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31 July 2018

Ms Karen Bartlett
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Request on ZYPADHERA® (OLANZAPINE DEPOT)

Dear Ms Bartlett,

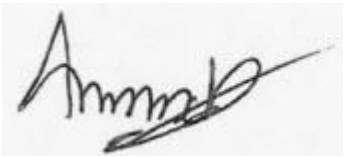
Thank you for your request for medical information.

Please find enclosed the response to your request for medical information on ZYPADHERA.

This is intended only as a scientific exchange in response to a specific unsolicited request. The answer may contain off-label information. Should you require any further assistance, please do not hesitate to contact us.

Current Summaries of Product Characteristics for Lilly products can be found at www.medicines.co.uk.

Yours sincerely



Ammar Nahidh Jawad
Lilly Medical Information
Lilly UK

You asked for information on when to give the next injection if a patient experiences post injection syndrome with olanzapine depot.

If olanzapine LAI therapy is continued, the dose and timing of the next injection may occur as previously scheduled or earlier if clinically indicated for exacerbation of schizophrenia symptoms (Data on file). Alternatively, oral olanzapine supplementation may be considered. The combined total dose of olanzapine from both formulations should not exceed the maximum dose allowed per local product labeling.

Please find attached the following medical letter that we hope you will find useful:

- Olanzapine Long-Acting Injection Post-Injection Syndrome

References

- Data on file, Eli Lilly and Company and/or one of its subsidiaries.
- The ZypAdhera Summary of Product Characteristics, February 2018, is available at: https://www.medicines.org.uk/emc/product/6429/smpc

Olanzapine Long-Acting Injection
Post-Injection Syndrome

The following medical letter contains information regarding treatment with olanzapine long-acting injection and post-injection syndrome. This document is not intended to be an all-inclusive report on this subject as this may be limited by Eli Lilly and Company and/or one of its subsidiaries to include only the information we believe is relevant to your question. For additional prescribing information, please refer to your local product labeling.

SUMMARY

Information on olanzapine long-acting injection therapy and post-injection syndrome is briefly summarized below. This information is discussed in more detail in the sections that follow. Information excluded may pertain to trial methods and limitations, patient population, non-endpoint results, and statistical information.

- During premarketing clinical studies, events that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of olanzapine LAI (Data on file). These events occurred in <0.1% of injections and in approximately 2% of patients. Most of these patients developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, or other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, or possible convulsion.
- In most cases (analysis of 30 post-injection syndrome events in 29 patients in premarketing clinical trials through 14 October 2008), initial signs and symptoms related to this event have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 1.5 to 72 hours after injection (Detke, 2010a). The potential for onset of an event is greatest within the first hour. Events occurred rarely (<1 in 1000 injections) between 1 and 3 hours, and very rarely (<1 in 10 000 injections) after 3 hours (ZypAdhera Summary of Product Characteristics, 2016). Healthcare providers are advised to discuss this potential risk with patients each time they prescribe and administer olanzapine LAI (Detke, 2010a; Data on file).
- Olanzapine LAI should be administered in a healthcare facility (Data on file). After each injection, appropriately qualified healthcare professionals administering olanzapine LAI should observe the patient at the healthcare facility for at least 3 hours for signs and symptoms consistent with olanzapine overdose; and immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose (Detke, 2010a; Zyprexa Relprevv Package Insert, 2016; ZypAdhera Summary of Product Characteristics, 2016).
- For the remainder of the day of the injection, patients should be advised to be vigilant for symptoms of post-injection adverse reactions, should be able to obtain medical assistance if needed, and should not drive or operate machinery (Data on file).
- If an overdose is suspected at any time, close medical supervision and monitoring should be instituted until examination indicates signs and symptoms have resolved

(Detke, 2010a; Data on file). The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose (ZypAdhera Summary of Product Characteristics, 2016).

