{max} dehydro-aripiprazole concentrations were reached within 6–13 days. Approximate dose proportional increase in AUC was observed after multiple doses of 300 mg and 400 mg.

Table 3: Pharmacokinetic (PK) Parameters (mean (SD)) of aripiprazole (Ara) and dehydro-aripiprazole (DeA) after multiple gluteal administration of IM depot formulation

Parameter	Aripiprazole LAI Multiple Dose Administered					
	200 mg (n=4)		300 mg (n=8)		400 mg (n=10)	
	Ara	DeA	Ara	DeA	Ara	DeA
C_{max ss} (ng/ml)	100 (68.4)	30.3 (19.8)	269 (128)	74.7 (20.8)	316 (160)	89.4 (37.9)
C_{min ss}^a (ng/ml)	95.0 (86.2)	26.2 (24.7)	156 (67.7)	54.1 (21.1)	212 (113)	64.1 (27.0)
C_{ave ss} (ng/ml)	81.1 (58.7)	N/R	208 (87)	N/R	242 (132)	N/R
AUC_τ (hr×µg/mL)	54.5 (39.4)	14.7 (9.47)	140 (58.4)	38.9 (13.2)	163 (88.8)	47.8 (19.1)
T_{max}^b (day)	5.0 (4.0-27.9)	5.5 (0-27.9)	6.5 (0.5-21.2)	12.5 (0.5-22.2)	7.1 (3.0-11.2)	6.6 (3.0-14.0)
T_½ (day)	N/D	N/R	29.9 (8.0) ^c	N/R	46.5 (10.8) ^e	N/R

^a C_{min ss} = concentration measured at 672 hrs (28 days) post-injection

^b median (min-max)

^c n = 4

^d n = 6

N/D = Not Determined

N/R = Not Reported

Based upon data in NDA 202971 Clin Pharm Review, Tables 7, 8; P 20–21

Distribution

Dehydro-aripiprazole, circulates at a level about ~ 30% of the parent at steady state (oral tablet steady state: ~40%). Ratios of dehydro-aripiprazole to aripiprazole for mean C_{max} and AUC_{0-τ} (the Area Under the Curve from dose administration until the next dose, AKA dose interval AUC, equal to the amount of drug

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absorbed) after the fifth monthly injection of aripiprazole LAI in the range of 200–400 mg were 29.1–33.2%. This metabolite:parent ratio is comparable to the oral dosing ratio.

Protein binding is not reported for aripiprazole in the NDA, but DrugBank and NIH Daily Med report 99%, but do not provide a primary reference or which proteins are bound. Similarly, DrugBank reports a volume of distribution (Vd) of 4.9 L/kg.

DrugBank <<http://www.drugbank.ca/drugs/DB01238>>

NIH Daily Med <<http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=3650>>

Metabolism

Aripiprazole is extensively metabolized, primarily by CYP3A4 and CYP2D6. Dehydro-aripiprazole, circulates at a level about ~ 30% of the parent at steady state (oral tablet steady state: ~40%). Notably, the ratios of dehydro-aripiprazole to aripiprazole for mean C_{max} and AUC_{0-T} (the Area Under the Curve from dose administration until the next dose, AKA dose interval AUC, equal to the amount of drug absorbed) after the fifth monthly injection of aripiprazole LAI in the range of 200–400 mg were 29.1–33.2%. This metabolite:parent ratio is comparable to the oral dosing ratio.

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes.

Aripiprazole does not undergo direct glucuronidation.

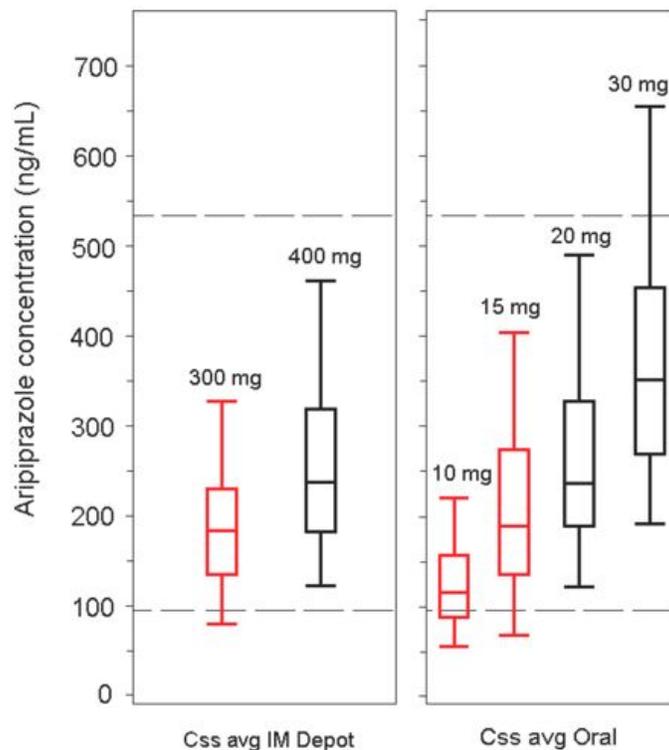
Elimination

The aripiprazole mean terminal elimination half-life was 29.9 days following every 300 mg injection given every 4-weeks and 46.5 days following every 400 mg injection given every 4-weeks.

Steady state concentrations were reached by the fourth dose (16 weeks) with no significant accumulation after additional doses. (Abilify Maintena Product Label §12.3; NDA 202971 Clin Pharm p6–7, 10)

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Illustration 3: Simulated Average Steady State Aripiprazole Concentrations for LAI (left) and Oral (right). The dashed lines represent the therapeutic window for aripiprazole.



NDA 202971 Clin Pharm Review p10

Special Populations

Pregnancy Category C: Risk Summary

Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including aripiprazole LAI) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1–10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m² body surface area.

Aripiprazole LAI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Adequate documentation and appropriate obstetrical consultation is essential. See *Unlabeled Indications* section of this monograph for documentation recommendations.

Nursing Mothers

Aripiprazole is excreted in human breast milk. A decision should be made with the mother and other involved parties whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the safety of the child.

Pediatric Use

Safety and effectiveness of aripiprazole LAI in people <18 years of age have not been evaluated.

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Geriatric Use

Safety and effectiveness of aripiprazole LAI in people >60 years of age have not been evaluated.

In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18–64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects.

No dosage adjustment of aripiprazole LAI is recommended for elderly.

Pharmacogenomic Considerations

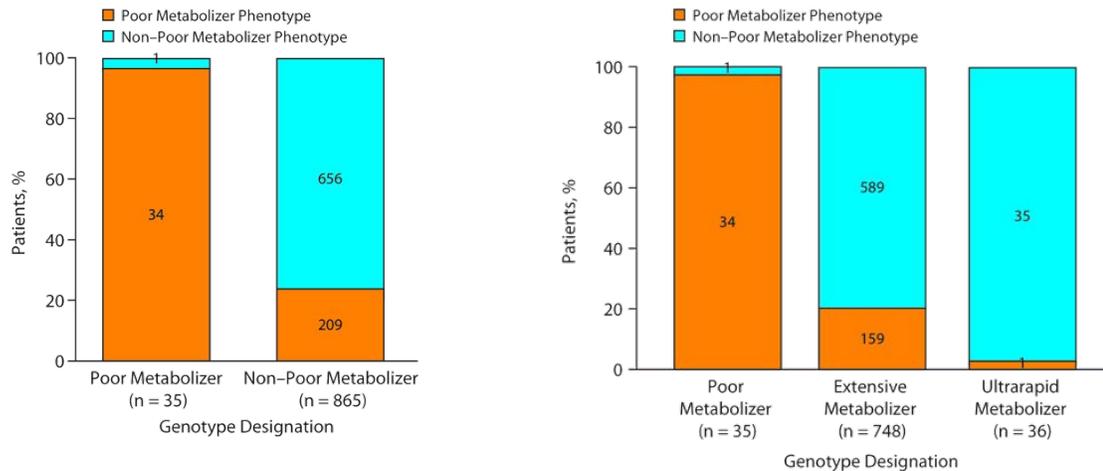
In the United States, ~8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). (Abilify Maintena Product Label §8.6) Normal metabolism is termed an extensive metabolizer (EM), and an intermediate metabolizer (IM) is between them. Some individuals are ultrarapid metabolizers (UM). Anyone with a history of unusual effects to low doses of several medications that are primarily metabolized by CYP2D6 *might* have a PM genotype.

Dosage adjustment is recommended in CYP2D6 PMs due to high aripiprazole concentrations. See [Drug Interactions](#) section of this monograph for details on dosage adjustment. There is no requirement for genomic studies prior to use of aripiprazole.

The presence of drug interactions can reduce metabolism by CYP2D6 from being a phenotypic EM to PM *without regard to their genotype*. Those patients with genomic IM or PM status are more easily phenoconverted to a more impaired phenotype. See Illustration 4. The patient's medication profile should be examined for potential CYP2D6 interactions for all medications, not necessarily aripiprazole, that are metabolized by this pathway. Preskorn SH, Kane CP, Lobello K, Nichols AI, Fayyad R, Buckley G, Kristen Focht K, Guico-Pabia CJ. Cytochrome P450 2D6 Phenoconversion Is Common in Patients Being Treated for Depression: Implications for Personalized Medicine. *J Clin Psychiatry* 2013;74(6):614–621. DOI:10.4088/JCP.12m07807.

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Illustration 4: CYP2D6 Genotypes and Phenotype Rates



Poor Metabolizer Phenotype Rates for Poor Metabolizer Versus Non-Poor Metabolizer Genotype Designations in Study Completers

Preskorn, et al.

