New Formulation – Risperidone Subcutaneous LAI (Perseris®)
FDA Approved July 2018

Indication: Risperidone Subcutaneous LAI is indicated for the treatment of schizophrenia in adults

Mechanism:

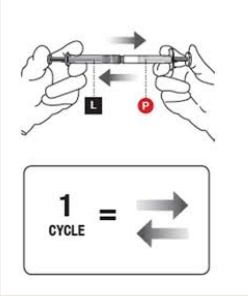
Risperidone functions as a potent 5-HT_2 & dopamine-D_2 receptor antagonist. Alpha$_1$, α_2 adrenergic, & histaminergic receptors are also antagonized with high affinity. Risperidone exhibits low to moderate affinity for 5-HT_{1C}, 5-HT_{1D}, & 5-HT_{1A} receptors and weak affinity for D_1 receptors. The clinical effect results from the concentrations of both risperidone and its major metabolite 9-hydroxyrisperidone (paliperidone)

Dosage

- Establish tolerability with oral risperidone
- Risperidone SC may be initiated at a dose of 90 mg or 120 mg once monthly
    - 90-mg dose corresponds to 3 mg/day oral risperidone and 120-mg dose corresponds to 4 mg/day oral risperidone
- Total monthly dose 90 mg or 120 mg - do not give more than one dose a month
- Supplementation with oral risperidone is not recommended
- Renal or hepatic impairment: Cautiously titrate on oral risperidone up to at least 3 mg before starting treatment with risperidone SC dose of 90 mg

Administration

- Constitute the product by coupling the liquid (L) and powder (P) syringes & passing the contents back & forth between the syringes
- Complete mixing involves 60 cycles (back-and-forth process; 5 premixing cycles & 55 additional cycles)
- Incorrectly mixed medication could result in incorrect dosage
- Administer by subcutaneous injection only in the abdomen by a healthcare professional



How supplied: Available in dosage strengths of 90 mg & 120 mg

Storage: Store the risperidone SC kit in refrigerator and allow to come to room temperature for at least 15 minutes prior to preparation for administration. Unopened kits may be stored at room temp for up to 7 days prior to administration (use within 7 days or discard)

DDI

- Strong CYP3A4 inducers decrease risperidone plasma concentrations (eg. carbamazepine)
- Strong CYP 2D6 inhibitors increase risperidone plasma concentrations (eg. paroxetine & fluoxetine)

Pharmacokinetics

Onset	"clinically relevant levels" reached after the 1st injection
Half-life elimination	9 to 11 days
Metabolism	▪ extensive hepatic metabolism via CYP2D6 to 9-hydroxyrisperidone ▪ 2nd minor pathway: N-dealkylation
T_{max}	1st peak 4 to 6 hours (initial drug release d/t depot formation process) 2nd peak 10 to 14 days post-dose (slow release from the SC depot)
Steady state	attained by the end of the 2nd inj; maintained for 4 weeks after the last inj
Excretion	Urine (70%); feces (14%)

**may take up to 2 weeks to fully assess tolerability based on oral aripiprazole half life
1. With the addition of the single Aristada Initio and a 30-mg oral aripiprazole with the 1st Aristada dose

Clinical Studies

Efficacy: The efficacy of risperidone SC LAI was evaluated in an 8-week randomized, double-blind, placebo-controlled study

- To establish tolerability, participants received 2 doses of 0.25 mg oral risperidone (24 hrs apart) at the screening visit (3 to 8 days prior to treatment initiation)
- 354 participants (18 to 55 yo) experiencing acute exacerbations of schizophrenia were randomized to receive risperidone SC 90 mg, 120 mg or placebo 28 days apart
- The primary endpoint was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the study (day 57). The secondary endpoint was the Clinical Global Impression Severity of Illness (CGI-S) scale score at day 57
- Both 90 & 120 mg doses of risperidone SC showed statistically significant improvement in the primary & secondary efficacy endpoints
    - Improvement in the PANSS total score (placebo-subtracted difference)
    - risperidone SC 90 mg: -6.50 [95% CI: -10.87, -2.13], risperidone SC 120 mg: -10.24 [95% CI: -14.64, -5.85]

Safety: Safety was evaluated in 814 participants with schizophrenia who received at least one dose of risperidone SC during clinical trials

- 322 patients received risperidone SC for at least six months, of which 234 pts received the medication for at least 12 months
- Risperidone SC systemic safety profile was consistent with that of oral risperidone
- The most commonly observed adverse reaction (incidence ≥5% & at least twice that for placebo) in the Phase 3 trial were
    - increased weight, sedation/somnolence & musculoskeletal pain
- The most common injection site reactions (≥5% of all patients) were
    - injection site pain & erythema
- Adverse reactions occurring ≥5% in any risperidone SC treated group & greater than placebo during the 8-week double blind study were
    - increased weight, constipation, sedation/somnolence, pain in extremity, back pain, akathisia, anxiety & musculoskeletal pain

Role in Therapy

Perseris® the first SC risperidone-containing long-acting injection appears to be effective and offers a new once-monthly injectable treatment option that does not require a loading dose or a supplemental oral dose

- the SC depot formulation helps achieve the 1st peak of risperidone within 4 to 6 hours due to an initial drug release during the depot formation process
    - a quicker time to therapeutic concentration, however
    - other LAI options available which do not require concurrent oral therapy (please see comparison table below)