- If parenteral benzodiazepines are required for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended (Data on file).
- At final clinical trial datalock, a total of 39 post-injection syndrome cases were reported in 38 patients in clinical trials (1 patient experienced 2 events) (Data on file). Based on over 59 000 olanzapine LAI injections given to 2054 patients in clinical trials through 31 December 2010, post-injection syndrome events occurred in approximately 0.07% of injections, or 1.85% of patients. There have been no active Lilly olanzapine LAI interventional clinical trials conducted after 31 December 2010.
- A total of 720 postmarketing cases of post-injection syndrome events have been reported worldwide through 30 August 2016 (Data on file). The clinical profile of the postmarketing spontaneously reported events is generally consistent with the clinical trial cases of post-injection syndrome (Detke, 2010b; Bushe, 2015; Data on file).
- In a multinational, non-interventional, prospective, real-world, observational post-authorization safety study (PASS) conducted to estimate the incidence per injection and per patient of post-injection syndrome events in patients with schizophrenia receiving olanzapine LAI, post-injection syndrome occurred in 0.044% of injections (n=46) and in 1.17% of patients (n=45) (Data on file. Based on an estimation generated of the cumulative probabilities of at least one post-injection syndrome event for a patient over time, it was estimated that it would take 20 injections before the estimated probability of at least one post-injection syndrome event surpasses 1%. These results highlight that the estimated risk at each injection is the same and very rare, and that although the estimated cumulative probability of experiencing at least one event at any injection over time increases, it still remains low.

REVIEW OF LILLY PREMARKETING CLINICAL TRIALS THROUGH 14 OCTOBER 2008

An analysis of post-injection syndrome cases from 8 Lilly premarketing clinical trials (August 2000 through October 2008) in patients aged 18 to 75 years with schizophrenia or schizoaffective disorder receiving olanzapine long-acting injection (LAI; mean exposure, 14 months; range, 2 weeks to 3.8 years) therapy has been conducted (Detke, 2010a). Depending on the specific study, olanzapine LAI doses ranged from 45 to 405 mg, and injection intervals could be of 2, 3, or 4 weeks. Injections given at 2-week intervals could not exceed a dose of 300 mg. Please note this section provides a summary of the first 30 post-injection syndrome events reported in clinical trials.

Full Description of Post-Injection Syndrome Cases

Table 1 in Appendix 1 includes a summary of the 30 post-injection syndrome cases reported in 29 patients in clinical trials through 14 October 2008 (Detke, 2010a). Events occurred at various olanzapine LAI doses, cumulative exposure lengths, and injection numbers.

Clinical Symptoms Observed with Post-Injection Syndrome Events

Signs and symptoms of post-injection syndrome were consistent with some of those observed in oral olanzapine overdose (Detke, 2010a). Based on 30 post-injection syndrome events, Table 1 provides a summary of clinical symptoms of post-injection syndrome observed in at least 2 cases during clinical trials. Delirium-related adverse events (AEs) (disorientation, confusion, ataxia, and dysarthria) were reported in 97% of the events. Sedation-related AEs, defined as somnolence, sedation, or other change in level of consciousness (for example, unconsciousness, such that the patient could not be aroused), were reported in 87% of the events. All cases presented with at least 1 symptom related to either delirium or sedation; both delirium- and sedation-related symptoms were reported in 83% of the post-injection syndrome events. Initial symptoms included delirium-related symptoms in 47% of cases and sedation-related symptoms in 40% of cases. However, in another 40% of cases, the first symptoms noted did not include signs of sedation or delirium, but were instead related to general malaise or other symptoms, such as extrapyramidal symptoms (EPS), agitation, anxiety, or irritability. In those cases, the delirium or sedation developed subsequent to the initial symptoms. Of the 7 patients who lost consciousness during the post-injection syndrome event, the longest period of unconsciousness was 12 hours. Appendix 2 includes the case definition utilized to evaluate and identify post-injection syndrome events.

