# Formulary Monograph

## ARISTADA ™ for Extended-Release Injectable Suspension (Aripiprazole Lauroxil)

**Pharmacological class**

- Atypical antipsychotics

**Active ingredient:**

- Aripiprazole lauroxil extended-release injectable suspension
  - 441 mg/1.6 mL
  - 662 mg/2.4 mL
  - 882 mg/ 2.3 mL

**FDA approved indication** (Aristada Prescribing Information §1)

- Aripiprazole lauroxil was approved on 10-05-2015 with an indication for the treatment of schizophrenia

**Dosage** (Aristada Prescribing Information §2)

- Establish tolerability to oral aripiprazole prior to initiating aripiprazole lauroxil
- Initiate aripiprazole lauroxil based on current oral aripiprazole (Table 1)

Table 1. Dosing conversation from oral aripiprazole to Aristada

| Oral Aripiprazole Dose | Intramuscular Aristada Dose |
|---|---|
| **10 mg daily** | 441 mg monthly |
| **15 mg daily** | 662 mg monthly |
| **20 mg or higher daily** | 882 mg monthly |

- Administer Aristada in deltoid muscle (441 mg dose only) or gluteal muscle

- Overlap 21 consecutive days of concurrent oral aripiprazole
- Adjust dose and dosing interval as necessary
    - Approved doses and dosing interval include
        - 441 mg monthly
        - 662 mg monthly
        - 882 mg monthly
        - 882 mg every 6 weeks

- **Missed doses**
    - Administer the next injection as soon as possible
    - If last dose is more than 8 weeks (6 weeks for 441 mg monthly), supplemental oral aripiprazole (same dose as when patient starts on Aristada) is recommended (Table 2)

Table 2. Oral aripiprazole supplementation for missed Aristada doses

| Dose of last Aristada injection | No oral supplementation required | Supplementation with 7 day oral aripiprazole | Supplementation with 21 days oral aripiprazole |
|---|---|---|---|
| **441 mg monthly** | ≤ 6 weeks | >6 and ≤ 7 weeks | >7weeks |
| **662 mg monthly** | ≤ 8 weeks | >8 and ≤ 12 weeks | >12 weeks |
| **882 mg monthly** | ≤ 8 weeks | >8 and ≤ 12 weeks | >12 weeks |
| **882 mg every 6 weeks** | ≤ 8 weeks | >8 and ≤ 12 weeks | >12 weeks |

- Early dosing
    - Aristada injection should not be given earlier than 14 days after the previous injection
- Dose adjustments for CYP450

- If CYP450 modulators are added during the first 21 days of concomitant oral aripiprazole and the first dose of Aristada, refer to the prescribing information for oral aripiprazole
- Once the patient is stabilized on Aristada
  - No recommendation for dosage change if CYP450 modulators are added for less than 2 weeks
  - If CYP450 modulators are added for more than 2 weeks, adjust Aristada according to Table 3.

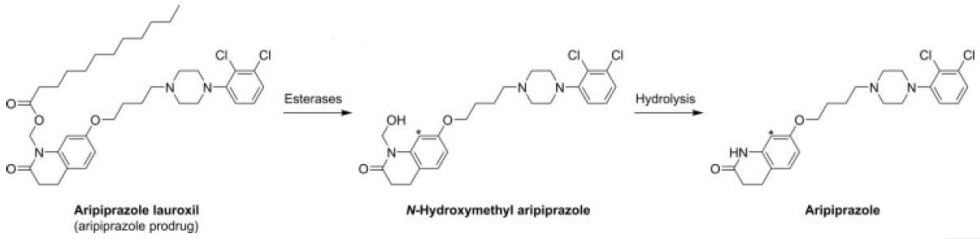
Table 3. Recommendation for adjusting Aristada for concomitant CYP450 modulator use

