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Oregon State  
UNIVERSITY

**Drug Use Research & Management Program**

Oregon State University, 500 Summer Street NE, E35

Salem, Oregon 97301-1079

College of Pharmacy

Phone 503-947-5220 | Fax 503-947-1119



## Literature Scan: Parenteral Antipsychotics

**Date of Review:** September 2017

**Date of Last Review:** September 2016

**Literature Search:** July 22, 2017

**Current Status of PDL Class:**

See **Appendix 1**.

**Conclusions:**

- Since the last literature scan one new systematic review has been published to compare the safety and tolerability of oral antipsychotics to long acting injectable versions of the same drug.<sup>1</sup> There were no significant differences between long acting injectable agents and oral antipsychotics on the incidence of serious adverse events or treatment discontinuation due to adverse events.<sup>1</sup>

**Recommendations:**

- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

**Previous Conclusions:**

- One new high quality systematic review was published since the parenteral antipsychotic agents were last reviewed in May 2016. Otherwise, no new clinical practice guidelines, formulations, indications, or safety alerts were identified.
- One systematic review with meta-analysis specifically evaluated long-acting injectable risperidone. Evidence shows the drug may have similar efficacy and harms as oral second-generation antipsychotics and other long-acting parenteral antipsychotics.
- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

**Previous Recommendations:**

- No further review or research needed at this time.
- After comparison of drug costs in the executive session, add Abilify Maintenna (aripiprazole) extended-release injectable suspension and Aristada (aripiprazole lauroxil) extended-release injectable suspension to the Oregon Health Plan fee-for-service Preferred Drug List contingent upon executed supplemental rebates.

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**Background:**

Schizophrenia is the most common psychotic disease, with a global prevalence of less than 1%.<sup>2</sup> However, because it is a disabling condition that adversely impacts productivity, it is ranked by the World Health Organization as one of the top 10 illnesses that contributes to global burden of disease.<sup>2</sup> In a 2010 study, the mean annual health care costs of an American patient with schizophrenia were estimated at approximately \$15,000 per year.<sup>3</sup> Schizophrenia is slightly more common in men compared to women. Symptom onset generally occurs between late adolescence and the third decade of life. Schizophrenia is characterized by positive symptoms (delusions and hallucinations), negative symptoms (impaired motivation and social withdrawal) and cognitive impairment.<sup>4</sup> The positive symptoms tend to relapse and remit. The negative and cognitive symptoms tend to be chronic and can have a long term impact on social function. The most effective treatment for schizophrenia is a multipronged approach including medication, psychological treatment and social support.

First line medication treatments for schizophrenia are either first generation antipsychotics (FGA) or second generation antipsychotic (SGA) agents. The FGA parenteral antipsychotics include chlorpromazine, fluphenazine, and haloperidol while SGA parenteral antipsychotics include aripiprazole, olanzapine, paliperidone, risperidone and ziprasidone. Long-acting injection (LAI) depot preparations of antipsychotics are widely used, especially for treating patients who show non-adherence or partial adherence to oral therapy. The proposed benefits of LAI's are their relapse-preventing properties, patient convenience, and improved compliance.<sup>5</sup> Drug adherence is essential in improving clinical and social outcomes in schizophrenia. The dosing and administration of the long acting parenteral antipsychotic agents is presented in **Table 1**. Chlorpromazine and ziprasidone are not available as long acting parenteral agents and are used to manage acute symptoms in schizophrenic patients.

In 2012 an Agency for Healthcare Research and Quality (AHRQ) systematic review evaluated the comparative benefits and harms of FGAs to SGAs in treating schizophrenia and found there were few differences in total symptom score improvement between the 2 classes of drugs.<sup>6</sup> The FGAs are dopamine antagonists while the SGAs are partial dopamine antagonists but also block serotonin and norepinephrine.<sup>7</sup> It is the differences in pharmacologic activity that appear to result in different adverse effect profiles between the 2 generations of antipsychotics. The FGAs appear to cause more extrapyramidal symptoms while the SGAs seem to cause more weight gain and metabolic changes (hyperglycemia and lipid abnormalities).<sup>7</sup>

In Oregon, drugs for mental health conditions, including antipsychotics, are exempt from the traditional Preferred Drug List (PDL) and prior authorization (PA) requirements. However, specific clinical PA criteria may be placed to restrict medically inappropriate use or to address specific safety risks. In the second quarter of 2017 (April 1, 2017 through July 1, 2017) there were total of 2070 claims for the long acting parenteral antipsychotics. The most utilization was seen with Invega Sustenna (37%) followed by Risperdal Consta (20%), Abilify Maintena (18%), and Haloperidol Decanoate (15%). Minimal utilization of Fluphenazine Decanoate, Invega Trinza or Aristada was noted. Similar trends were observed in the first quarter of 2017. Most LAI's are administered once a month except for Risperdal Consta which must be administered twice a month. Aristada may be administered every 4, 6 or 8 weeks depending on the dose and Invega Trinza is given every 3 months.