Table 1. Summary of Clinical Symptoms of Post-Injection Syndrome Events in Clinical Trials (Detke, 2010a)

Clinical Symptoms of Post-Injection Syndrome Events[a] – Grouped	Presented Initially, N (%)	Occurred at Any Time, N (%)
Sedation (eg, somnolence, sedation, unconsciousness)	12 (40)	26 (87)
Delirium (combined)	14 (47)	29 (97)
Speech impairment (eg, dysarthria)	7 (23)	21 (70)
Motor impairment (eg, ataxia)	7 (23)	12 (40)
Cognitive impairment (eg, confusion, disorientation)	8 (27)	17 (57)
EPS, akathisia, tension, or cramps in extremities	3 (10)	7 (23)
Agitation, aggression, irritability, anxiety, restlessness[b]	2 (7)	9 (30)
General malaise (eg, weak, dizzy, felt bad)	19 (63)	20 (67)
Hypertension	1 (3)	2 (7)
Possible seizure/convulsion	0 (0)	2 (7)

Abbreviations: EPS = extrapyramidal symptoms; N = number of patients.

[a]Based on 30 events.

[b]Restlessness may also be a manifestation of EPS (akathisia).

Incidence Rates

In clinical trials through 14 October 2008, a total of 30 post-injection syndrome events were reported in 29 patients (Detke, 2010a). Based on approximately 45 000 injections of olanzapine LAI given to 2054 patients in clinical trials as of that date, post-injection syndrome events had occurred in approximately 0.07% of injections, or 1.4% of patients. This is consistent with a reported rate of Hoigne's syndrome following accidental intravascular injection of intramuscular (IM) procaine penicillin G (0.08% of injections) (Downham, 1978). Based on an analysis from a locked database conducted earlier in April 2008 (which included 29 post-injection syndrome events), the mean exposure to

olanzapine LAI therapy was 14 months (range, 2 weeks to 3.8 years) or 20 injections per patient (range, 1 to 100 injections), for a total of 2353.5 patient-years of exposure (Detke, 2010a). This yielded a post-injection syndrome incidence rate of 1.2 events per 100 patient-years.

Onset and Progression

The mean time to onset of symptoms for a post-injection syndrome event was 49 minutes (median, 25 minutes; range, 0 to 300 minutes), with 80% occurring within 1 hour post-injection (Detke, 2010a). Time to incapacitation was defined as the presence of clinically significant disorientation, ataxia, or sedation, such that the patient would not have been able to seek assistance on his own. Of the 22 cases that met criteria for incapacitation, 21 cases contained enough information to determine when the patient was first observed in an incapacitated state. The mean time to incapacitation was 75 minutes post-injection (median, 60 minutes; range, 10 to 300 minutes). The mean time to hospitalization was 178 minutes (median, 150 minutes; range, 50 to 420 minutes). The median time to incapacitation was 35 minutes later than the median time of onset of the post-injection syndrome event. The median time to hospitalization for those hospitalized (23/30 total cases, or 77%) was approximately 2 hours after the median time of onset.

Post-injection syndrome events have not been characterized by a sudden onset of incapacitation, but usually began with milder symptoms that progressed in number and/or severity (Detke, 2010a). The duration of the post-injection event varied from 1.5 to 72 hours.

Vital Signs, ECGs, EEGs, and Other Testing

There were no clinically significant decreases in vital signs observed in the cases where this information was available (n=26) (Detke, 2010a). No orthostatic hypotension, bradycardia, or respiratory depression was reported. Two patients had clinically significantly increased blood pressure during the event, which subsequently responded to treatment with antihypertensives.

Based on available electrocardiogram (ECG) information (n=13), right bundle branch block was identified in 1 case (determined to be the result of long-standing arterial hypertension and not related to treatment with olanzapine LAI) (Detke, 2010a). No other clinically significant ECG changes were observed.