Poor Metabolizer Phenotype Rates by Poor Metabolizer, Extensive Metabolizer, or Ultrarapid Metabolizer Genotype Designations in Study Completers (Does Not Include IMs)

Use for Unlabeled Indications

While use in patients for indications that are not approved by the US FDA is explicitly not prohibited, additional documentation is essential. (Expanded from Edersheim JG. Off-Label Prescribing. *Psychiatric Times*. 2009;26(4).)

<http://www.psychiatrictimes.com/display/article/10168/1401983?pageNumber=2&verify=0>

The following documentation elements are suggested:

- Identify the specific problem(s) that require intervention in this patient.
- Describe of all therapeutic intervention(s), including taking no action, that could be considered for these problem(s) and why they are not appropriate in this specific patient.
- State the scientific rationale for use of this medication and dose, in this patient, with explicit discussion of any possible warnings, precautions, drug interactions, adverse effects, and other considerations that pertain to this patient. Include any consultations or discussions with colleagues regarding this unlabeled indication.
- Describe when and how the patient (and caregiver) has been prospectively informed of this unlabeled use. If there are known or suspected risks associated with a particular unlabeled use, the patient (and caregiver) should be warned of this risk and instruct the patient (and caregiver) on how to recognize the symptoms and what to do if they are noticed. This should include instructions about whom to contact in the event the patient (and caregiver) believes that they might have an adverse effect or has any concerns about the medication. Responsible caregivers should be included if this patient is a minor, has a guardian, requires assistance, or when requested by the patient.
- State that patient (and caregiver) has had any questions answered, understands the risks and what to do if they have any concerns, and have agreed to the use of this medication.

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Administration Instructions (adapted from Abilify Maintena Product Label §2.4–2.9)

Preparation Prior to Reconstitution of the Lyophilized aripiprazole LAI Powder

- For deep intramuscular gluteal injection by healthcare professionals only.
- Do not administer by any other route.
- Inject immediately after reconstitution.
- Administer once monthly.

(a) Lay out and confirm that components listed below are provided in the kit:

- One vial of either 300 mg or 400 mg of aripiprazole LAI for extended-release injectable suspension lyophilized powder
- One 5 mL vial of Sterile Water for Injection, USP
- One 3 mL Luer Lock™ syringe with pre-attached 21 gauge, 1.5 inch (38 mm) Hypodermic Needle-Pro® safety needle with needle protection device
- One 3 mL Luer-Lok™ disposable syringe
- One vial adapter
- One 21 gauge, 1.5 inch (38 mm) Hypodermic Needle-Pro® safety needle with needle protection device for non-obese patients
- One 21 gauge, 2 inch (50 mm) Hypodermic Needle-Pro® safety needle with needle protection device for obese patients



(b) Aripiprazole LAI should be suspended using the Sterile Water for Injection as supplied in the kit.

(c) The Sterile Water for Injection and aripiprazole LAI vials are for *single-use only*.

(d) Use appropriate aseptic techniques throughout reconstitution and reconstitute at room temperature.

(e) Select the amount of Sterile Water for Injection needed for reconstitution

- 300 mg Aripiprazole Vial add 1.5 mL Sterile Water for Injection
- 400 mg Aripiprazole Vial add 1.9 mL Sterile Water for Injection

Important: The Sterile Water for Injection vial contains more volume (5 mL) than needed to reconstitute either size aripiprazole LAI for extended-release injectable suspension. *Discard the punctured Sterile Water for Injection vial after use.*

Reconstitution of the Lyophilized Powder

(a) Remove the cap of the vial of Sterile Water for Injection and remove the cap of the vial containing aripiprazole LAI lyophilized powder and wipe the tops with a sterile alcohol swab.

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(b) Using the syringe with pre-attached Hypodermic Needle-Pro needle, withdraw the pre-determined Sterile Water for Injection volume from the vial of Sterile Water for Injection into the syringe. Residual Sterile Water for Injection will remain in the vial following withdrawal; discard any unused portion.

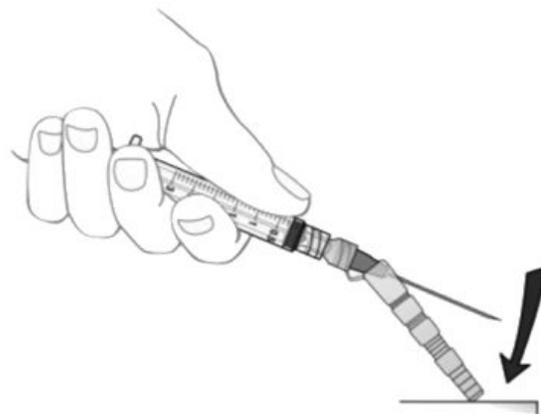


(c) Slowly inject the Sterile Water for Injection into the vial containing the aripiprazole LAI lyophilized powder (see Figure 2).



(d) Withdraw a volume of air (equal to the volume of Sterile Water for Injection that was added) to equalize the pressure in the vial by pulling back on the plunger. Subsequently, remove the needle from the vial.

Engage the needle safety device using one hand. Gently press the sheath against a flat surface until the needle is firmly engaged in the needle protection sheath. Visually confirm that the needle is fully engaged into the needle protection sheath, and discard.



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(e) Shake the vial vigorously for 30 seconds until the reconstituted suspension appears uniform.



(f) Visually inspect the reconstituted suspension for particulate matter and discoloration prior to administration. The reconstituted aripiprazole LAI should appear to be a uniform, homogeneous suspension that is opaque and milky-white in color.

(g) If the injection is not performed immediately after reconstitution keep the vial at room temperature and shake the vial vigorously for at least 60 seconds to re-suspend prior to injection.

(h) Do not store the reconstituted suspension in a syringe.

Preparation Prior to Injection

(a) Use appropriate aseptic techniques throughout injection of the reconstituted aripiprazole LAI suspension.

(b) Wipe the top of the vial of the reconstituted aripiprazole LAI suspension with a sterile alcohol swab.

(c) Remove the cover from the vial adapter package.
Do not remove the vial adapter from the package.



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(d) Using the vial adapter package to handle the vial adapter, attach the prepackaged Luer-Lok™ syringe to the vial adapter.



(e) Use the Luer-Lok™ syringe to remove the vial adapter from the package and discard the vial adapter package.

Do not touch the sterile spike tip of the adapter at any time.



(f) Determine the recommended volume for injection. See Table 4.

Both 300 and 400 mg vials contain a final reconstituted aripiprazole concentration of 200 mg/mL. Use the smallest single vial available to obtain the dose to be administered.

Table 4: Aripiprazole LAI Reconstituted Suspension Volume to Inject

Dose Administered (mg)	Injection Volume (mL)
400	2.0
300	1.5
200	1.0
160	0.8

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(g) Place and hold the vial of the reconstituted aripiprazole LAI suspension on a hard surface. Attach the adapter-syringe assembly to the vial by holding the outside of the adapter and pushing the adapter's spike firmly through the rubber stopper, until the adapter snaps in place.



(h) Slowly withdraw the recommended volume from the vial into the Luer-Lok™ syringe to allow for injection.

A small amount of excess product will remain in the vial.



Injection Procedure

(a) Detach the BD Luer-Lok syringe containing the recommended volume of reconstituted aripiprazole LAI suspension from the vial.

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(b) Select one of the following Hypodermic Needle-Pro needles and attach the needle to the Luer-Lok™ syringe containing the suspension for injection based upon the patient's Body Mass Index. See Table 5.

- **BMI ≤28 kg/m²**: 21 gauge, 1.5 inch (38 mm) Hypodermic Needle-Pro safety needle with needle protection device.
- **BMI >28 kg/m²**: 21 gauge, 2 inch (50 mm) Hypodermic Needle-Pro safety needle with needle protection device.



Ensure the needle is firmly seated on the Needle-Pro safety device with a push and clockwise twist and then pull the needle cap straight away from the needle.

Table 5: Body Mass Index in Customary Units

		Height (inches)								
		58	60	62	64	66	68	70	72	74
Weight (pounds)	80	16.8	15.7	14.7	13.8	12.9	12.2	11.5	10.9	10.3
	90	18.8	17.6	16.5	15.5	14.6	13.7	12.9	12.2	11.6
	100	20.9	19.6	18.3	17.2	16.2	15.2	14.4	13.6	12.9
	110	23.0	21.5	20.2	18.9	17.8	16.8	15.8	14.9	14.2
	120	25.1	23.5	22.0	20.6	19.4	18.3	17.3	16.3	15.4
	130	27.2	25.4	23.8	22.4	21.0	19.8	18.7	17.7	16.7
	140	29.3	27.4	25.7	24.1	22.6	21.3	20.1	19.0	18.0
	150	31.4	29.4	27.5	25.8	24.3	22.9	21.6	20.4	19.3
	160	33.5	31.3	29.3	27.5	25.9	24.4	23.0	21.7	20.6
	170	35.6	33.3	31.2	29.2	27.5	25.9	24.4	23.1	21.9
	180	37.7	35.2	33.0	31.0	29.1	27.4	25.9	24.5	23.2
	190	39.8	37.2	34.8	32.7	30.7	28.9	27.3	25.8	24.4
	200	41.9	39.1	36.7	34.4	32.3	30.5	28.8	27.2	25.7
	210	44.0	41.1	38.5	36.1	34.0	32.0	30.2	28.5	27.0
	220	46.1	43.1	40.3	37.8	35.6	33.5	31.6	29.9	28.3
230	48.2	45.0	42.2	39.6	37.2	35.0	33.1	31.3	29.6	
240	50.3	47.0	44.0	41.3	38.8	36.6	34.5	32.6	30.9	
250	52.4	48.9	45.8	43.0	40.4	38.1	35.9	34.0	32.2	

BMI ≤28 kg/m² (orange region): 21 gauge, 1.5 inch (38 mm) Hypodermic Needle-Pro safety needle with needle protection device.

