

My name is Dr. Paul Thomspson, Medical Science Liason at Alkermes. Thank you for the opportunity to provide testimony on **aripiprazole lauroxil (ARISTADA), an extended release injectable atypical antipsychotic for Intramuscular (or IM) use.** I will highlight a few key clinical points today.

### **ARISTADA**

#### **INDICATION and MOA:**

ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia. ARISTADA is a prodrug of aripiprazole. Following intramuscular injection, ARISTADA is likely converted to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. The mechanism of action of aripiprazole in schizophrenia is unknown.<sup>1</sup>

#### **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<sup>2</sup>. ARISTADA 441 mg and 882 mg every 4 weeks in conjunction with 21 days of oral supplementation was studied<sup>1</sup>.

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 ARISTADA dose group.<sup>1</sup>

- The LS mean changes from baseline in PANSS total score for ARISTADA 441 mg, ARISTADA 882 mg, and placebo were -20.9, -21.8, and -9.8, respectively.<sup>1</sup>

#### **SAFETY/ADVERSE EVENTS:**

The most common TEAEs were insomnia, akathisia and headache.<sup>1</sup>

- Akathisia was the most commonly observed adverse reaction with ARISTADA (incidence  $\geq 5\%$ )<sup>1</sup>
- 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)<sup>1</sup>

#### **IMPORTANT SAFETY INFORMATION<sup>1</sup>:**

**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.**

Please see ARISTADA Full Prescribing Information for complete safety information.

#### **DOSING<sup>1</sup>:**

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, or 1064 mg administered every two months, which corresponds to 300 mg, 450 mg, 600 mg, and 724 mg of aripiprazole, respectively. Treatment may also be initiated with the 882 mg dose every 6 weeks.

Administer ARISTADA in either the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg, 882 mg, or 1064mg).

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.

#### **INITIATION OF TREATMENT:**

- 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.<sup>1</sup>

New Clinical Information effective June 2018<sup>3</sup>:

- **ARISTADA INITIO** is part of a 1-day initiation regimen (along with a single 30mg aripiprazole dose) given in conjunction with the first dose of ARISTADA. The 1-day initiation regimen is an alternative to 21 days of oral aripiprazole prescribed with the first dose of ARISTADA.<sup>3</sup>

#### **Indication and Usage:**

ARISTADA INITIO, in combination with oral aripiprazole, is indicated for the initiation of ARISTADA when used for the treatment of schizophrenia in adults<sup>3</sup>.

ARISTADA INITIO is not interchangeable with ARISTADA due to their differing pharmacokinetic profiles<sup>3</sup>.

#### **Dosage and Administration:**

- Administer one 675 mg injection of ARISTADA INITIO and one 30 mg dose of oral aripiprazole in conjunction with the first ARISTADA injection.<sup>3</sup>
- ARISTADA INITIO is only to be used as a single dose and is not for repeated dosing.<sup>3</sup>
- ARISTADA INITIO is to be administered by intramuscular injection in either the deltoid or gluteal muscle by a healthcare professional. Avoid injecting both ARISTADA INITIO and ARISTADA concomitantly into the same deltoid or gluteal muscle.<sup>3</sup>
- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA INITIO.<sup>3</sup>
- See Dosage and Administration for detailed preparation and administration instructions.
- Avoid use in known CYP2D6 poor metabolizers.<sup>3</sup>
- Avoid use with strong CYP2D6 or CYP 3A4 inhibitors and strong CYP3A4 inducers.<sup>3</sup>
- The main formulation difference between ARISTADA® and ARISTADA INITIO is the particle size of the aripiprazole lauroxil crystals in the injection suspension.<sup>4,5</sup>
- ARISTADA is comprised of micron-sized particles chosen for very slow dissolution.<sup>4,5</sup>
- ARISTADA INITIO has much smaller-sized particles in the nanometer range and, after injection, will release aripiprazole faster than ARISTADA.<sup>4,5</sup>