Of the 4 cases where electroencephalograms (EEGs) were obtained, 2 cases had clinical presentations described as convulsive movements, although the EEG results did not provide evidence of seizure (Detke, 2010a). In 1 of these 2 cases, the EEG was reported as normal. In the second case, an EEG performed approximately 10 days after the event was interpreted as abnormal based on the presence of diffuse disorganization. This, however, was not supportive of paroxysmal activity or epileptic foci. In a third patient on whom an EEG was performed, the EEG was reported as normal. In a fourth case involving a patient with diabetes, the EEG showed generalized slowing of waves consistent with metabolic and/or pharmacological encephalopathy.

There were no clinically significant findings in the cases where a computed tomography (CT) scan was performed (n=9) (Detke, 2010a).

A urine and/or blood toxicology screen was performed in 9 of the cases (Detke, 2010a). In 8 cases, the screens were negative for alcohol, sedatives, or illicit substances. In 1 case, the patient was treated with benzodiazepines upon arriving at the hospital, resulting in a blood toxicology screen that was positive for benzodiazepines.

Hospitalization and Treatment

Seventy-seven percent of the patients were hospitalized during the post-injection syndrome event (Detke, 2010a). The majority (63%) of post-injection syndrome events resolved either with no treatment or were managed with only observation and fluids. In the remainder of the events, the patient was hospitalized and received medical treatment beyond observation and fluids, often to treat specific symptoms or concomitant medical illness, although some treatments appear to have been administered prophylactically. Six patients received treatment with oral or parenteral benzodiazepines. Three patients were catheterized: 1 due to urinary retention and 2 prophylactically. One patient was placed in mechanical restraints because of agitation. Two patients were ventilated as a precautionary measure following benzodiazepine administration; 1 due to an apparent seizure and the other to manage severe agitation so that a CT scan could be performed. No respiratory depression was noted in either case.

Recovery and Post-Recovery Outcomes

All patients fully recovered from the post-injection syndrome event within 1.5 to 72 hours after onset (Detke, 2010a). In the majority (70%) of events, patients continued to receive further treatment with olanzapine LAI following the event. At the time of datalock, the median number of additional days of study participation following a post-injection syndrome event was 184 days, and the median number of subsequent injections received following the event was 9. Only 1 patient experienced a second post-injection syndrome event, with the second event occurring approximately 6 months after the first event. The absolute number of AEs overall did not appear to increase following a post-injection syndrome event compared with prior to the post-injection syndrome event. Median number of AEs experienced by patients prior to the post-injection syndrome event was 1; median number of AEs reported by patients at any time after the post-injection syndrome event was 0.

In 13 cases, there was no change in dose following the post-injection syndrome event, whereas in 8 cases, the olanzapine LAI dose was decreased at the next injection following the event (Detke, 2010a). No patients received oral olanzapine supplementation following a post-injection syndrome event.

UPDATE OF POST-INJECTION SYNDROME CASES THROUGH 30 AUGUST 2016

Clinical Trials

At final clinical trial datalock, a total of 39 post-injection syndrome cases were reported in 38 patients in clinical trials (1 patient experienced 2 events) (Data on file). The longest patient exposure to olanzapine LAI during these trials was approximately 6 years (McDonnell, 2014). Based on over 59 000 olanzapine LAI injections given to 2054 patients in clinical trials through final clinical trial datalock, post-injection syndrome events occurred in approximately 0.07% of injections, or 1.85% of patients (Data on file). The rate per injection in clinical trials has remained constant over time. The findings of

this analysis are consistent with the earlier analysis of clinical trial cases (Detke, 2010a). There have been no active Lilly olanzapine LAI interventional clinical trials conducted after 31 December 2010. Please refer to Table 1 in Appendix 1 for a full summary of the post-injection syndrome cases observed in clinical trials through final clinical trial datalock (Detke, 2010a; Detke, 2010b; Data on file).