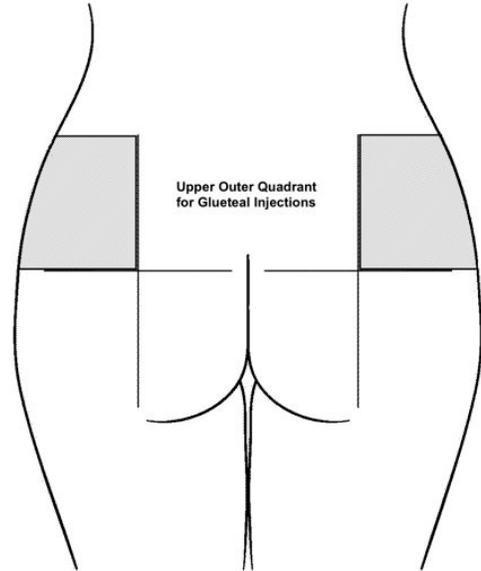
BMI >28 kg/ m² (blue region): 21 gauge, 2 inch (50 mm) Hypodermic Needle-Pro safety needle with needle protection device.

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(c) After the needle is fully inserted into the upper outer quadrant of the patient's gluteal muscle and prior to injecting, slightly pull back on the plunger to insure that the needle is not in a blood vessel.

Slowly inject the recommended volume as a single intramuscular injection into the gluteal muscle. Wait a few seconds after the injection is completed, then withdraw the needle.

- Do not massage the injection site.
- Do not administer intravenously or subcutaneously.

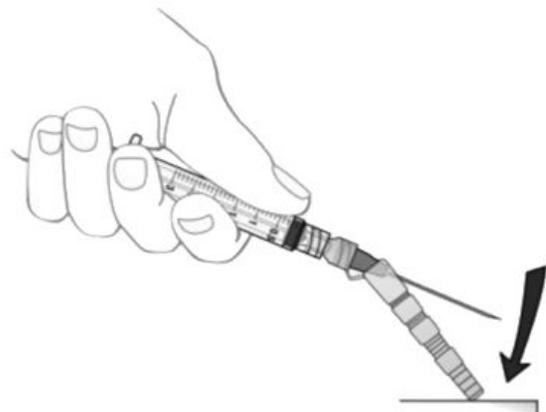


Procedures After Injection

(a) Engage the needle safety device using one hand. Gently press the sheath against a flat surface until the needle is firmly engaged in the needle protection sheath. Visually confirm that the needle is fully engaged into the needle protection sheath, and discard.

Dispose of the vials, adapter, needles, and syringe appropriately after injection.

The Sterile Water for Injection and aripiprazole LAI vials are for single-use only.



(b) Rotate subsequent injections between the left and right gluteal muscles or by patient preference. Documentation of injection should include site of injection.

Different Aripiprazole Injection Formulations

Important: There are two aripiprazole formulations for intramuscular use with different dosages, dosing frequencies, indications, and appearance.

Aripiprazole LAI is a long-acting aripiprazole formulation (300 mg or 400 mg per vial) with 4 week dosing intervals indicated for the treatment of schizophrenia. In contrast, aripiprazole injection (9.75 mg per vial) is a short-acting formulation indicated for agitation in patients with schizophrenia or mania.

Do not substitute these products.

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Clinical Trials Program

The New Drug Application (NDA) was submitted to the FDA on 09-26-2011. The cutoff date for safety data in that original submission was 01-07-2011. The 120-Day Safety Update was submitted on 01-23-2012, with a cutoff date of 08-15-2011. See Table 6.

A total of 287 studies that were indexed under aripiprazole are currently registered in NIH's *ClinicalTrials.gov* service as of 06-29-2013. To obtain the current listing, see <<http://clinicaltrials.gov/ct2/results?term=aripiprazole>>.

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Table 6: Aripiprazole LAI Development Program

Study Phase	Study Number	Study Description	Number of Subjects
Phase 1 Clinical Pharmacology Trials These three trials were conducted in patients with schizophrenia or schizoaffective disorder. All were complete as of the safety cutoff date for the original application submission.	CN138-020	<i>In vivo</i> release characteristics of single dose aripiprazole IM depot (15, 50, 100, 200, 300, and 400 mg).	20
	31-07-002	Single dose PK and tolerability (100, 200, 300, and 400mg).	26
	31-05-244	Multiple dose PK & tolerability (200, 300, and 400 mg q4 weeks for 5 months)	39
Controlled Phase 3 Trials Trial 31-07-246 was complete as of the cutoff date for the original application submission. The other two trials were ongoing and blinded as of the cutoff date for the 120-Day Safety Update.	31-07-246	Stabilization of schizophrenic patients on aripiprazole LAI for 12 weeks followed by 2:1 randomization to aripiprazole LAI (300 or 400 mg q4 weeks) or placebo for 52 weeks. This is the pivotal efficacy study for this NDA.	576
	31-07-247	Stabilization of schizophrenic patients on oral aripiprazole followed by 2:2:1 randomization to 38 weeks of aripiprazole LAI 300 or 400 mg q4 weeks, aripiprazole LAI 50 or 25 mg q4 weeks, or oral aripiprazole (10–20 mg/day) to demonstrate non-inferiority of aripiprazole LAI versus oral aripiprazole as maintenance treatment. Estimated blinded enrollment of 1224. Estimated last patient, last visit 07-2013.	Ongoing
	31-08-003	Stabilization of schizophrenic patients on oral aripiprazole followed by 1:1 randomization to 26 weeks of aripiprazole LAI (300 or 400mg q4 weeks) or oral aripiprazole (6–24 mg/day) to demonstrate non-inferiority of aripiprazole LAI versus oral aripiprazole as maintenance treatment.	Ongoing
Open-label uncontrolled trials Studies 31-08-248 and 31-10-270 were ongoing as of the cutoff date for the 120-Day Safety Update	31-08-248	52-week open-label study enrolling <i>de novo</i> patients and rollover patients from 31-07-246 or 31-07-247	928
	31-10-270	Open-label extension study for patients who completed 31-08-248.	148
	31-10-002	Open-label, multiple dose clinical pharmacology trial in Japan to evaluate the pharmacokinetics and safety of aripiprazole IM depot 300 and 400mg IM monthly in patients with schizophrenia.	Not Reported
	31-11-283	Open-label study in the U.S. to assess inpatient psychiatric hospitalization rates in patients receiving standard oral antipsychotic treatment for 6 months (historically) versus rates in patients after switching to once monthly aripiprazole IM depot injections for 6 months (prospectively). Patients completing this study could enter an open-label extension trial.	Not Reported
Total Subjects	All Completed Studies		1190
	Multiple Dose Completed Studies		1144
	Phase 3 Completed Studies		1105
	Completed Studies of 300–400 mg Doses		1153
Based upon data in NDA 202971 Medical Review, §5, Table 1, p12-13			

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Pivotal Efficacy Study (OPDC 31-07-246) Information Sources:

Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, McQuade RD, Carson WH, and Fleischhacker WW. Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients With Schizophrenia: A 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. *J Clin Psychiatry*. 2012;73(5):617–624.

DOI: 10.4088/JCP.11m07530. PMID: 22697189 <<http://www.ncbi.nlm.nih.gov/pubmed/22697189>>

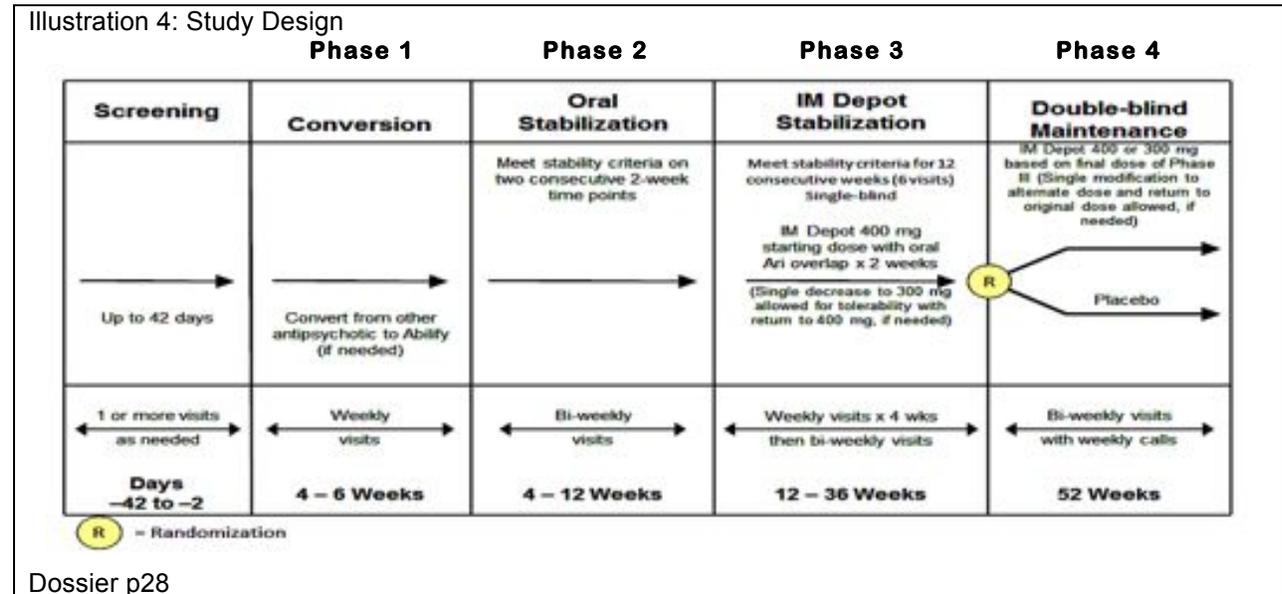
ClinicalTrials.gov identifier: NCT00705783 <<http://clinicaltrials.gov/ct2/show/study/NCT00705783>>

Drugs @ FDA: Approval History, Letters, Reviews, and Related Documents for NDA 202971 <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist>

Otsuka America Pharmaceutical and Lundbeck: *Dossier on Submission of Clinical and Economic Data Supporting Formulary Consideration of Abilify Maintena™* (Available upon request: 800-441-6763)

Objective:

To evaluate the efficacy and tolerability of a once-monthly intramuscular (IM) depot formulation of the dopamine partial agonist aripiprazole as maintenance treatment in adults meeting *DSM-IV-TR* schizophrenia criteria.