#### **Safety**

- AEs were comparable between the 1-day and 21-day initiation regimens.<sup>4,5</sup>
- In pharmacokinetic studies, the safety of the 1-day initiation regimen was generally consistent with that observed for ARISTADA.<sup>3</sup>

#### **GUIDELINES:**

According to APA guidelines, patients with recurrent relapses related to not taking their oral medication are candidates for a long-acting injectable antipsychotic<sup>6</sup>, 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.<sup>7</sup>

#### **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).<sup>1</sup>

#### **CONTRAINDICATIONS:**

Known hypersensitivity to aripiprazole.<sup>1</sup>

## **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.<sup>1</sup>

## **LinkeRx® PHARMACOKINETICS**

The proprietary technology utilized to develop ARISTADA allows for controlled release after injection and extends exposure to the active molecule. LinkeRx® technology produces a non-ester prodrug of aripiprazole. Conversion of ARISTADA to aripiprazole in vivo is governed by slow dissolution of the ARISTADA particles followed by hydrolysis, resulting in extended systemic exposure of aripiprazole.<sup>8,9</sup> 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 14,524 plasma concentration records from 700 patients)<sup>10</sup> 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 (C<sub>min</sub>) achieved following oral aripiprazole 10 mg/day and mean steady-state maximum concentrations (C<sub>max</sub>) following oral aripiprazole 30 mg/day.<sup>11</sup> Steady-state is achieved with ARISTADA four months following treatment.<sup>1</sup>

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.<sup>10</sup> If a 441 mg dose is administered within 6 weeks, no additional oral supplementation is required.<sup>1</sup> If a 662 mg or 882 mg dose is administered within 8 weeks, no additional oral supplementation is required.<sup>1</sup> If a 1064 mg dose is administered within 10 weeks, no additional oral supplementation is required.<sup>1</sup> 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.<sup>1</sup>

## **SUMMARY:**

- ARISTADA INITIO is part of a 1-day initiation regimen (along with a single 30mg aripiprazole dose) given in conjunction with the first dose of ARISTADA, and is an alternative to 21 days of oral aripiprazole prescribed with the first dose of ARISTADA<sup>2</sup>.
- ARISTADA is the first long-acting atypical antipsychotic with both once-monthly, six-week, and every two months 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 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 and ARISTADA INITIO).**

## **References:**

1. Alkermes, Inc. ARISTADA® (package insert). Waltham, MA; 2018.
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3. Alkermes, Inc. ARISTADA INITIO™ (package insert). Waltham, MA; 2018.
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5. Data on file. Waltham, MA: Alkermes, Inc.
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7. Moore T, Buchanan, R, Buckley, P, Chiles, J., Conley, R., Crismon, M. et al. (2007) The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry* 68:1751–1762.
8. Remenar, J. Making the Leap from Daily Oral Dosing to Long-Acting Injectables: Lessons from the Antipsychotics. *Molecular Pharmaceutics*. 2014;11:1739-1749.
9. Turncliff R, et al. 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.
10. Hard ML, et al. Pharmacokinetic profile of a 2-month dose regimen of aripiprazole lauroxil: A phase I study and a population pharmacokinetic model. *CNS Drugs*. 2017 Jul;31(7):617-624.
11. FDA Web Site. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/207533Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207533Orig1s000ClinPharmR.pdf). Accessed June 7, 2017.

August 15<sup>th</sup>, 2018

A letter to the OHA Pharmacy & Therapeutics Committee in response to proposed updates to the Hepatitis C Direct-Acting Antivirals.

These opinions represent the individual endorsers and not those of their representative organizations.

Dear Colleagues in the OHA P&T Committee,

It comes again with great sadness, exasperation, and disbelief to the hepatitis C treatment and advocacy community to find the continued baseless treatment restrictions for people who use drugs. We would take both scientific and moral issue with several components of the draft Direct-Acting Antivirals update issued on 8/6/18.