Postmarketing Observational Study

A multinational, non-interventional, prospective, real-world, observational post-authorization safety study (PASS) was conducted to estimate the incidence per injection and per patient of post-injection syndrome events in patients with schizophrenia receiving olanzapine LAI (Data on file). Patients (mean age = 41 years) included in the study had an average duration of 544 days of continuous exposure to olanzapine LAI and received an average of 26 olanzapine LAI injections per period of continuous exposure. A total of 103 505 olanzapine LAI injections were administered to 3858 patients enrolled in the study between April 2009 and December 2015. Post-injection syndrome occurred in 0.044% of injections (n=46) and in 1.17% of patients (n=45). Based on the per injection rate of 0.044% and accounting for the possible outcome of multiple events per patient, an estimation was generated of the cumulative probabilities of at least one post-injection syndrome event for a patient over time. The results indicate that it takes 20 injections before the estimated probability of at least one post-injection syndrome event surpasses 1%. If a patient were to continuously use olanzapine LAI for five years, with a 2 or 4 week injection schedule, the estimated cumulative probability of at least one post-injection syndrome event is 3.9% and 2.5%, respectively. These results highlight that the estimated risk at each injection is the same and very rare, and that although the estimated cumulative probability of experiencing at least one event at any injection over time increases, it still remains low.

The secondary objectives were to further characterize the clinical presentation, outcomes, and risk factors associated with post-injection syndrome events, and hospitalizations at baseline (previous 6- or 12- month) and post-baseline (Data on file). 40/46 post-injection syndrome events occurred with 300 or 405 mg injections, which were the most commonly prescribed doses. At onset of event, the five most frequently reported post-injection syndrome symptoms were somnolence (52.2%), confusional state (43.5%), dysarthria (41.3%), sedation (34.8%), and dizziness (32.6%). The time of onset was ≤1 hour in 41/45 reported time to onset of post-injection syndrome events. 95.6% of patients had a time to recovery of ≤72 hours from the event (range 6 hours to 11 days) of which 62.2% reported recovery in ≤24 hours . In 34/46 events, patients were hospitalized. One patient was hospitalized prior to the event, 2 were seen in the emergency room but not admitted, and 9 were not hospitalized. Treatment included observations/monitoring and/or fluids (n=15), medications (n=25), intubation (n=2), physical restraints (n=2), and oxygen (n=1). No fatal outcomes were reported.

Potential risk factors were assessed based on per-injection level and per-patient level (Data on file). Injection-level risk factors for post-injection syndrome included male gender (p=.017), and high dose (p=.006). Patient level risk factors included male gender (p=.020), and total number of injections (p=.002). Twelve months prior to study enrollment, 48% of patients had a psychiatric hospitalization. After enrollment in the study, the median rate of psychiatric hospitalization per year was 0 with only 425 patients admitted for a total of 911 psychiatric hospitalizations over the course of study participation. The average

number of days hospitalized was 3.3 days for all patients, and the median length of stay was 10 days per hospitalized patient.

Limitations include inclusion of new and previous users of olanzapine LAI, bias due to missing or incorrect data reporting from either the healthcare provider or patient, and no validation of medical records in the collection of data (Data on file).

Postmarketing Experience

A total of 720 postmarketing reports evaluated as post-injection syndrome events were received through 30 August 2016 (Data on file). (See Appendix 2 for the case definition utilized to evaluate and identify post-injection syndrome events.) Of these, 124 events were reported through postmarketing studies, and 596 were reported spontaneously. The rate of spontaneous cases appears to be consistent with the rate observed in clinical trials. The clinical profile of the postmarketing spontaneously reported events is generally consistent with the clinical trial cases of post-injection syndrome.