Dossier p28

Method:

The pivotal maintenance study was conducted from July 2008 until February 2011. See Illustration 4.

Subjects requiring chronic treatment with an antipsychotic entered a 4- to 12-week oral stabilization phase and received oral aripiprazole (10–30 mg/d).

Subjects meeting stability criteria (Table 7) for 4 weeks entered an aripiprazole LAI stabilization phase in which they received 400 mg aripiprazole LAI injections every 4 weeks (with a single decrease to 300 mg permitted for tolerability and a single increase to 400 mg for efficacy) with co-administration of oral aripiprazole tablets in the first 2 weeks.

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Table 7: Stability Criteria *

- Outpatient status
- Positive and Negative Syndrome Scale (PANSS) total score ≤ 80
- Lack of specific psychotic symptoms on the PANSS, as measured by a score of ≤ 4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content
- Clinical Global Impressions-Severity of Illness (CGI-S) score ≤ 4 (moderately ill)
- Clinical Global Impression for Severity of Suicidality (CGI-SS) score ≤ 2 (mildly suicidal) on part 1 and ≤ 5 (minimally worsened) on part 2

All are required to meet stability criteria
Kane, *et al.*

Subjects meeting stability criteria for 12 consecutive weeks were randomly assigned (2:1) to aripiprazole LAI or placebo during a 52-week, double-blind maintenance phase.

The primary outcome measure was *time to exacerbation* of psychotic symptoms/impending relapse (event). See Table 8.

Table 8: Criteria for Exacerbation of Psychotic Symptoms or Impending Relapse *

Category	Operational Definition
Clinical Worsening	CGI-Improvement score of ≥ 5 and an increase on any of 4 individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content) to a score > 4 with an absolute increase of ≥ 2 on that specific item since randomization or an increase > 4 on these PANSS items and an absolute increase of ≥ 4 on the combined score of these items since randomization
Hospitalization	Due to worsening of psychotic symptoms
Risk of Suicide	CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on part 1 or a score of 6 (much worse) or 7 (very much worse) on part 2
Violent Behavior	Resulting in clinically significant self-injury, injury to another person, or property damage

* Any one or all are sufficient for meeting the primary outcome event criteria
Kane, *et al.*

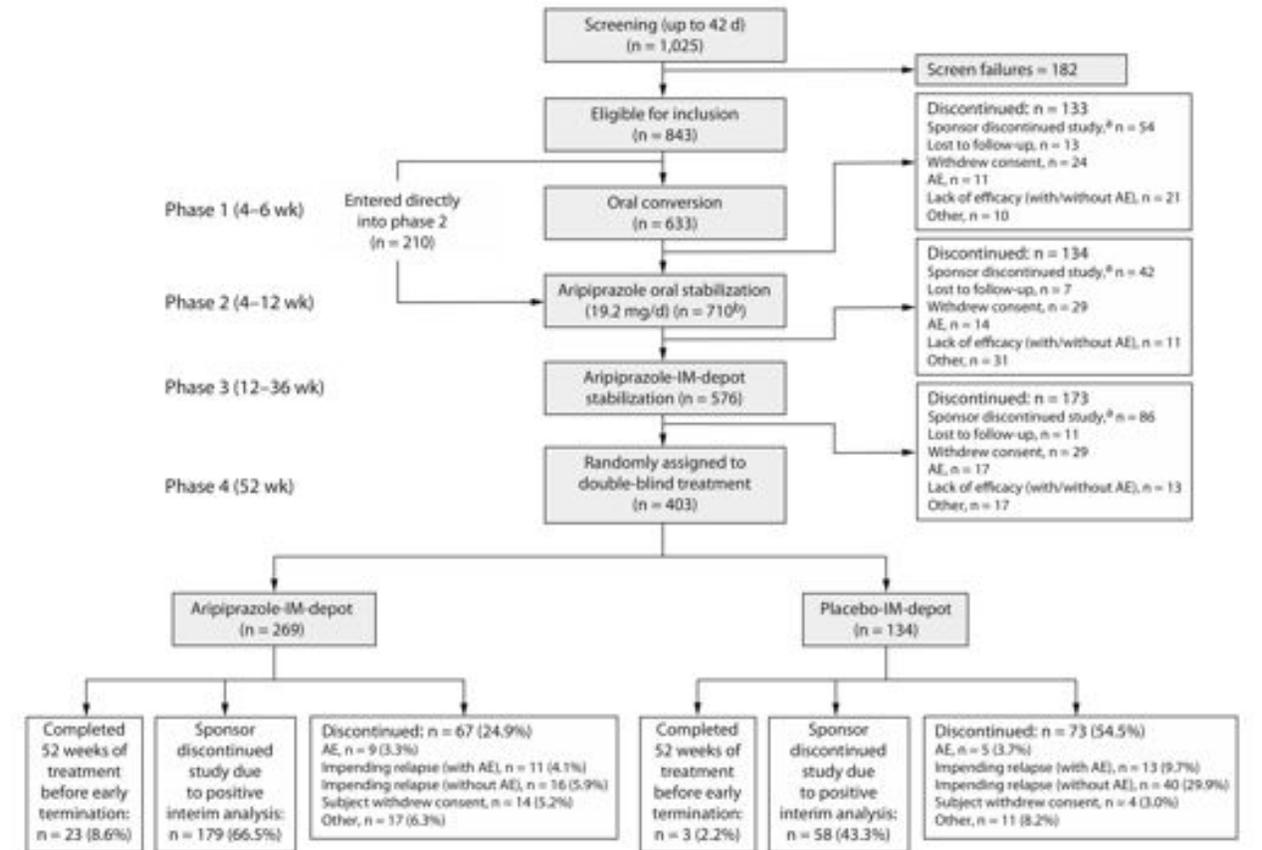
Safety and tolerability were also assessed.

Results:

710 patients entered oral stabilization, 576 progressed to IM-depot stabilization, and 403 were randomly assigned to double-blind treatment. The study was terminated early on 07-26-2010 because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 events). Last patient was discontinued on 08-24-2010. All discontinued patients were given the option to enroll in open label extension trial 31-08-248. See Illustration 5. Dosing, duration, and sample size during Stabilization Phase 3 is shown in Illustration 6. Similarly, Illustration 7 shown Double Blind Phase 4 dosing, duration, and sample size.

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Illustration 5: Patient Disposition Throughout the Study, Enrolled Sample



^a Sponsor discontinued study early as efficacy was demonstrated in the preplanned interim analysis.

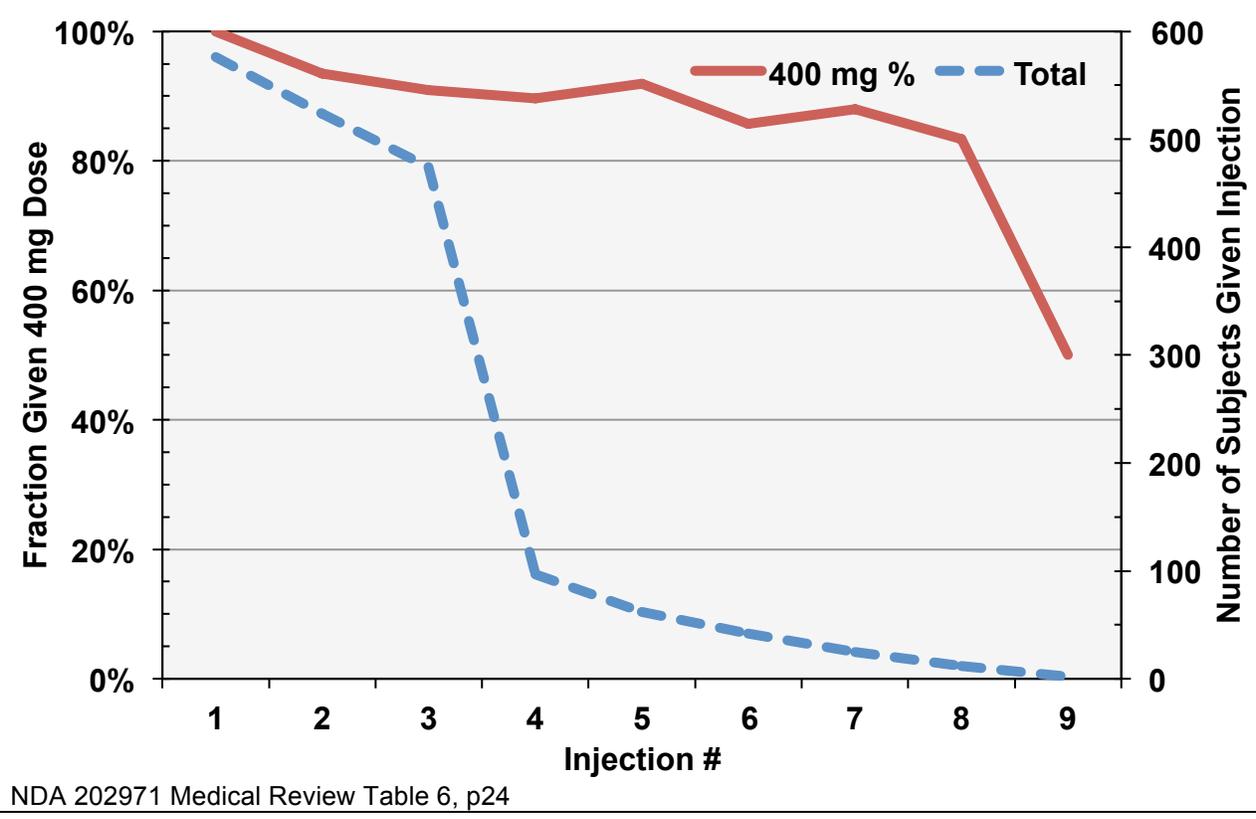
^b Includes one patient who was enrolled, but did not take aripiprazole.

