Medicaid Testimony for Aripiprazole Lauroxil (ARISTADA®)

My name is Dr. Timothy Birner, Medical Science Director at Alkermes. Thank you for the opportunity to provide testimony on Aripiprazole Lauroxil (ARISTADA), a recently approved extended release injectable atypical antipsychotic for Intramuscular (or IM) use.

I will highlight a few key clinical points today.

INDICATIONS and MOA:
ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia, and a prodrug of aripiprazole. Following intramuscular injection, ARISTADA is likely converted to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole.

Efficacy:
The efficacy of ARISTADA is, in part, based on the 12 week randomized, double blind, placebo-controlled registration trial published by Meltzer et al. in the Journal of Clinical Psychiatry, in 2015.² The primary efficacy variable was the change from baseline to endpoint (day 85) in PANSS total score. Statistically significant separation from placebo, on PANSS total score change, was observed for each aripiprazole lauroxil (ARISTADA) dose group
• the LS mean changes from baseline in PANSS total score for AL 441 mg, AL 882 mg, and placebo were -20.9, -21.8, and -9.8, respectively.

Safety/Adverse Events:
The most common TEAEs were insomnia, akathisia and headache
• Akathisia was the most commonly observed adverse reaction with ARISTADA (incidence ≥5%)
Injection site reactions were reported by 4% of patients treated with 441 mg ARISTADA and 5% of patients treated with 882 mg ARISTADA compared to 2% of patients treated with placebo (most of these were injection site pain).

Important Safety Information:
ARISTADA has a Black Boxed WARNING for 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.
ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

Dosing:
ARISTADA is only to be administered as an intramuscular injection by a healthcare professional.
For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability.
Depending on individual patient’s needs, treatment with ARISTADA can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly, which corresponds to 300 mg, 450 mg and 600 mg of aripiprazole, respectively. Treatment may also be initiated with the 882 mg dose every 6 weeks.
Administer ARISTADA either in the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg or 882 mg)
In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days.
With the addition of oral aripiprazole supplementation for 21 days at the time of the first ARISTADA dose, aripiprazole concentrations reach therapeutic levels within 4 days. When making dose and dosing interval adjustments, the pharmacokinetics and prolonged-release characteristics of ARISTADA should be considered. In the event of early dosing, an ARISTADA injection should not be given earlier than 14 days after the previous injection.
Dose or dosing interval adjustments may be required for other factors including, but not limited to drug interactions (i.e., CYP2D6 poor metabolizers; patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than 2 weeks) and missed doses beyond 6-8 weeks depending on the amount of time lapsed and dose of ARISTADA administered.
Specifics for these types of dose & dosing interval adjustments in addition to oral daily equivalent dosing for aripiprazole and IM ARISTADA dose are outlined in the prescribing information.

Guidelines:
According to APA guidelines, patients with recurrent relapses related to not taking their oral medication are candidates for a long-acting injectable antipsychotic³, while the TMAP (Texas Medication Algorithm Project) recommends that the clinicians consider Long Acting Injectable Antipsychotics in patients who are inadequately adherent ‘at any stage’ of schizophrenia.⁴

How Supplied:
ARISTADA is available in a pre-filled syringe containing ARISTADA sterile aqueous suspension and does not require refrigeration. ARISTADA should be stored at room temperature with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

**CONTRAINDICATIONS:**
Known hypersensitivity to aripiprazole.

**ABSORPTION AND DISTRIBUTION:**
Based on population pharmacokinetic analysis, the apparent volume of distribution of aripiprazole following intramuscular injection of ARISTADA was 268 L, indicating extensive extravascular distribution following absorption. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 mg/day to 30 mg/day oral aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

**LinkeRx® PHARMACOKINETICS**
Aripiprazole Lauroxil’s unique formulation along with the LinkeRx® technology provides controlled and predictable pharmacokinetics of aripiprazole and extends exposure to the active molecule. Median simulated steady-state aripiprazole plasma concentrations following administration of ARISTADA (based on a population pharmacokinetic (PK) model that incorporated data from four Phase I studies and the pivotal Phase III efficacy study and included a total of 21,620 plasma concentration records from 616 patients) demonstrate that, at steady-state, all approved dosing regimens for ARISTADA result in aripiprazole concentrations within the therapeutic range of 102-435 ng/mL, which was established by Alkermes based on mean steady-state minimum concentrations (Cmin) achieved following oral aripiprazole 10 mg/day and mean steady-state maximum concentrations (Cmax) following oral aripiprazole 30 mg/day. Steady-state is achieved with ARISTADA following the fourth monthly injection.

Due to the prolonged release characteristics of ARISTADA, median simulated aripiprazole concentrations following a missed dose demonstrate that marginal decreases in median aripiprazole plasma concentrations were observed for each of the evaluated dosing regimens. If a 441 mg dose is administered within 6 weeks, no additional oral supplementation is required. If a 662 mg or 882 mg dose is administered within 8 weeks, no additional oral supplementation is required. When a dose is missed, administer the next dose of ARISTADA as soon as possible. Whether oral supplementation is required depends on the strength of the last dose administered and the amount of time that has lapsed and that information is contained in the full prescribing information.

**SUMMARY:**
ARISTADA is the first long-acting atypical antipsychotic with both once-monthly and six-week dosing options. Aripiprazole lauroxil (ARISTADA) is indicated for the treatment of schizophrenia based on a 12-week, randomized, double-blind, placebo controlled, fixed-dose study in adult patients with schizophrenia meeting DSM IV TR criteria. This study showed an improvement of psychotic symptoms that was statistically significant and clinically meaningful, based on:
Symptom improvement, as measured by PANSS total scores; and both ARISTADA treatment groups demonstrated statistically significantly better CGI-I scores versus placebo.
The most common adverse event was akathisia.
These results support aripiprazole lauroxil (ARISTADA) as an important new treatment option for schizophrenia.
Therefore, we respectfully request your consideration to minimize restrictions relative to ARISTADA.

**For the complete boxed warning and additional information, I have available for you today the full Prescribing Information for Aripiprazole Lauroxil (ARISTADA).**

**References:**