Postmarketing data do not necessarily represent the rate of occurrence of an AE in a treated population, but they represent a reporting rate of a particular AE to the company. Spontaneous reporting of AEs can be highly variable and is not appropriately controlled clinical information on which to base an assessment of whether a particular drug product caused an event (Goldman, 1998). Spontaneous reporting has limited use due to lack of control population, under-reporting or reporting bias, and missing or incomplete information regarding medical history or concomitant medications.

Summary

The signs and symptoms for the 759 post-injection syndrome events (clinical trials, n=39; postmarketing studies n=124 [Zyprexa Relprevv Patient Care Program, n=78; postmarketing observational study, n=46]; spontaneous cases, n=596) reported through 30 August 2016 continue to be consistent with some of those AEs observed with an oral olanzapine overdose (Detke, 2010b; Bushe, 2015; Data on file).

In clinical trials, there was no apparent pattern for when events occurred with regard to the number of injections the patient received (Data on file). Data regarding time of onset in the 39 clinical trial events indicate that the risk of a post-injection syndrome event is greatest within the first hour post-injection (Data on file); events have occurred rarely (<1 in 1000 injections) between 1 and 3 hours post-injection and very rarely (<1 in 10 000 injections) after 3 hours (ZypAdhera Summary of Product Characteristics, 2016). Time to onset was reported to be within the first hour post-injection in 605 of the 720 postmarketing study and spontaneous cases (84%) through 30 August 2016, between 1 and 2 hours post-injection in 44 cases, between 2 and 3 hours post-injection in 18 cases, unspecified but reported as <3 hours in 3 cases, and unknown in 47 cases (Data on file). Three spontaneous cases occurred after 3 hours (at 3.5 hours, 4 hours, and 5-6 hours).

In the majority of post-injection syndrome events (520/759; 69%), patients have been hospitalized during the event (Data on file). In addition, 27 patients were already hospitalized when the injection was administered. Of the 759 events, 678 (89%) reported recovery. Of these 678 events, 567 (84%) reported recovery in ≤72 hours, 415 (61%) reported recovery in ≤24 hours, 26 (3.8%) reported recovery in >72 hours, and 84 (12.4%) reported an unknown time to recovery. Outcome of the event was reported as “not

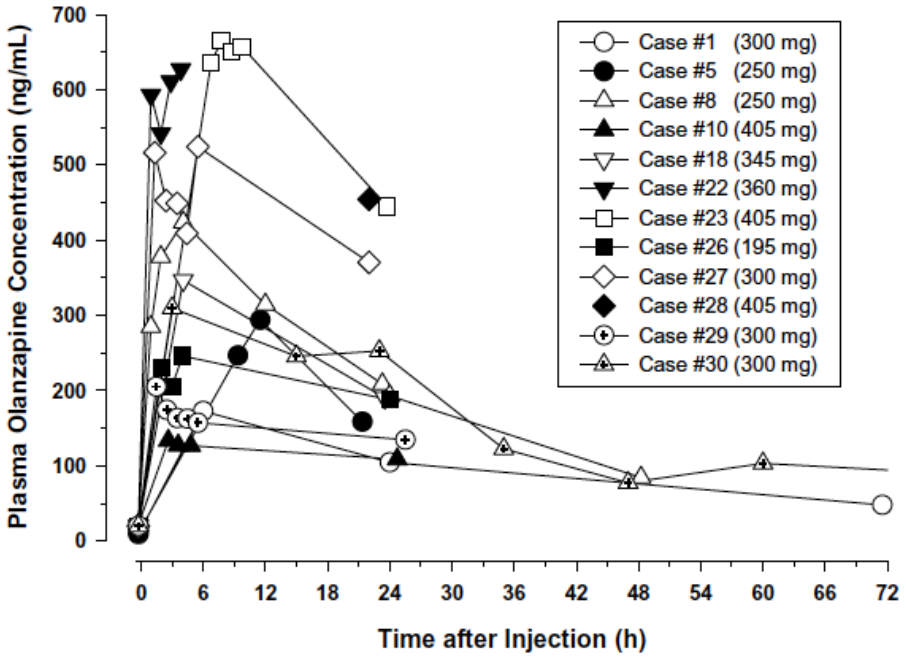
recovered" in 14 cases at the time of the report (reported on the day of the event), and as "unknown" after 67 events. Olanzapine LAI was continued after 268events. Discontinuation of the drug was reported in 229 cases. Continuation information was unknown for 262 patients. To date, Lilly is not aware of any confirmed cases of post-injection syndrome associated with a fatal outcome reported in either clinical trials or in post-marketing use (Data on file).

