Aripiprazole Lauroxil Long-Acting Injectable: The Latest Addition to Second-Generation Long-Acting Agents

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Abstract

Antipsychotics have long been the mainstay for the treatment of schizophrenia and other psychotic disorders. Long-acting injectables (LAI) of antipsychotics—provided once every two weeks to once every three months—promise to reduce the incidence of nonadherence. ARISTADA™ (aripiprazole lauroxil; ALLAI) extended-release injectable suspension was approved by the U.S. Food and Drug Administration in October 2015 for the treatment of schizophrenia, and is the newest entrant in the LAI market. ALLAI is available as a single-use, pre-filled syringe, can be started in three different dosages, and also has the option of every six-week dosing. Treatment with oral aripiprazole is recommended for the first twenty-one days after the first ALLAI injection, which is a potential disadvantage. Adverse effects include sensitivity to extrapyramidal symptoms, especially akathisia, which is well documented in other aripiprazole preparations. There is no available data comparing ALLAI to other antipsychotics, and more head-to-head trials comparing different LAI formulations are needed. Based on the available data, ALLAI is an effective and safe option for treatment of schizophrenia. Further studies and post-marketing data will provide better understanding of this formulation.

Key Words: Adherence, Antipsychotic, Aripiprazole, Psychopharmacology

Introduction

Antipsychotics have long been the mainstay for the treatment of schizophrenia and other psychotic disorders. Over the last few decades, they have gained popularity for use in non-psychotic disorders; for example, bipolar disorder—either as an augmenting agent to an antidepressant, monotherapy for bipolar depression or acute mania (1, 2). Recently, they have also been used in the treatment of various anxiety disorders (3). In the last decade, several new antipsychotics have gained approval by the U.S. Food and Drug Administration (FDA) for use in schizophrenia, major depression and bipolar disorder.

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A number of first-generation (FGAs) or typical antipsychotics (e.g., phenothiazines and butyrophenones) was developed between the 1950s and the 1990s (4). They all predominately blocked the dopamine (D2) receptor blockers leading to significant motor and cholinergic side effects to varying degree among the individual drugs. Second-generation (SGAs) or atypical antipsychotics offered to treat both positive and negative symptoms in schizophrenia with lower incidence of extrapyramidal symptoms (EPS). Regardless of the class of medication, patients who are prescribed antipsychotics are often nonadherent, leading to exacerbations and poor outcomes (5). Long-acting injectables (LAI) of antipsychotics—provided once every two weeks to once every three months—promise to reduce the incidence of nonadherence. Multiple studies have been conducted to evaluate the efficacy of LAIs in comparison to oral antipsychotics. The verdict is currently split based on the type of study one considers. Randomized controlled trials (RCTs) overall have failed to demonstrate an advantage of LAIs over their oral counterparts (6). However, a meta-analysis that

evaluated fifty-eight studies with various designs showed a significant advantage of LAIs in reducing hospitalization rates among patients with schizophrenia (7). This is consistent with another meta-analysis including only mirror-image studies that compared periods of treatment with LAI versus oral antipsychotics in the same patients (8). LAIs showed a clear advantage over oral antipsychotics in preventing hospitalization and in decreasing the number of hospitalizations in multiple, clinically relevant subpopulations and treatment groups. The discrepancy in findings between the RCTs and naturalistic observational studies has been largely attributed to the structure RCTs provide to patients when they are in the study, which tends to attenuate differences in the groups (9).

Review of Current LAIs

The arrival of SGAs in the 1990s provided optimism for improved adherence due to a better side effect profile compared to FGAs, rendering LAIs less popular (10). The continued problem with poor compliance, despite the emergence of the SGAs and the growing number of indications for antipsychotics, has led to a number of SGAs being available in long-acting formulations. Currently, LAIs available in the U.S. include two first-generation antipsychotics (haloperidol and fluphenazine) and four second-generation antipsychotics (olanzapine, risperidone, paliperidone and aripiprazole).