- Risperidone SC available in 90 mg (0.6ml) & 120 mg (0.8ml) dosage strengths only
    - 90-mg dose corresponds to 3 mg/day oral risperidone and 120-mg dose corresponds to 4 mg/day oral risperidone based on average plasma concentration of risperidone and total active drug
        - Clts on stable oral risperidone doses <3 mg/day or >4 mg/day may not be candidates for risperidone SC LAI
- Risperidone SC may improve adherence, but like other LAI antipsychotics, its effects cannot be reversed if toxicity occur. Use of risperidone SC may lead to side-effects like weight gain, constipation, sedation/somnolence, pain, akathisia, & anxiety

**may take up to 2 weeks to fully assess tolerability based on oral aripiprazole half life

1. With the addition of the single Aristada Initio and a 30-mg oral aripiprazole with the 1st Aristada dose

- Also available as generic oral tablet, ODT & solution, as well as brand LAI Risperdal Consta®
    - PO formulations approved for schizophrenia, bipolar mania, & irritability associated with autistic disorder. Risperdal Consta approved for schizophrenia & bipolar I disorder

Formulary Recommendation

BHRS: PA required
CA/CMC: PA required
HPSM MC/HF/HW: NF

APPROVAL CRITERIA

Covered Uses: All medically accepted indications

Required Medical Information: History of noncompliance with oral antipsychotics or difficulty in swallowing oral medications

Prescriber Restrictions: none

Duration of Approval: 12 months

QL: 90mg or 120mg per 28DS, MADD

Refrences

- Aristada Initio [prescribing information]. Waltham, MA. Alkermes, Inc; June 2018.
- Abilify Maintena [prescribing information]. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd; March 2018.
- Invega Sustenna [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; June 2017.
- Invega Trinza [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; March 2018.
- Jann, Michael W., and Scott R. Penzak. "Long-Acting Injectable Second-Generation Antipsychotics: An Update and Comparison between Agents." *CNS drugs* (2018): 1-17.
- Lexicomp Online. Accessed July 20, 2018.
- Isitt, John J., et al. "Health-related quality of life in acute schizophrenia patients treated with RBP-7000 once monthly risperidone: An 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study." *Schizophrenia research* 174.1-3 (2016): 126-131.
- Micromedex Online. Accessed July 20, 2018.
- Nasser, Azmi F., et al. "Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study." *Journal of clinical psychopharmacology* 36.2 (2016): 130-140.
- Perseris [prescribing information]. North Chesterfield, VA: Indivior, Inc; July 2018.
- Risperdal Consta [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; March 2018.

**may take up to 2 weeks to fully assess tolerability based on oral aripiprazole half life
1. With the addition of the single Aristada Initio and a 30-mg oral aripiprazole with the 1st Aristada dose

Comparison of 2nd generation long-acting injectable antipsychotics

Generic (Brand)	Indication	Dosing	Oral dosing at initiation	Administration/Storage
Aripiprazole lauroxil (Aristada Initio®)	Schizophrenia	675 mg IM once + 30 mg aripiprazole PO once + one Aristada IM inj within 10 days	Yes, aripiprazole 30 mg PO once	▪Tap & shake syringe vigorously for at least 30 seconds prior to use ▪Store at room temperature
Aripiprazole lauroxil (Aristada®)	Schizophrenia	441, 662, 882 mg IM once monthly, or 882 mg Q6-weeks or 1064 mg Q2-months	Yes, aripiprazole PO for 21 days	▪Tap 10 times, shake syringe vigorously for at least 30 seconds prior to use ▪ Inject over *<10 seconds* into deltoid or gluteal muscle (441 mg), gluteal only (662 or 882 mg) ▪Store at room temperature
Aripiprazole (Abilify Maintena®)	Schizophrenia Bipolar I	300 or 400 mg IM once monthly	Yes, aripiprazole PO for 14 days	• Shake syringe vigorously for 20 seconds, shake vials for 30 sec • Inject *slowly* into deltoid or gluteal muscle (300 or 400 mg) •Protect from light. Store in the original package
Paliperidone palmitate (Invega Trinza®)	Schizophrenia	273 mg, 410 mg, 546 mg, or 819 mg IM Q3-months. Previous treatment with once monthly Invega Sustenna is required	Not needed	▪Shake syringe vigorously for at least 15 seconds within 5 minutes prior to use ▪Administer using only the needles provided in the kit
Paliperidone palmitate (Invega Sustenna®)	Schizophrenia	▪Initiation: 234 mg IM followed by 156 mg IM one week later ▪39 mg, 78 mg, 117 mg, 156 mg, or 234 mg IM once monthly	Not needed	▪Administer using only the needles provided in the kit
Olanzapine (Zyprexa Relprevv®)	Schizophrenia	▪150 or 210 mg IM Q-2 weeks ▪300 or 405 mg IM Q-4 weeks	Not needed	Reconstituted suspension may be stored at room temperature and used within 24 hours. Shake vigorously to resuspend prior to use
Risperidone (Risperdal Consta®)	Schizophrenia Bipolar I	12.5 mg, 25 mg, 37.5 mg, and 50 mg IM Q-2 weeks	Yes, 21 days	Store dose pack in the refrigerator, protect from light
Perseris®	Schizophrenia	90 mg or 120 mg once monthly SC injection in the abdomen	Loading or supplemental PO dose not recommended	▪Constitute by coupling the liquid & powder syringes & passing the contents back & forth between the syringes. Incorrectly mixed medication could result in incorrect dosage ▪Administer using the prepackaged syringe & enclosed safety needle

**may take up to 2 weeks to fully assess tolerability based on oral aripiprazole half life

1. With the addition of the single Aristada Initio and a 30-mg oral aripiprazole with the 1st Aristada dose