**Table 1. Dosing and Administration of Long Acting Parenteral Antipsychotics<sup>8</sup>**

	<b>Aripiprazole extended release</b>	<b>Aripiprazole lauroxil</b>	<b>Fluphenazine decanoate</b>	<b>Haloperidol decanoate</b>	<b>Olanzapine pamoate</b>	<b>Paliperidone palmitate (4-week)</b>	<b>Paliperidone palmitate (12-week)</b>	<b>Risperidone microspheres</b>
<b>Brand name</b>	Abilify Maintena	Aristada	Prolixin	Haldol Decanoate	Zyprexa Relprevv	Invega Sustenna	Invega Trinza	Risperdal Consta
<b>Injection interval</b>	4 weeks	4 weeks (662 mg) 6 weeks (882 mg) 8 weeks (1064 mg)	2 to 4 weeks	4 weeks	2 to 4 weeks	4 weeks	12 weeks	2 weeks
<b>Available dosage strengths</b>	300 mg 400 mg	441 mg 662 mg 882 mg 1064 mg	25 mg/mL (variable dose)	50 mg/mL 100 mg/mL (variable dose)	210 mg 300 mg 405 mg	39 mg 78 mg 117 mg 156 mg 234 mg	273 mg 410 mg 546 mg 819 mg	12.5 mg 25 mg 37.5 mg 50 mg
<b>Dose range (adult)<sup>†</sup></b>	200 to 400 mg	441 to 1064 mg	12.5 to 100 mg	20 to 450 mg	150 to 405 mg	39 to 234 mg	273 to 819 mg	12.5 to 50 mg
<b>Maximum recommended dose</b>	400 mg every 4 weeks	882 mg every 4 weeks	100 mg every 2 weeks	450 mg every 4 weeks	300 mg every 2 weeks	234 mg every 4 weeks	819 mg every 12 weeks	50 mg every 2 weeks
<b>Injection site</b>	Deltoid or gluteal	Deltoid (441 mg only)	Gluteal	Gluteal	Gluteal	Deltoid only (load)	Deltoid or gluteal	Deltoid or gluteal

		Gluteal (441, 662, 882, or 1064 mg)				Deltoid or gluteal (maintenance)		
<b>Injection technique</b>	Standard	Standard	Z-Track	Z-Track	Standard	Standard	Standard	Standard

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

A meta-analysis and systematic review evaluated randomized controlled trials (RCTs) to assess the safety and tolerability of LAIs versus oral antipsychotics (OAPs).<sup>1</sup> Given that LAIs are administered in large single doses that cannot be rapidly discontinued there was concern that LAIs are underutilized due to the risk of possible adverse effects.<sup>9</sup> Only RCTs that randomized patients to the same antipsychotic, either as an LAI or OAP, were included in the analysis. The primary outcome was treatment discontinuation due to adverse events in trials that were conducted for at least 8 weeks (mean duration=52 weeks). Secondary outcomes included serious adverse events, death, greater than one adverse event and individual adverse event rates.<sup>1</sup>

Sixteen RCTs evaluating treatment of schizophrenia with antipsychotic therapy (n=4902) were included in the analysis. The studies were of low to moderate quality due to unclear randomization and blinding of outcome assessors which increased the risk of selection and detection biases. However, the systematic review was evaluated as having good methodological quality using the AMSTAR tool.<sup>10</sup>

Treatment discontinuation due to adverse events was not significantly different between LAIs and OAPs (RCTs = 14, n = 3570, relative risk (RR) 1.163, 95% confidence interval (CI) 0.88–1.52, p = 0.275).<sup>1</sup> The incidence of serious adverse events was not significantly different between LAIs and OAPs (RR 0.907, 95% CI 0.66–1.24, p = 0.542).<sup>1</sup> Altogether, 3 deaths occurred in the LAI groups (n = 2311) and 6 deaths occurred in the OAP group (n = 1816), without significant group difference (RR 0.613, 95% CI 0.17–2.12, p = 0.441).<sup>1</sup> The incidence of patients with at least one adverse event was not significantly different between LAIs and

OAPs (RR 1.026, 95% CI 0.98–1.07,  $p = 0.231$ ).<sup>1</sup> With respect to specific adverse effects, LAIs were associated with significantly more akinesia (RR 20.54, 95% CI 1.24–337.94,  $p = 0.034$ , NNH = 3), low-density lipoprotein cholesterol increases (standardized mean difference (SMD) 0.096, 95% CI 0.006–0.18,  $p = 0.037$ ) and anxiety (RR 1.495, 95% CI 1.13–1.97,  $p = 0.005$ , NNH = 40) compared to OAPs.<sup>1</sup> Conversely, LAIs were associated with significantly lower prolactin change (SMD – 0.152, 95% CI – 0.26 to – 0.043,  $p = 0.006$ ) than OAPs. This meta-analysis concluded there were no significant differences between LAIs and OAPs on the incidence of serious adverse events or treatment discontinuation due to adverse events.