Abbreviations: AE = adverse event, IM = intramuscular.

Source: Kane, *et al.* p620

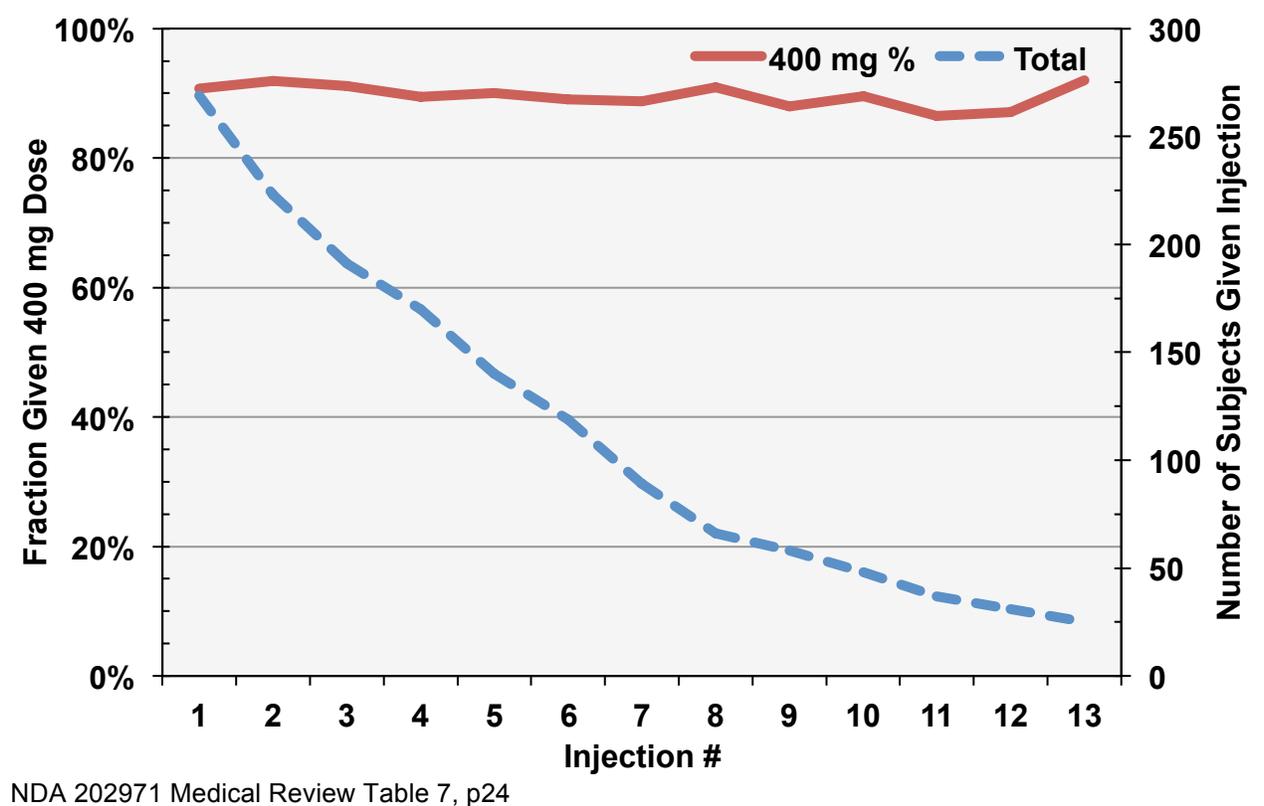
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Illustration 6: Stabilization Phase 3 Dosing and Sample Size



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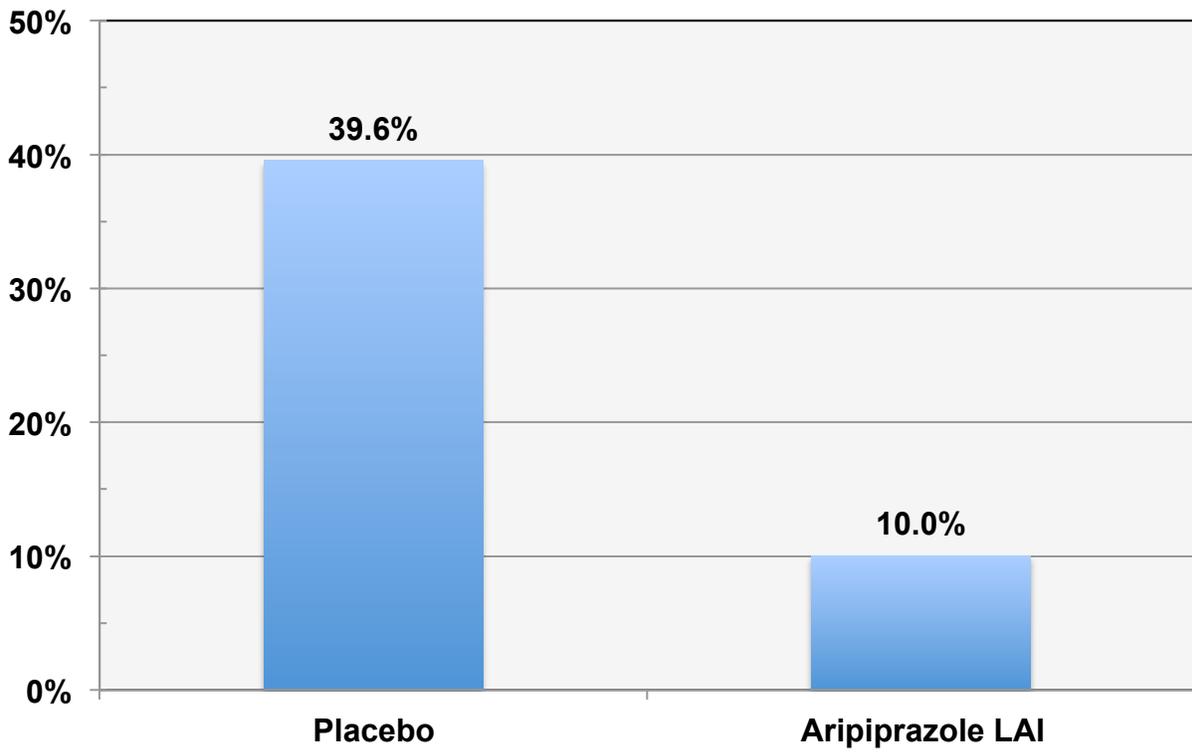
Illustration 7: Double Blind Phase 4 Dosing and Sample Size



Time to impending relapse was significantly delayed with aripiprazole-IM-depot treatment compared with placebo in both the interim analysis and the final analysis (NNTB = 3.38, $P < 0.0001$, log-rank test). See Illustration 8. The hazard ratio (placebo/aripiprazole-IM-depot) at final analysis was 5.03 (95% CI, 3.15–8.02). See Illustrations 9 and 10.