Haloperidol (HLAI) and fluphenazine LAI (FLAI) tend to have a higher incidence of extrapyramidal symptoms (EPS) than the second-generation LAIs (11). Both HLAI and FLAI are available in U.S. as esters suspended in an oil vehicle. The conventional administration of either of these medications requires an overlap with oral medications for a few weeks to reach steady levels. A strategy to attain the steady level faster is to provide loading doses of these medications at the cost of an increased incidence of side effects (12).

Risperidone long-acting injection (RLAI) was not only the first available LAI of an SGA, but was the only LAI to use a microsphere preparation. There is a lag before the medication is released from muscle due to slow biodegradation of the microspheres, delaying the time to peak to about four weeks from initiation. The ensuing requirement for patients to take oral risperidone for at least 3–4 weeks after initiation and the biweekly regimen are important drawbacks of RLAI. Compared to oral risperidone, RLAI offers no clear advantage regarding safety (13). Risk of hyperprolactinemia, requirement of refrigeration before administration and inability to load the medication are other important impediments.

Paliperidone long-acting injection (PLAI) contains the palmitate ester of 9-hydroxyrisperidone, the active metabolite of risperidone. The crystalline-based preparation of paliperidone is an aqueous-based nanosuspension. PLAI and RLAI are closely related and share some of the side effects like EPS, weight gain, tachycardia and hyperprolactinemia (14). PLAI, however, sought to address some of the key challenges with RLAI. PLAI allows loading injections without any required oral supplementation. It also has a four-week dosing interval as opposed to the biweekly regimen with RLAI. Prefilled syringes with no need for refrigeration improved the ease of administration (15).

In 2015, the FDA approved a three-month formulation of paliperidone under the trade name of Invega Trinza™ (PLT) for the treatment of schizophrenia. Patients have to be stable on PLAI for four months before switching to the every three-month PLT injections, with the last two doses at the same dose (16). At the time of the writing of this article, this is the only LAI which can be provided every three months, resulting in four injections a year. The side effect profile of the three-month formulation is similar to the once-monthly injection (17). The characteristics of PLAI and the availability of the every three-month PLT make PLAI a popular choice over the other LAIs in various clinical settings.

Olanzapine long-acting injection (OLAI) is an aqueous suspension of olanzapine pamoate. Despite lower concentrations, therapeutic levels of olanzapine are achieved after a single injection, negating the need of any oral supplementation during initiation. A higher dosing is recommended in the first eight weeks to overcome the lower concentration initially. A variety of dosing options (150 mg, 210 mg, 300 mg and 405 mg) are available, which can be given every two to four weeks (18). OLAI has demonstrated efficacy in short-term and maintenance treatment of schizophrenia (19). Similar to its oral counterpart, common adverse effects of OLAI include weight gain and higher rates of metabolic effects (20).

The incidence of Post-Injection Delirium Sedation Syndrome (PDSS) proved to be the biggest deterrent in the widespread use of OLAI. PDSS is understood to be due to inadvertent intravascular injection of OLAI leading to an olanzapine-intoxication state. It is characterized by a relatively sudden development of symptoms like dizziness, confusion, slurred speech, altered gait, agitation, extrapyramidal symptoms, convulsion, and altered level of consciousness ranging from mild sedation to coma (18). An analysis of about 45,000 OLAI injections indicated an incidence of about 0.07% of injections or 1.4% of patients. This has resulted in a mandatory continuous observation in a certified clinical setting for three hours after every injection, restricting the use of this medication in various clinical settings (21).