**New Guidelines:** No new guidelines have been published since the last literature scan.

**New FDA Drug Approvals:** No new drugs have been FDA approved since the last literature scan.

**New Formulations/Indications:**

The Food and Drug Administration (FDA) approved Abilify Maintena® for maintenance monotherapy treatment of bipolar I disorder in adults as of July 2017. The approval is based on RCT findings that indicated extended release injections of aripiprazole delayed time to recurrence of mood episode in adults with manic episodes.<sup>11</sup> To assess efficacy and safety of aripiprazole once-monthly (AOM) 400 mg injection, researchers conducted a 52-week, phase 3, double-blind, randomized withdrawal trial among adults with bipolar I disorder who experienced a manic or mixed episode that required hospitalization. The primary endpoint was time from randomization to recurrence of any mood episode. Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study.<sup>11</sup> The researchers imputed the data from patients who discontinued therapy using 3 different sensitivity analyses including a worst case analysis which assumed discontinued patients were to have recurrences one day after discontinuation.

AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo over one year (hazard ratio 0.45; 95% CI 0.30 to 0.68;  $P < 0.0001$ ).<sup>11</sup> Significantly fewer patients ( $P < 0.0001$ ) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%) over 52 weeks, with the effects observed predominantly on manic episodes ( $P < 0.0001$ ).<sup>11</sup> Treatment-emergent adverse events which were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety (total incidence >5%).<sup>11</sup> During the stabilization phase (transition from oral tablets to long acting injectable agent), treatment-emergent adverse events included akathisia (17.4%), weight increase (11.1%), insomnia (9.6%), anxiety (7.1%), restlessness (5.6%), fatigue (5.2%), and nasopharyngitis (5.2%).<sup>11</sup>

A new dosing regimen for Aristada® (aripiprazole laurixil) was FDA approved for every 2 months as of June 2017.<sup>12</sup> Prior to the latest approval, aripiprazole laurixil was only approved to be administered intramuscularly in doses ranging from 441, 662, or 882 mg every month or 882 mg every 6 weeks. A 1064 mg/3.9 ml strength kit designed to be administered every 2 months is now being marketed by the manufacturer. Tolerability to oral aripiprazole should be established before initiating treatment with long acting injectable doses of aripiprazole.

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**New FDA Safety Alerts:**

The labeling for Invega Sustenna® (paliperidone palmitate) was updated to include long term data on hyperprolactinemia associated with paliperidone palmitate therapy in June 2017.<sup>13</sup> Data was obtained from one 33 week double blind placebo controlled trial in patients with schizophrenia. Four females (4.2%) in the paliperidone palmitate group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1).<sup>13</sup> One male (0.9%) in the paliperidone palmitate group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.<sup>13</sup>

In another trial conducted in patients with schizoaffective disorder over 15 months, 11 females (13.9%) with elevated prolactin levels in the paliperidone palmitate group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3). Only 5 females (5.8%) in the placebo group had 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1).<sup>13</sup> Six males (7.1%) in the paliperidone palmitate group experienced 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) in the placebo group experienced adverse reaction of increased blood prolactin.<sup>13</sup>

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## References:

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13. Invega Sustenna (paliperidone extended release injection) Prescribing Information. Titusville, NJ; Janssen Pharmaceuticals. 06/2017. <https://www.invegasustennahcp.com/sites/www.invegasustennahcp.com/files/prescribing-information-invegasustenna.pdf>. Accessed 8/8/17.

**Appendix 1: Current Status on Preferred Drug List**

Brand	Generic	Route	Formulation	PDL	Carve out
CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	INJECTION	AMPUL	Y	Y
FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	INJECTION	VIAL	Y	Y
FLUPHENAZINE HCL	FLUPHENAZINE HCL	INJECTION	VIAL	Y	Y
HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y	Y
HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALDOL	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y	Y
HALOPERIDOL	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y	Y
HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	INJECTION	VIAL	Y	Y
RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	INTRAMUSC	SYRINGE	Y	Y
ABILIFY MAINTENA	ARIPIRAZOLE	INTRAMUSC	SUSER VIAL	Y	Y
ABILIFY MAINTENA	ARIPIRAZOLE	INTRAMUSC	SUSER SYR	Y	Y
ARISTADA	ARIPIRAZOLE LAUROXIL	INTRAMUSC	SUSER SYR	Y	Y
OLANZAPINE	OLANZAPINE	INTRAMUSC	VIAL	V	Y
ZYPREXA	OLANZAPINE	INTRAMUSC	VIAL	V	Y
GEODON	ZIPRASIDONE MESYLATE	INTRAMUSC	VIAL	V	Y
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	INTRAMUSC	SYRINGE	V	Y
INVEGA TRINZA	PALIPERIDONE PALMITATE	INTRAMUSC	SYRINGE	V	Y
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	INTRAMUSC	VIAL	V	Y

## Appendix 2: New Clinical Trials

A total of 18 citations were manually reviewed from the literature search. After further review, 17 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. The full abstract is included in **Appendix 3**.