The most glaring issues in the report is that it continues to answer the wrong question, which is, "What is the minimum length of abstinence to improve outcomes associated with treatment of CHC." Study after study has demonstrated that people who use drugs have equivalent outcomes when it comes to efficacy for treatment, whether that drug is injected, smoked, or consumed orally. As an addiction medicine specialist and health care for the homeless physician, I can say unequivocally that the base assumption should always be that people who use drugs should be treated the same as people who do not, *unless we have evidence pointing to the contrary*, as opposed to making the assumption that they cannot be treated. People with mental illness were also excluded from HCV treatment in most DAA trials, why are they not also excluded (clearly I am pointing out inconsistency, not advocating for this exclusion)? It seems that the committee is awaiting that massively powered, randomized controlled trial comparing people who use drugs and people who do not. This study will not happen, at least in the near future given lack of funding opportunities, and no study will ever be approved again comparing DAAs and placebo, as it would be decidedly unethical. And so we are left with the studies we do have, which are multiple, non-controlled prospective clinical trials looking at people who use drugs, including CO-STAR, SIMPLIFY, and others, as well as a plethora of pre-DAA or mixed DAA and INF based studies, all of which show no meaningful differences in SVR12 outcomes between PWUDs and those who do not.

Abstinence, dear colleagues, has nothing to do with it. Motivation? Perhaps. In our experience with more than a 100 people who currently or recently use drugs as Old Town Clinic, we have had zero virologic failures and excellent adherence. The only people we have struggled with are those who are less than exuberant about engaging in treatment, and this was regardless of active substance use. While the committee can and has attributed this to the addiction resources available at Old Town Clinic and assert that is the reason for the addiction specialist restriction, this is just not the case. These patients make it through treatment due to the hard work and motivation first and foremost of the patients, and secondarily due to case management and pharmacy support by our excellent HCV coordinator and pharmacist. Any addiction support I can give them as a provider is really ancillary and a requirement for such engagement is not evidence-based and is redundant to the existing case management requirement. The requirement for addiction specialist engagement provides barriers to care without clinical benefit.

While restricting treatment to people who inject drugs is the most damaging for our community health given that it limits our ability to prevent the spread of HCV, restricting treatment in people who drink alcohol is perhaps the most damaging to individual patients with alcohol use disorder, given the multiplicative effect of alcohol and chronic HCV. As has been presented to the committee previously, Dr. Tsui at the University of Washington has taken the question of alcohol use affecting SVR12 outcomes off the table as well as it likely ever will be. Let us erase this blemish from our public documents.

In summary, we, the community of academic hepatologists and infectious disease specialists, addictionologists, providers, advocates, and patients agree that without question and caveat, all mention of substance use should be removed from prior authorization requirements to hepatitis C treatment. The National Viral Hepatitis Roundtable in conjunction with the Harvard Center for Health Law and Policy Innovation has given us a D rating for hepatitis C coverage, behind the state of Mississippi, in large part due to our baseless substance use restrictions. Let's all hold our heads high again and start caring for our most vulnerable in an unbiased, evidence-based, stigma-free manner as is our calling and sworn oath.

As always, please reach out if you want hard copies of supporting literature..



Sincerely,

Andrew Seaman, MD  
Assistant Professor of Medicine, OHSU  
Central City Concern



Lorren Sandt  
Executive Director  
Caring Ambassadors Program, Inc.



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**Oregon  
Law Center**

WORKING TOGETHER TO ACHIEVE JUSTICE FOR LOW INCOME OREGONIANS

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Comments for P&T Committee Meeting on 9-27-18

Topic: DAA provision for Hepatitis C provision

Submitted on 9-26-18 by Beth Englander, Oregon Law Center Attorney

To the members of the Oregon Pharmacy and Therapeutics Committee:

The Oregon Law Center requests that the P&T Committee recommend that the Oregon Health Plan cover DAA treatment for all individuals diagnosed with Hepatitis C, irrespective of their Fibrosis score. We are extremely concerned that the state of Oregon continues to restrict Medicaid enrollees' access to lifesaving treatment for a progressive, deadly, and communicable disease.