Abilify Maintena™ (AMLAI) is a once-monthly LAI

formulation of aripiprazole monohydrate, which has been marketed since 2013. The exact mechanism of action of aripiprazole in schizophrenia remains unknown; it is believed to exert its effects through partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors (22). The efficacy and tolerability of AMLAI has been established through pivotal trials and other studies (23-25). The common side effects associated with AMLAI are insomnia and akathisia, which are mild to moderate in severity (23, 24, 26, 27). The medication is marketed in either a dual-chamber, pre-filled syringe or a vial of either 400 mg or 300 mg, which can be used to administer a wide variety of doses. AMLAI was initially approved for gluteal injections only, but recently received approval for deltoid injections. Due to the metabolism of aripiprazole by CYP450 system, dose modifications are recommended for patients who are poor metabolizers and among patients who are using concomitant CYP3A4 inhibitors and/or CYP2D6 inhibitors. AMLAI has a low risk of weight gain and dysregulation of glucose/lipid metabolism similar to the oral aripiprazole. Along with low risk of hyperprolactinemia, the metabolic profile of AMLAI is the most distinctive advantage of AMLAI. Monthly injection intervals place AMLAI either on par with or in an advantageous position compared to the other LAIs. Supplementation with oral aripiprazole for fourteen days following initiation is an important drawback for AMLAI.

Few head-to-head studies have been conducted to date to evaluate the comparative effectiveness between the various LAIs available in the U.S. A Danish nationwide retrospective study of 4,532 patients followed over 2,700 patient years concluded that FGA-LAIs and RLAI were equally effective regarding rehospitalization rates, duration of hospitalization and all-cause discontinuation (28). A Swedish phamacoeconomic study comparing PLAI, OLAI, RLAI, HLAI and oral olanzapine showed that PLAI followed by OLAI had the lowest cost/patient and highest quality-adjusted life-year (QALY) for chronic schizophrenia (29). A Comparison of Long-Acting Injectable Medications for Schizophrenia (ACLAIMS) was a double-blind, randomized trial at twenty-two U.S. sites which failed to demonstrate an advantage in efficacy of PLAI over HLAI. PLAI was associated with weight gain and hyperprolactinemia compared to increased risk of akathisia with HLAI (30). The QUALIFY (QUAlity of LIfe with AbiliFY Maintena®) study was a multicenter, 28-week, randomized, noninferiority study that compared effectiveness of ALAI with PLAI for schizophrenia (31). The study established the superiority of AMLAI in improvement of clinician-rated, health-related, quality-of-life scales. It also demonstrated a favorable tolerability profile of AMLAI vs. PLAI.

Aripiprazole Lauroxil Long-Acting Injectable (ALLAI)

ARISTADA™ (aripiprazole lauroxil) extended-release injectable suspension was approved by the U.S. FDA in October 2015 for the treatment of schizophrenia and is the newest entrant in the LAI market. The approval was based partly on the results of a Phase 3 study (32) and partly on the established safety and efficacy of oral aripiprazole and AMLAI.

Pharmacology

Aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which, in turn, is a prodrug of aripiprazole. The aripiprazole molecule is attached to a lauroyloxymethyl chain via a carbon-nitrogen (C-N) bond (33, 34). After an intramuscular injection, ALLAI undergoes a two-step bioconversion: first step is an enzyme-mediated hydrolysis to form N-hydroxymethyl aripiprazole followed by a water-mediated hydrolysis to form aripiprazole (34). After ALLAI intramuscular injection, aripiprazole becomes detectable in systemic circulation at day 5–6 and continues to be released for an additional thirty-six days. When oral aripiprazole supplementation is added to the intramuscular injection, the aripiprazole levels reach therapeutic level within four days (35). The mean terminal elimination half-life calculated after every four-week injection of ALLAI ranged from 29.2 days to 34.9 days (35).

The metabolism of aripiprazole is mediated primarily through cytochrome P450 (CYP) 3A4 and CYP2D6 and dose modifications are recommended in patients taking CYP450 modulators for greater than two weeks (35).

Efficacy of ALLAI in Schizophrenia

The efficacy of aripiprazole lauroxil (ALLAI) was evaluated in an international, multicenter, randomized, double-blind, placebo-controlled trial conducted between December 2011 and March 2014 and consisted of 623 patients (32). The patients were between the ages of 18–70 years and had a diagnosis of schizophrenia (using the *DSM-IV TR* criteria) experiencing an acute exacerbation.