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Illustration 8: Impending Relapse Comparison



NDA 202971 Medical Review, Table 8, p25

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Illustration 9: Hazard Ratio Comparison

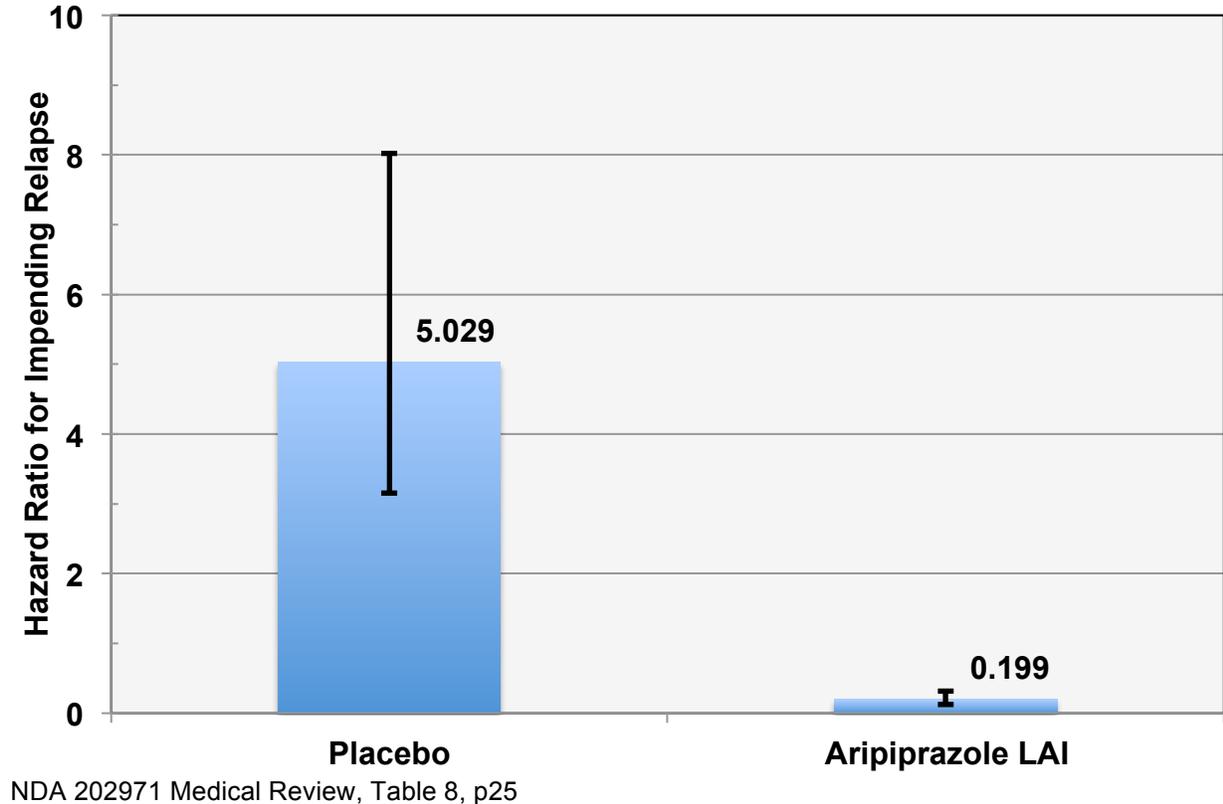
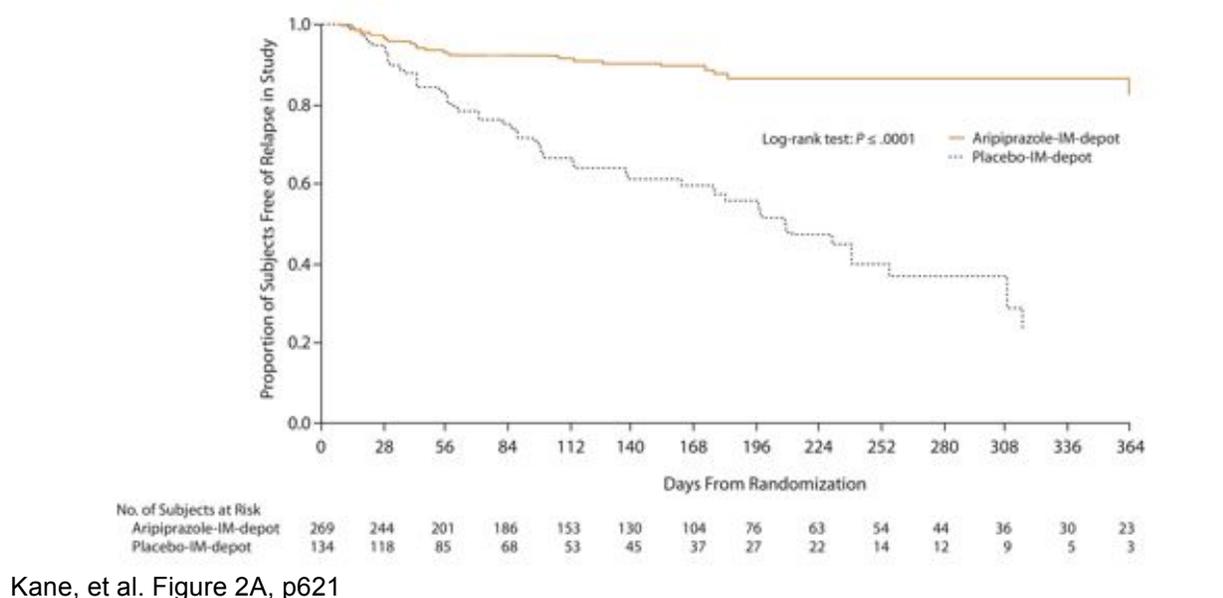


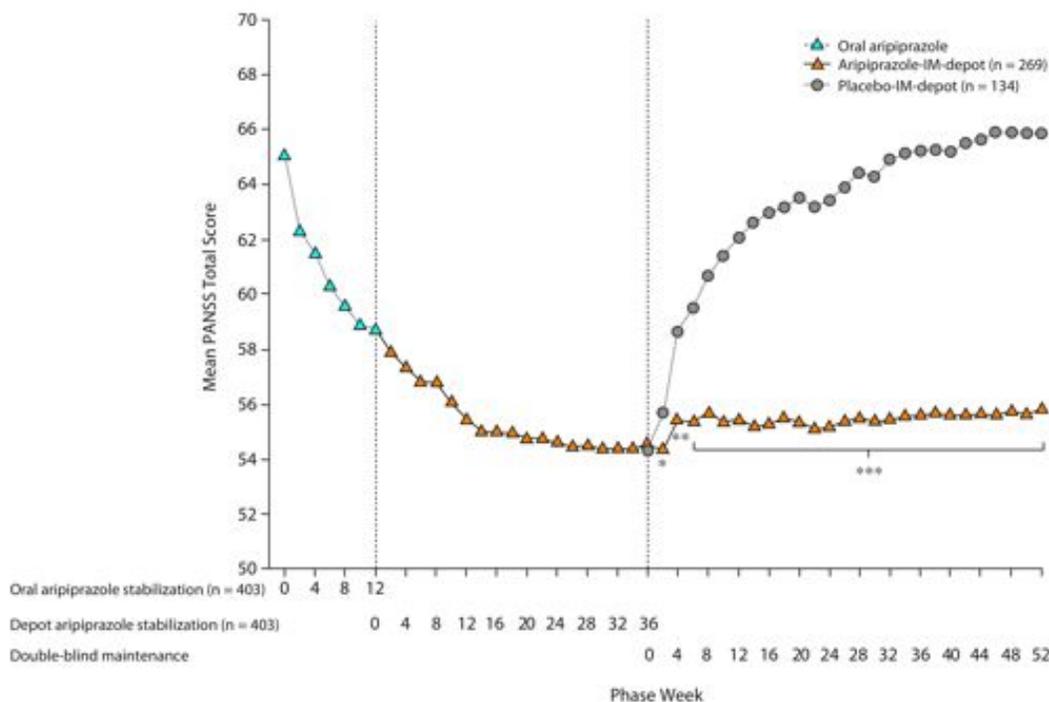
Illustration 10: Time From Randomization to Impending Relapse During Double-Blind Treatment



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The rate of impending relapse was significantly lower with aripiprazole-IM-depot than placebo at endpoint (final analysis, 10.0% [n = 27/269] vs 39.6% [n = 53/134]). Improvements in Clinical Global Impressions-Severity of Illness scale and Positive and Negative Syndrome Scale (PANSS) total scores were maintained with aripiprazole-IM-depot treatment but showed significant worsening with placebo (change from double-blind baseline, $P < 0.0001$ for aripiprazole-IM-depot vs placebo). See Illustration 11.

Illustration 11: PANSS Total Scores (LOCF) Over the Course of Treatment (Phase 4 Efficacy Sample)



Kane, *et al.* Figure 3, p622

Warnings and Precautions (Abilify Maintena Product Label §5)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. aripiprazole LAI is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, in oral aripiprazole-treated patients (mean age: 84 years; range: 78-

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88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with oral aripiprazole. Aripiprazole LAI is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole LAI. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, aripiprazole LAI should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with aripiprazole LAI drug discontinuation should be considered. However, some patients may require treatment with aripiprazole LAI despite the presence of the syndrome.

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Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving aripiprazole LAI as well.

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes), who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 9 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 9: Glucose Category Change

Category Change	Aripiprazole (%)	Placebo (%)	NNTH
Normal → High	31/822 (3.8)	22/605 (3.6)	741
Borderline → High	31/176 (17.6)	13/142 (9.2)	12

At least once compared to Baseline
Normal = Fasting Glucose <100 mg/dL
Borderline = Fasting Glucose ≥100–<126 mg/dL
Normal = Fasting Glucose ≥126 mg/dL
NNTH = Number Needed to Treat to Harm. This represents the number of patients that would need to be treated with Aripiprazole LAI or Placebo to see one more adverse event. (Negative values mean that Placebo group had higher rate of AEs)
(Abilify Maintena Product Label Table 4)

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

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There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Table 10 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21–25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39–45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40–42 days).

<i>Table 10: Lipid Category Changes</i>			
Category Change	Aripiprazole (%)	Placebo (%)	NNTH
Total Cholesterol Normal (<200 mg/dL) → High (≥240 mg/dL)	34/1357 (2.5)	27/973 (2.8)	-372
Fasting Triglycerides Normal (<150 mg/dL) → High (≥200 mg/dL)	40/539 (7.4)	30/431 (7.0)	218
Fasting LDL Cholesterol Normal (<100 mg/dL) → High (≥160 mg/dL)	2/332 (0.6)	2/268 (0.7)	-696
HDL Cholesterol Normal (≥40 mg/dL) → Low (<40 mg/dL)	121/1066 (11.4)	99/794 (12.5)	-90

At least once compared to Baseline
 NNTH = Number Needed to Treat to Harm. This represents the number of patients that would need to be treated with Aripiprazole LAI or Placebo to see one more adverse event. (Negative values mean that Placebo group had higher rate of AEs)
 (Abilify Maintena Product Label Table 5)

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to -0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was -1.5 kg (n=73) compared to -0.2 kg (n=46) in placebo-treated patients.