| **Concomitant CYP450 modulator** | **Dose change for Aristada*** |
|---|---|
| **Strong CYP3A4 inhibitor** | Reduce the dose of Aristada to the next lower strength. No dosage adjustment required for 441 mg, if tolerated. **For patients known to be poor metabolizers of CYP2D6:** Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated. |
| **Strong CYP2D6 inhibitor** | Reduce the dose of Aristada to the next lower strength. No dosage adjustment required for 441 mg, if tolerated. **For patients known to be poor metabolizers of CYP2D6:** No dose adjustment required. |
| **Both strong CYP3A4 inhibitor and strong CYP2D6 inhibitor** | Avoid use for patients at 662 mg or 882 mg dose. No dosage adjustment required for 441 mg, if tolerated. |
| **CYP3A4 inducers** | No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg. |

*For 882 mg every 6 weeks, the next lower strength is 441 mg every 4 weeks

**Pharmacology/pharmacokinetics** (Aristada Prescribing Information §12)

- Aripiprazole lauroxil is a pro-drug of aripiprazole
  - Following injection and slow dissolution, aripiprazole lauroxil is converted by enzyme mediated hydrolysis to N-hydroxymethyl aripiprazole, which subsequently undergoes water-mediated hydrolysis to aripiprazole




Source: FDA; Aristada NDA Summary Review

- **Absorption and distribution**
  - Reach to steady state after the 4th monthly injection
  - With 21 days of oral aripiprazole overlap, therapeutic level is reached within 4 days

- **Metabolism and elimination**
  - Prodrug of aripiprazole; undergoes enzyme-mediated hydrolysis, and then water mediated hydrolysis to form aripiprazole. Aripiprazole is eliminated hepatically by CYP3A4 & CYP2D6
  - Mean elimination half-life: 29.2 days to 34.9 days

**Clinical trial**

- The efficacy of Aristada in schizophrenia was established on the basis of established efficacy from oral aripiprazole
- Meltzer HY, 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.

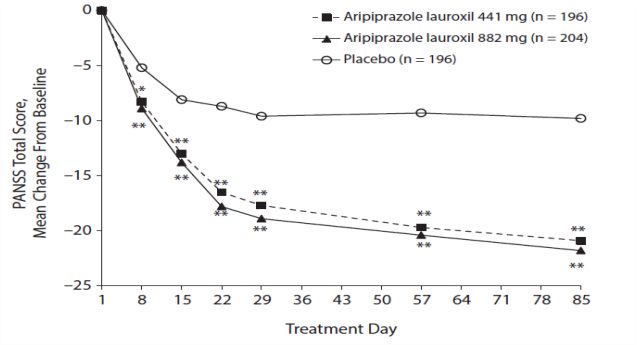
| **Patient population**<br>**Adult (18-70 y/o); schizophrenia (DSM-IV-TR)** |
|---|
| **Design**<br>• **12-week trial**<br>• **1:1:1 randomization to aripiprazole lauroxil 441 mg, 882 mg, placebo**<br>○ **3 week oral overlap**<br>○ **Active arms: aripiprazole 15 mg PO daily** |
| **Outcomes**<br>• **Primary: change in PANSS total score from baseline to day 85**<br>• **Secondary: CGI-I score at day 85** |

**Patient population**
**Adult (18-70 y/o); schizophrenia (DSM-IV-TR)**

**Results**

| **Aripiprazole Lauroxil** | | **Placebo** |
|---|---|---|
| **441 mg ( n=207)** | 882 mg (n=208) | (n=208) |