**Table 1:** Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Calabrese JR et al <sup>11</sup>  DB, PC, MC, RCT  52 weeks	AOM 400mg IM  Vs.  Placebo IM once monthly	Men and women aged 18-65 years with a diagnosis of BP-1 with ≥ 1 manic or mixed episode requiring hospitalization and treatment  N = 266 enrolled, 102 (38.3%) completed the study	Time to recurrence of any mood episode in patients with BP-1	Time to recurrence over 1 year - AOM 400 vs PBO HR = 0.45; 95% CI 0.30 to 0.68 p < 0.0001  Proportion of patients with mood episode recurrence AOM 400 mg 35/132 (26.5%) PBO 68/133 (51.1%) P<0.0001 (CI not reported)

Abbreviations: AOM = aripiprazole once monthly; BP-1 = bipolar disorder type I; CI = confidence interval; DB =double blind; HR = hazard ratio; MC = multi-center; PBO = placebo; PC = placebo controlled; RCT = randomized controlled trial

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### Appendix 3: Abstracts of Clinical Trials

1. Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, Perry P, Hertel P, Such P, Salzman PM, McQuade RD, Nyilas M, Carson WH. *J Clin Psychiatry*. 2017 Mar; 78(3):324-331. doi: 10.4088/JCP.16m11201.

**OBJECTIVE:**

To evaluate efficacy, safety, and tolerability of long-acting injectable antipsychotic aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment for bipolar I disorder (BP-I).

**METHODS:**

In a double-blind, placebo-controlled, 52-week randomized withdrawal study conducted from August 2012 to April 2016, patients with a DSM-IV-TR diagnosis of BP-I currently experiencing a manic episode were stabilized sequentially on oral aripiprazole and AOM 400 and then randomized to AOM 400 or placebo. The primary end point was time from randomization to recurrence of any mood episode. Other end points included proportion of patients with recurrence of any mood episode and recurrence by mood episode type.

**RESULTS:**

Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study. AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio: 0.45; 95% CI, 0.30 to 0.68;  $P < .0001$ ). Significantly fewer patients ( $P < .0001$ ) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%), with the effects observed predominantly on manic episodes ( $P < .0001$ ). Patients were not depressed at study entry, and between-group differences in depressive episodes were not significant ( $P < .864$ ). The treatment-emergent adverse events (incidence  $> 5\%$ ) that were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety.

**CONCLUSIONS:**

AOM 400 delayed the time to and reduced the rate of recurrence of mood episodes and was generally safe and well tolerated. These findings support the use of AOM 400 for maintenance treatment of BP-I.

**TRIAL REGISTRATION:**

ClinicalTrials.gov identifier: NCT01567527.

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**Appendix 4: Medline Search Strategy**

*Ovid MEDLINE(R) without Revisions 1996 to July Week 3 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July*

1	exp Chlorpromazine/	1571
2	exp Haloperidol/	5624
3	exp Fluphenazine/	294
4	exp Aripiprazole/	1909
5	exp Paliperidone Palmitate/	600
6	exp Risperidone/	5385
7	olanzapine.mp.	8001
8	1 or 2 or 3 or 4 or 5 or 6 or 7	19463
9	parenteral.mp.	31727
10	Injections, Intramuscular/	12393
11	Injections/	19278
12	9 or 10 or 11	62671
13	8 and 12	605
14	limit 13 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	18

## Risperdal® Consta® Quantity Limit

**Goal(s):**

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

**Length of Authorization:**

- Date of service or 12 months, depending on criteria

**Requires PA:**

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	<b>Yes:</b> Go to #2	<b>No:</b> Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? <ul style="list-style-type: none"> <li>Medication lost</li> <li>Medication dose contaminated</li> <li>Increase in dose or decrease in dose</li> <li>Medication stolen</li> <li>Admission to a long term care facility</li> <li>Any other reasonable explanation?</li> </ul>	<b>Yes:</b> Approve for date of service only (use appropriate PA reason)	<b>No:</b> Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	<b>Yes:</b> Approve for 1 year (use appropriate PA reason)	<b>Note:</b> This medication should NOT be denied for clinical reasons.

P&T Review: 9/17(DM); 9/16; 5/05  
 Implementation: 10/13/16; 11/18/04