Table 11 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

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Table 11: Weight Changes

Weight Gain ≥7%*	Aripiprazole (%)	Placebo (%)	NNTH
Schizophrenia ^a	69/852 (8.1)	12/379 (3.2)	21
Bipolar Mania ^b	16/719 (2.2)	16/598 (2.7)	-223

From Baseline
^a 4–6 weeks duration
^b 3 weeks duration
 NNTH = Number Needed to Treat to Harm. This represents the number of patients that would need to be treated with Aripiprazole LAI or Placebo to see one more adverse event. (Negative values mean that Placebo group had higher rate of AEs)
 (Based on Abilify Maintena Product Label Table 6)

Orthostatic Hypotension

Aripiprazole may cause orthostatic hypotension. This is routinely attributed to α_1 -adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with aripiprazole LAI during the stabilization phase, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥ 20 mmHg accompanied by an increase in heart rate ≥ 25 /min when comparing standing to supine values) was 0.2% (1/575).

Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including oral aripiprazole. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of aripiprazole LAI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue aripiprazole LAI in patients with severe neutropenia (absolute neutrophil count $< 1000/\text{mm}^3$) and follow their WBC counts until recovery.

Seizures

As with other antipsychotic drugs, use aripiprazole LAI cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

Aripiprazole LAI, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole LAI does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole LAI for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

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Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole LAI. Aripiprazole LAI and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Adverse Effects

The most common treatment-emergent adverse events in the clinical trial of aripiprazole LAI (occurring in ≥5% of aripiprazole-IM-depot subjects and greater than placebo) were insomnia, tremor, and headache. See Table 12.

Table 12: Treatment-Emergent Adverse Events Occurring in > 5% of Patients Receiving Aripiprazole LAI During Any Phase, Treatment Phase Safety Sample

Adverse Event	Phase 3 (Stabilization)	Phase 4 (Double-blind Treatment)		
	Aripiprazole LAI (n=576)	Aripiprazole LAI (n=269)	Placebo (n=134)	NNTH
	n (%)	n (%)	n (%)	
Any AE	345 (59.9)	170 (63.2)	83 (61.9)	77
Akathisia	36 (6.3)	15 (5.6)	8 (6.0)	-250
Anxiety	38 (6.6)	16 (5.9)	10 (7.5)	-62.5
Headache	34 (5.9)	16 (5.9)	7 (5.2)	143
Injection-site Pain	34 (5.9)	8 (3.0)	5 (3.7)	-143
Insomnia	46 (8.0)	27 (10.0)	12 (9.0)	100
Tremor	21 (3.6)	16 (5.9)	2 (1.5)	23
Weight Increased	40 (6.9)	26 (9.7)	13 (9.7)	-2773

NNTH = Number Needed to Treat to Harm. This represents the number of patients that would need to be treated with Aripiprazole LAI or Placebo to see one more adverse event. (Negative values mean that Placebo group had higher rate of AEs)

Based on Kane, et al. Table 3, p622 and NDA 202971 Medical Review §7.4.1, p48

The adverse effects in the product label (Table 13) are from oral aripiprazole short term studies. The NDA explains this with a comment by the FDA’s reviewer, closely paraphrased below.

Generally, this section of labeling is based on safety data from one or more randomized, placebo-controlled, parallel group trials in drug-naïve patients. Such trials have not been conducted with aripiprazole LAI, in large part because treatment with LAI mandates previous exposure to the oral formulation. Nonetheless, with the exception of injection site reactions, it is expected that the nature, frequency, and severity of adverse events associated with aripiprazole LAI will be very similar to those observed with oral aripiprazole. Therefore, this section of labeling be based on the adverse reaction information contained in Abilify tablet labeling. (NDA 202971 Medical Review §9.2, p48).

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Table 13: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients with Any Indication Treated with Oral Aripiprazole

System Organ Class Preferred Term	Oral Aripiprazole (n=1843)	Placebo (n=1166)	NNTH
Eye Disorders			
Blurred Vision	3	1	50
Gastrointestinal Disorders			
Nausea	15	11	25
Constipation	11	7	25
Vomiting	11	6	20
Dyspepsia	9	7	50
Dry Mouth	5	4	100
Toothache	4	3	100
Abdominal Discomfort	3	2	100
Stomach Discomfort	3	2	100
General Disorders and Administration Site Conditions			
Fatigue	6	4	50
Pain	3	2	100
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal Stiffness	4	3	100
Pain in Extremity	4	2	50
Myalgia	2	1	100
Muscle Spasms	2	1	100
Nervous System Disorders			
Headache	27	23	25
Dizziness	10	7	33
Akathisia	10	4	17
Sedation	7	4	33
Extrapyramidal Disorder	5	3	50
Tremor	5	3	50
Somnolence	5	3	50
Psychiatric Disorders			
Agitation	19	17	50
Insomnia	18	13	20
Anxiety	17	13	25
Restlessness	5	3	50
Respiratory, Thoracic, and Mediastinal Disorders			
Pharyngolaryngeal Pain	3	2	100
Cough	3	2	100

NNTH = Number Needed to Treat to Harm. This represents the number of patients that would need to be treated with Aripiprazole Oral or Placebo to see one more adverse event.

Data from Abilify Maintena Product Label, Table 7.

Common Drug-related Adverse Effects

The only common drug-related adverse effects (those with an incidence $\geq 5\%$ in any dose group and $\geq 2 \times$ placebo) based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day was akathisia (aripiprazole 8%; placebo 4%; NNTH 25). Note that this differs slightly from the data presented in Table 12 as that is based on a different group that included manic patients as well.

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Discontinuation for Adverse Effects

This is usually a very informative area to measure the severity of adverse effects, but the design of the aripiprazole LAI relapse prevention study prevented inclusion of aripiprazole naive subjects. Therefore, patients that may have had a lack of tolerability to aripiprazole were not included in the Double Blind Phase 4. The dropout rate by study phase is shown in Table 14.

Table 14: Discontinuation Due to Adverse Events by Study Phase

Phase	Description	Discontinuations
1	Conversion to Oral Aripiprazole	11/633 (1.7%)
2	Aripiprazole oral stabilization	14/710 (2.0%)
3	Aripiprazole LAI Stabilization	17/576 (3.0%)
4	Double Blind	9/269 (3.3%)

Data from Kane, Figure 1, p620.

Open-label Aripiprazole LAI Stabilization Phase 3

The dropouts were from adverse effects that suggested a lack of efficacy in 15/576 (2.6%), akathisia in 2/576 (0.3%) and a scattering of other single events (dry mouth, chest pain, injection site pain, irritability, hyperkalemia, ovarian cancer, dyskinesia, somnolence, insomnia, schizoaffective disorder, and allergic dermatitis) for a total of 28/576 (4.9%). (NDA 202971 Medical Review, p 34–35.)

Double-Blind Aripiprazole LAI Maintenance Phase 4

Aripiprazole LAI treated patients had 19/269 (7.1%) drop out due to treatment-emergent adverse events compared to 18/134 (13.4%) that dropped out in the Placebo group (NNTH = -16). The adverse events leading to dropping out were again most commonly related to a lack of efficacy. The aripiprazole LAI group 9/269 (3.3%) had compared to the Placebo group 14/134 (10.4%) (NNTH = -15). Table 15 displays the frequency of dropout due to adverse experiences by MedDRA preferred term and treatment group. (NDA 202971 Medical Review, p 35.)

Table 15: Incidence of Adverse Events Leading To Discontinuation in Double-Blind Maintenance Phase 4

MedDRA Preferred Term	Aripiprazole IM (N=269) n(%)	Placebo IM (N=134) n(%)
Psychotic disorder	7 (2.6)	8 (6.0)
Schizophrenia	2 (0.7)	5 (3.7)
Suicidal ideation	2 (0.7)	0 (0.0)

NDA 202971 Medical Review, p 35.

Injection Site Reactions

Injection site assessments included both subject pain ratings and investigator ratings of pain (Table 16), redness (Table 17), swelling (Table 18), and induration (Table 19) at the injection site. The subjects were given a visual analog scale (VAS) to rate their subjective pain, where 0 mm = no pain and 100 mm = unbearable pain. The investigators used a four-point scale (ranging from absent to severe). Ratings were done within 30 minutes before injection that were a follow-up of the previous injection site and one hour after the current injection was given.