The study included patients having an acute exacerbation or relapse of schizophrenia with onset of less than two months prior to screening and less than two weeks duration of hospitalization (if inpatient at the time of screening), a history of previous clinically beneficial response to treatment with an antipsychotic medication, no history of receiving clozapine and outpatient status for more than three months during the year prior to enrollment. Further inclusion criteria also included a Positive and Negative Syndrome Scale (PANSS) total score of 70–120 and a Clinical Global

Impression–Severity of illness scale (CGI-S) of ≥4.

Exclusion criteria for the study included having a diagnosis of schizoaffective disorder, bipolar disorder, major depressive disorder, dementia, delirium, amnestic or any other cognitive disorder currently or within the past two years, any clinically significant medical illness or laboratory abnormality, prior inadequate response to oral aripiprazole, and a long-acting injectable antipsychotic treatment within sixty days of screening. Patients with a diagnosis of substance dependence within six months or substance abuse within three months of screening and women who were pregnant, lactating or breastfeeding were also excluded from the study.

After the screening, patients were randomized in a double-blind fashion to three arms in a 1:1:1 ratio: ALLAI 441 mg, ALLAI 882 mg or placebo. Patients in either of the ALLAI groups received oral aripiprazole 15 mg daily for the first three weeks, and patients randomized to the placebo group received matching oral placebo for that duration. The injections were only given in the gluteal muscle to maintain blinding to the study drug. The intramuscular injections were administered on days 1, 29 and 57.

The median age for the randomized patients was 39.0 years and about two-thirds (67.9%) were male. Variables like age, gender, race, ethnicity and region were evenly distributed among the three groups. The primary efficacy end point that was used for the study was a change in PANSS total score from baseline to day 85 and was analyzed using an analysis of covariance (ANCOVA). The study noted clinically meaningful and statistically significant improvement in both the ALLAI groups, with separation from placebo as early as day 8. The placebo-adjusted least squares mean difference was -10.9 (1.8) with a p value <0.001 in the ALLAI 441 mg group, and -11.9 (1.8) with a p value <0.001 for the ALLAI 882 mg group. The secondary efficacy end point was Clinical Global Impression–Improvement scale (CGI-I) at day 85, and both ALLAI groups had significantly better CGI-I scores compared to placebo, with a p value <0.001.

Safety and Tolerability of ALLAI

In the study conducted by Meltzer et al. (32), most common treatment-emergent adverse effects in the ALLAI groups were insomnia, akathisia, headache and anxiety. Akathisia was the only adverse event reported in ≥5% patients in either ALLAI groups and at least twice the rate in the placebo group. The overall incidence of pain at the injection site was low and was reported in 3.9% of patients in the ALLAI 441 mg group, 5.8% of patients in the ALLAI 882 mg group and 1.9% of patients in the placebo group.

In a separate Phase 1 randomized, open-label, single-dose study, the safety and bioavailability of ALLAI was evaluated (33). This study consisted of forty-six randomized subjects and compared ALLAI administered via either the deltoid or the gluteal region. The study noted that injection site pain was the most common reported adverse effect, with an incidence of 43.5% and was higher with deltoid administration. There was a higher mean exposure to aripiprazole and two metabolites when injected into the deltoid muscle. The study concluded that deltoid and gluteal injection sites can be used interchangeably for administering ALLAI 441 mg.

The product label for ALLAI contains a boxed warning for increased risk of death in elderly patients with dementia-related psychosis treated with antipsychotic drugs consistent with the boxed warning for all antipsychotics.

Table 1 Comparison of ARISTADA™ and Abilify Maintena™

	ALLAI ARISTADA™	AMLAI Abilify Maintena™
Recommended starting dose	441 mg, 662 mg or 882 mg	400 mg (300 mg for known CYP2D6 poor metabolizers)
Dose frequency	Monthly, the 882 mg dose can be given every 6 weeks	Monthly
Site of injection	Deltoid (441 mg dose only) or gluteal (441 mg, 662 mg or 882 mg) muscle	Deltoid or gluteal muscle
Oral aripiprazole coverage required with the first injection	21 days	14 days
Dosage form(s)	Single-use, pre-filled syringes	Single-dose, pre-filled, dual- chamber syringe or single-dose vial
Need for reconstitution	No	Yes

Comparison of ALLAI and AMLAI

The two aripiprazole LAIs have subtle differences that are outlined in Table 1.