**Primary:**

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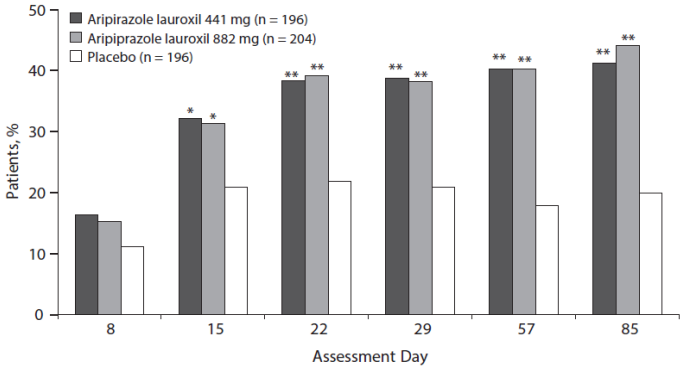

| Patient population<br>Adult (18-70 y/o); schizophrenia (DSM-IV-TR) | | | |
|---|---|---|---|
| **Safety** | | | |
| | **Aripiprazole** | | |
| | **441 mg** | **882 mg** | **Placebo** |
| **Any TEAE*** | 58.9% | 57.2% | 62.3% |
| **Akathisia** | 11.6% | 11.5% | 4.3% |
| **Injection site pain** | 3.4% | 4.8% | 1.9% |
| **Weight increase** | 2.9% | 2.4% | 0.5% |
| **Sedation** | 1.9% | 2.4% | 1.4% |
| **Restlessness** | 2.9% | 1.9% | 1.9% |

*Treatment emergent adverse effect

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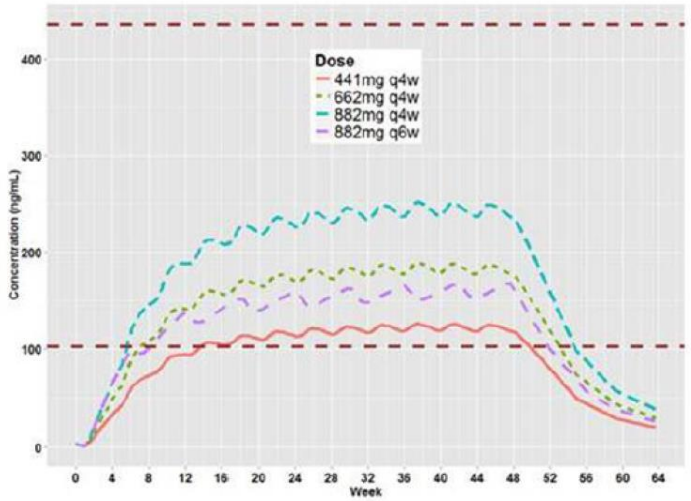
**Pharmacokinetic stimulation study for Aristada 662 mg monthly and 882 mg every 6 weeks**

- For the two unstudied dosing regimens (662 mg monthly and 882 mg every 6 weeks), simulated pharmacokinetic modeling demonstrated the steady state levels of both regimen fall between 441 mg monthly and 882 mg every 6 weeks




Source: FDA; Aristada NDA Summary Review

**Current DSHS formulary alternative**

- Abilify Maintena

**Comparison between Aristada and Abilify Maintena**

Comparison of equivalent aripiprazole content in Aristada and Abilify Maintena

| Aristada Dose | Abilify Maintena Dose | Aripiprazole Content |
|---|---|---|
| **441 mg** | 300 mg | 300 mg |
| | 400 mg | 400 mg |
| **662 mg** | | 450 mg |
| **882 mg** | | 600 mg |

Comparison in TEAE between Aristada and Abilify Maintena Expressed in Number Needed to Harm (NNTH)

| | Aristada | | Abilify Maintena |
|---|---|---|---|
| | **441 mg** | **882 mg** | **400 mg** |
| **Akathisia** | 13 | 13 | 14 |
| **Injection site pain** | 66 | 34 | 21 |

| | Aristada | | Abilify Maintena |
|---|---|---|---|
| | **441 mg** | **882 mg** | **400 mg** |
| **Weight increase** | 41 | 52 | 10 |
| **Sedation** | 200 | 100 | 24 |

Source: Kane JM, et al. J Clin Psychiatry 2014;75(11):1254–1260. & Meltzer HY, et al. J Clin Psychiatry 2015;76(8):1085–1090.

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