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Table 16: Injection Site Pain Ratings in Aripiprazole LAI Stabilization Phase 3 (Safety Sample)

Assessment	Injection #1		Injection #2		Last Injection
	Current	Follow-up	Current	Follow-up	
VAS N (mm)	568 (6.1)	518 (1.1)	517 (4.7)	471 (1.1)	571 (4.9)
Absent N (%)	419/568 (73.8%)	515/518 (99.4%)	382/514 (74.3%)	463/469 (98.7%)	436/570 (76.5%)
Mild N (%)	140/568 (24.6%)	3/518 (0.6%)	126/514 (24.5%)	4/469 (0.8%)	120/570 (21.0%)
Moderate N (%)	9/568 (1.6%)	0/518 (0%)	6/514 (1.2%)	1/469 (0.2%)	13/570 (2.3%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	1/469 (0.2%)	1/570 (0.2%)

NDA 202971 Medical Review Table 15, 16, p37–38

Table 17: Injection Site Swelling Ratings in Aripiprazole LAI Stabilization Phase 3 (Safety Sample)

Assessment	Injection #1		Injection #2		Last Injection
	Current	Follow-up	Current	Follow-up	
Absent N (%)	536/568 (94.4%)	518/518 (100%)	493/514 (95.9%)	468/469 (99.8%)	543/570 (95.3%)
Mild N (%)	32/568 (5.6%)	0/518 (0%)	20/514 (3.9%)	1/469 (0.2%)	25/570 (4.4%)
Moderate N (%)	0/568 (0%)	0/518 (0%)	1/514 (0.2%)	0/469 (0%)	2/570 (0.4%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	1/570 (0.2%)

NDA 202971 Medical Review Table 15, 16, p37–38

Table 18: Injection Site Redness Ratings in Aripiprazole LAI Stabilization Phase 3 (Safety Sample)

Assessment	Injection #1		Injection #2		Last Injection
	Current	Follow-up	Current	Follow-up	
Absent N (%)	506/568 (89.1%)	516/518 (99.6%)	469/514 (91.2%)	469/469 (100%)	518/570 (90.9%)
Mild N (%)	61/568 (10.7%)	2/518 (0.4%)	45/514 (8.8%)	0/469 (0%)	52/570 (9.1%)
Moderate N (%)	1/568 (0.2%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)

NDA 202971 Medical Review Table 15, 16, p37–38

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Table 19: Injection Site Induration Ratings in Aripiprazole LAI Stabilization Phase 3 (Safety Sample)

Assessment	Injection #1		Injection #2		Last Injection
	Current	Follow-up	Current	Follow-up	
Absent N (%)	544/568 (95.8%)	515/518 (99.4%)	493/514 (95.9%)	466/469 (99.4%)	549/570 (96.3%)
Mild N (%)	24/568 (4.2%)	3/518 (0.6%)	21/514 (4.1%)	3/469 (0.6%)	21/570 (3.7%)
Moderate N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)

NDA 202971 Medical Review Table 15, 16, p37–38

Monitoring: Laboratory Tests

According to the FDA-approved prescribing information, no specific laboratory tests are recommended.

Routine Monitoring Requirements

Independent on the specific medication selected, patients who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. The updated national consensus recommendations for routine monitoring of body weight and body mass index (BMI), waist circumference, blood pressure, glucose levels, and lipid levels for all patients receiving second-generation antipsychotics should be followed. See updated Table 20 reproduced below. (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27(2):2004 [Full Text <<http://care.diabetesjournals.org/content/27/2/596.full.pdf>>]).

Table 20: Routine Monitoring for Antipsychotics

Parameter	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually
Personal / family history	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X			X		
Blood pressure	X			X		X
Fasting plasma glucose	X			X		X
Fasting lipid profile	X			X		X

It is important to note that Table 20 reflects a change in the interval for fasting lipid profile from the APA/ADA 2004 recommendations. The original guidelines suggest a five-year interval that is based upon a recommendation in ATP III in the *absence of any risk factors*. Being on an antipsychotic is itself a risk factor and therefore the maximum repeat interval should be one year. (for updated schizophrenia guideline recommendations, see Stephen M. Stahl, Debbi A. Morrissette, Leslie Citrome, Stephen R. Saklad, Michael A. Cummings, Jonathan M. Meyer, Jennifer A. O'Day, Laura J. Dardashti and Katherine

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D. Warburton. “Meta-guidelines” for the management of patients with schizophrenia. *CNS Spectrums*, Available on CJO 2013 doi:10.1017/S109285291300014X.
[http://journals.cambridge.org/abstract_S109285291300014X.](http://journals.cambridge.org/abstract_S109285291300014X))

Drug Interactions

Aripiprazole is extensively metabolized by CYP2D6 and CYP3A4. After extensive population modeling, the dose adjustments shown in Table 21 are recommended.

Table 21: Dose Adjustments for CYP2D6 Poor Metabolizers and Patients Taking Concomitant Interacting Medications for Over 14 Days

Aripiprazole LAI Regimen	CYP2D6 PM	CYP2D6	CYP3A4	Adjusted Dose
New Start	Yes	—	—	300 mg
	Yes	—	Inhibitor	200 mg
400 mg	No	Strong Inhibitor	—	300 mg
	No	—	Strong Inhibitor	300 mg
	No	Inhibitor	Inhibitor	200 mg
	No	—	Inducer	Avoid use
300 mg	No	Strong Inhibitor	—	200 mg
	No	—	Strong Inhibitor	200 mg
	No	Inhibitor	Inhibitor	160 mg
	No	—	Inducer	Avoid use

CYP2D6 PM = Poor Metabolizer

Adapted from Abilify Maintena Product Label, Table 1

Late or Missed Doses

Based on the pharmacokinetic model, Table 22 will provide therapeutic concentrations to compensate for the late or dose.

Table 22: Late or Missed Dose Adjustments

Dose Missed	Weeks Since Last Injection	Oral Overlap 14 Days	Administer LAI
2 nd or 3 rd	≥4 & <5	No	Yes
	≥5	Yes	Yes
4 th or Later	>4 & ≤6	No	Yes
	>6	Yes	Yes

Abilify Maintena Product Label §2.2

Relative Cost of Drug Therapy

Daily cost is in the same general price range as other branded LAI. Specific pricing information that would be obtained by our purchasing system is confidential and therefore not included in this public document. The ability to know that a patient missed a dose and therefore be able to find them prior to relapse is a large potential cost savings over oral therapy. Based on a meta-analysis of LAI (“depot”) versus oral medications, the risk ratio for *relapse* was 0.70 with a 95% confidence interval of 0.57–0.87. This means that there is a 95% chance that the true risk for having a relapse is between 57% and 87% compared to oral medications. The registration trial for aripiprazole LAI showed a remarkably high hazard ratio (HR) of 5 and would be expected to have at least a similarly reduced relapse risk ratio in clinical practice. (Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for

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schizophrenia—A critical systematic review and meta-analysis of randomised long-term trials. *Schiz Research* 2011;127:83–92. DOI:10.1016/j.schres.2010.11.020.)

Patient Counseling

Patient's should be given the FDA-approved patient labeling (*Medication Guide*) at the time of dispensing or administration.

The product label contains the following statement: "Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY MAINTENA."

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with antipsychotic drugs are at increased risk of death. Aripiprazole is not approved for elderly patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome

Counsel patients and caregivers that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

Tardive Dyskinesia

Advise patients that abnormal involuntary movements have been associated with the administration of antipsychotic drugs. Counsel patients to notify their physician if they notice any movements which they cannot control in their face, tongue, or other body part.

Hyperglycemia and Diabetes mellitus

Advise patients of the symptoms of hyperglycemia and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during.

Orthostatic Hypotension

Advise patients of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC count or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while receiving ABILIFY.

Interference with Cognitive and Motor Performance

Because ABILIFY MAINTENA may have the potential to impair judgment, thinking, or motor skills, instruct patients to be cautious about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY MAINTENA therapy does not affect them adversely.

Heat Exposure and Dehydration

Advise patients regarding appropriate care in avoiding overheating and dehydration.

Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

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Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY MAINTENA.

Nursing

Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue ABILIFY MAINTENA, taking into account the importance of the drug to the mother.

Alcohol

Advise patients to avoid alcohol while taking ABILIFY MAINTENA.

Drug-related Adverse Effects

In addition to the product label recommended adverse effects, the drug-related adverse effects (those with an incidence $\geq 5\%$ and $\geq 2 \times$ placebo) should be mentioned to the patient: akathisia (restlessness), oral hypoesthesia (numbness of tongue), somnolence (sleepiness), dizziness, extrapyramidal symptoms (stiffness or shaking), and weight increased.

Storage and Handling

- Store at 25°C (77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature <<http://www.usp.org/hqi/practitionerPrograms/newsletters/qualityReview/qr401994-06-01c.html>>].
- Keep out of reach of children.
- Requires prescription.

Recommendation to DSHS Executive Formulary Committee

Addition to the DSHS Formulary is **recommended**. If started in an inpatient setting, the outpatient setting should be contacted to confirm that they will continue the aripiprazole LAI following discharge. This should be documented in the patient's clinical record. Audit criteria for oral aripiprazole are appropriate to be used with aripiprazole LAI.

QR Code

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See <http://en.wikipedia.org/wiki/QR_code> for background on QR Codes and updated list of free readers and generators.



<http://bit.ly/Aripiprazole-LAI>

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Author's Declaration of Interests

Employee of Texas Department of State Health Services (San Antonio State Hospital). Appointed to The University of Texas at Austin College of Pharmacy and School of Medicine, UT Health Science Center San Antonio. Speakers bureau or consultant for Merck, Novartis, Otsuka, and Sunovion. Speaker for several professional organizations. Secretary for Congregation Agudas Achim San Antonio. Research support in past year from Ortho-McNeil Janssen. Past Senior Editor of the College of Psychiatric and Neurologic Pharmacists' *Mental Health Clinician*. Expert witness on both defendant and plaintiff sides. No direct stock ownership in pharmaceutical corporations. Author's wife is research lead in UT Health Science Center San Antonio, Department of Neurology.

Monograph Change Log: (please send any corrections to Dr. Saklad for incorporation)

- 10 July 2013 Original version completed, including ADA Section 508 <<http://www.section508.gov/>> accessibility features.
- 11 July 2013 Clarified dosing instructions. Expanded discussion on relative cost of therapy. Added QR Code to allow printed copy to be obtained as PDF and expanded all URLs to be usable if document is printed.
- 12 July 2013 Corrected several typos.