The current limitations on access to treatment according to F score appear unreasonable considering the precipitous decline in the cost of DAA treatment since it was first on the market, and the consistent scientific and medical data supporting the efficacy of the treatment. Additionally, the continued restrictions on access to treatment appear increasingly indefensible given the current ranking of Oregon as the state with the #1 highest death rate from Hepatitis C in the entire nation. We also ask that the P&T committee, and the Oregon Health Authority as a whole, consider the impact of continued F-score based restrictions to DAA treatment on communities of color in Oregon. Within Oregon's shocking status as having the highest death rate in the U.S. from Hepatitis C, Native American and African American Oregonians die from Hepatitis C at nearly twice the rate of white Oregonians. Both the Oregon Health Authority and Governor Brown have stated their commitments to equity in the provision of health care. Continued limitations on access to Hepatitis C treatment in Oregon is a failure to address a deadly health care crisis that disproportionately impacts communities of color in our state, and contradicts those commitments made by our leaders.

Given the high rate of Hepatitis C infection and death from the disease in Oregon, the rate of DAA treatment of OHP enrollees who have Hepatitis C

is very low. Some CCOs are providing little or no DAA treatment to their members, despite the fact that they serve OHP enrollees in areas of the state with alarmingly high Hepatitis C infection rates.

There are many other scientific, medical, and legal reasons why we believe that the Oregon Health Authority should provide access to DAA treatment without F-score restriction, and we would be happy to discuss them upon request.

We request that the P&T Committee recommend, and that the Oregon Health Authority adopt, a proposal to eliminate the current F score based limitations on access to DAA treatment for Hepatitis C.

Sincerely,

A handwritten signature in black ink, appearing to read "Beth Englander", with a long horizontal flourish extending to the right.

Beth Englander  
Attorney at Law



## DUR / Pharmacy & Therapeutics Committee Public Comment/Testimony Declaration

The purpose of this form is disclosure declaration. Having an interest or affiliation with a corporate organization does not necessarily preclude a speaker from giving comment, but the relationship must be made known to the audience. Completion of this form shall not disqualify a speaker from giving comment, however, failure to disclose or false disclosure may prompt speaker disqualification.

**Instructions:** Please read all information. Questions marked with an asterisk (\*) are required fields. All required sections must be filled out prior to providing public comment.

SPEAKER INFORMATION	
*Name: <b>Beth Englander</b>	*Date: <b>9-26-18</b>
*Organization: <b>Oregon Law Center</b>	*Topic/Drug: <b>DAA and Hep C treatment</b>
Email Address: <b>benglander@oregonlawcenter.org</b>	Phone Number: <b>503-473-8321</b>
*Are you an employee of a pharmaceutical manufacturer? (If <b>yes</b> , please skip to the last question) <span style="float: right;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</span>	
*Are you an advocate or advocacy organization that receives funding from a Pharmaceutical manufacturer OR a foundation that receives funding from Pharmaceutical entities? <span style="float: right;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</span>	
*Have you been asked to provide testimony by any advocacy group or Pharmaceutical entity? <span style="float: right;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</span>	
*If <b>yes</b> , please identify the organization:	
*If you are a researcher or clinician, do you currently receive grants or other funding from any advocacy or Pharmaceutical entity? <span style="float: right;"><input type="checkbox"/> Yes <input type="checkbox"/> No</span>	
*Are you involved in or have you been involved in any research funded directly or indirectly from private funding? <input type="checkbox"/> Yes <input type="checkbox"/> No	
*If <b>yes</b> , please describe the type of compensation:	
Is there any other information about yourself that the committee should know (e.g. participation in clinical trials, direct ownership and control of investments in a pharmaceutical manufacturer, etc.)?	

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

9-26-18