ALLAI offers more dosing options and can be started in three different dosages: 441 mg, 662 mg or 882 mg, while AMLAI has only one recommended starting and maintenance dose of 400 mg. Based on preliminary studies, recommendations of dose conversion between oral aripiprazole and ALLAI provide clinicians a guide in appropriate dose selection during switching (see Table 2). ALLAI is available as a single-use, pre-filled syringe while AMLAI is available as either a pre-filled, dual-chamber syringe or as a vial (both of which need to be reconstituted before administration). Both of the solutions must be homogenous on injection, emphasizing the need to prevent delay between reconstitution and administration (36). The post-marketing approval of the deltoid site for AMLAI administration has put it on par with ALLAI.

As far as the dose frequency is concerned, ALLAI has the option of every six-week dosing (only with its highest dose), offering an advantage in a cohort of patients who may potentially receive fewer injections over the same time period compared to patients receiving AMLAI every four weeks.

Treatment with oral aripiprazole is recommended for the first twenty-one days after the first ALLAI injection, but the requirement for AMLAI is only fourteen days, which might be a potential disadvantage for the former.

Table 2 Recommended Dose for ALLAI (ARISTADA™) Based on Oral Aripiprazole Total Daily Dose

Oral Aripiprazole Dose	ALLAI Dose
10 mg per day	441 mg per month
15 mg per day	662 mg per month
20 mg or higher per day	882 mg per month

See reference #35

Conclusions

It is vital to have more LAIs of antipsychotics available at the disposal of clinicians considering the chronicity of schizophrenia and the high prevalence of nonadherence in this population. Recent developments targeting longer intervals between injections are promising and are likely to improve compliance and prevent relapses. Despite some differences between recently approved ALLAI and AMLAI, the utility of having two LAIs of the same drug (and possible superiority of one of them) has to be examined with time. There is no available data comparing ALLAI to other antipsychotics and more head-to-head trials comparing different LAI formulations are needed. Based on the available data, ALLAI is an effective and safe option for the treatment of schizophrenia. Further studies and post-marketing data will provide a better understanding of this formulation.

References

1. Quintin P, Thomas P. [Efficacy of atypical antipsychotics in depressive syndromes]. French. Encephale 2004;30(6):583-589.
2. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 2005;7 Suppl 3:5-69.
3. Maglione M, Maher AR, Hu J, Wang Z, Shanman R, Shekelle PG, et al. Off-label use of atypical antipsychotics: an update [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
4. Shen WW. A history of antipsychotic drug development. Compr Psychiatry 1999;40(6):407-414.
5. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas 2014;5:43-62.
6. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull 2014;40(1):192-213.
7. Lafeuille MH, Dean J, Carter V, Duh MS, Fastenau J, Dirani R, et al. Systematic review of long-acting injectables versus oral atypical antipsychotics on hospitalization in schizophrenia. Curr Med Res Opin 2014;30(8):1643-1655.
8. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry 2013;74(10):957-965.
9. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342(25):1887-1892.
10. Rauch AS, Fleischhacker WW. Long-acting injectable formulations of new-generation antipsychotics: a review from a clinical perspective. CNS Drugs 2013;27(8):637-652.
11. Heres S, Hamann J, Kissling W, Leucht S. Attitudes of psychiatrists toward antipsychotic depot medication. J Clin Psychiatry 2006;67(12):1948-1953.
12. Jann MW, Ereshefsky L, Saklad SR. Clinical pharmacokinetics of the depot antipsychotics. Clin Pharmacokineti 1985;10(4):315-333.
13. Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. Pharmacotherapy 2013;33(10):1087-1106.
14. Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. Cochrane Database Syst Rev 2012;6:CD008296.
15. Citrome L. Paliperidone palmitate - review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. Int J Clin Pract 2010;64(2):216-239.
16. Janssen Pharmaceuticals. Invega® Trinza® (paliperidone palmitate) Extended-Release Injectable Suspension package insert. United States Prescribing information. 2015. [Accessed November 12, 2015]. Available from: https://www.janssenmd.com/pdf/invega-trinza/INVEGA-TRINZA_PI.pdf.

17. Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. JAMA Psychiatry 2015;72(8):830-839.

18. Eli Lilly. Prescribing information for Zyprexa Relprevv. 2015. [Updated September 4, 2015; accessed November 11 2015]. Available from: http://pi.lilly.com/us/zyprexa_relprevv.pdf.

19. Chue P, Chue J. A review of olanzapine pamoate. Expert Opin Pharmacother 2012;13(11):1661-1670.

20. Schottle D, Kuhnigk O, Naber D. Drug safety evaluation of olanzapine pamoate. Expert Opin Drug Saf 2013;12(6):897-903.

21. U.S. FDA. Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa® Relprevv™ (olanzapine): NDA 22-173 2009. [Updated October 1, 2014]. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsand Providers/UCM202330.pdf.

22. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002;302(1):381-389.

23. Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, et al. 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.

24. Fleischhacker WW, Sanchez R, Johnson B, Jin N, Forbes RA, McQuade R, et al. Long-term safety and tolerability of aripiprazole once-monthly in maintenance treatment of patients with schizophrenia. Int Clin Psychopharmacol 2013;28(4):171-176.

25. Kane JM, Zhao C, Johnson BR, Baker RA, Eramo A, McQuade RD, et al. Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis. J Med Econ 2015;18(2):145-154.

26. Potkin SG, Raoufinia A, Mallikaarjun S, Bricmont P, Peters-Strickland T, Kasper W, et al. Safety and tolerability of once monthly aripiprazole treatment initiation in adults with schizophrenia stabilized on selected atypical oral antipsychotics other than aripiprazole. Curr Med Res Opin 2013;29(10):1241-1251.

27. Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry 2014;205(2):135-144.

28. Nielsen J, Jensen SO, Friis RB, Valentin JB, Correll CU. Comparative effectiveness of risperidone long-acting injectable vs first-generation antipsychotic long-acting injectables in schizophrenia: results from a nationwide, retrospective inception cohort study. Schizophr Bull 2015;41(3):627-636.

29. Einarson TR, Vicente C, Zilbershtein R, Piwko C, Bo CN, Pudas H, et al. Pharmacoeconomics of depot antipsychotics for treating chronic schizophrenia in Sweden. Nord J Psychiatry 2014;68(6):416-427.

30. McEvoy JP, Byerly M, Hamer RM, Dominik R, Swartz MS, Rosenheck RA, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 2014;311(19):1978-1987.

31. Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res 2015;168(1-2):498-504.

32. Meltzer HY, Risinger R, Nasrallah HA, Du Y, Zummo J, Corey L, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry 2015;76(8):1085-1090.

33. Turncliff R, Hard M, Du Y, Risinger R, Ehrich EW. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia. Schizophr Res 2014;159(2-3):404-410.

34. Rohde M, M Rk N, Hakansson AE, Jensen KG, Pedersen H, Dige T, et al. Biological conversion of aripiprazole lauroxil - an N-acyloxymethyl aripiprazole prodrug. Results Pharma Sci 2014;4:19-25.

35. Alkermes I. ARISTADA™ Prescribing Information, Waltham, MA. 2015. [Accessed November 18, 2015]. Available from: http://aristada.com/hcp/ARISTADA-prescribing-information.pdf.

36. Citrome L. Aripiprazole long-acting injectable formulations for schizophrenia: aripiprazole monohydrate and aripiprazole lauroxil. Expert Rev Clin Pharmacol 2015;9(2):169-186.