Management of post-injection syndrome events was documented for 75% (566/759) of the events; a large number of these cases required either no treatment (14%; 78/566) or only continued observation/monitoring with or without intravenous fluids (43%; 245/566) (Data on file). Medications were administered as a treatment for post-injection syndrome in 31% (174/566) of cases, and included beta-agonists, benzodiazepines, diuretics, and anticholinergics. A small percentage of cases required other treatment including: intubation/ventilation (6%; 32/566); mechanical restraints (4%; 24/566); oxygen (4%; 21/566), and urinary catheterization (1%; 7/566). Some cases involved more than 1 type of treatment.

Pharmacokinetic data have been collected or reported for a number of post-injection syndrome cases during clinical trials and spontaneous reports (Detke, 2010a; Detke, 2010b; McDonnell, 2010; Mitchell, 2013; Data on file). These data reveal that olanzapine plasma concentrations when measured during these events substantially exceeded the typical olanzapine plasma concentration values observed after oral or olanzapine LAI doses. Although for 1 case olanzapine plasma concentrations were not considered to be excessively high, they were in the higher percentile of those typically observed in patients receiving that olanzapine LAI dose. The clinical manifestations in this specific case were consistent with previously observed post-injection syndrome events and met case definition criteria. Olanzapine plasma concentrations from spontaneous and postmarketing study reports were not collected and processed with the same methodology as those obtained during clinical trials, which were collected at standard collection times and processed by a centralized laboratory.

Based on these results, no clinically significant differences in the clinical profile between clinical trial and spontaneous cases of post-injection syndrome have been observed (Detke, 2010b; Bushe, 2015; Data on file). Figure 1 shows olanzapine plasma concentrations observed over time in 12 post-injection syndrome events from 8 olanzapine LAI clinical trials (McDonnell, 2010).

Figure 1. Olanzapine Plasma Concentrations Observed Over Time in Post-injection Syndrome Events (McDonnell, 2010)[a]



[a]Figure from: Figure 2 in McDonnell DP, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. *BMC Psychiatry*. 2010;10:45.
Note: Case numbers correspond to the cases presented in Appendix 1

POTENTIAL RISK FACTORS

A logistic regression analysis of data from all Lilly completed and ongoing clinical trials through 30 April 2008 was conducted to examine baseline age, gender, race (categorized as Caucasian or non-Caucasian), geographic region (categorized as United States [US] or outside the US), olanzapine LAI dose, number of previous olanzapine LAI injections, and body mass index (BMI) for each patient who experienced a post-injection syndrome event and for all who did not experience such an event (Detke, 2010a). No clear risk factors for post-injection syndrome were identified. Only 3 variables met criteria to enter and remain in the model ($p<.20$): BMI ($p=.033$), age ($p=.035$), and olanzapine LAI dose ($p=.126$). However, the odds ratios (OR) clustered around 1.0, indicating a small incremental increase in risk for each unit decrease in BMI (OR, 0.92 [95% confidence interval (CI), 0.86 to 0.99]) and for each year increase in age (OR, 1.03 [95% CI, 1.00 to 1.07]), but no significant increase in risk based on olanzapine LAI dose (OR, 1.00 [95% CI, 1.00 to 1.01]).

No specific concomitant medications were identified as risk factors (Detke, 2010a). There was no drug class with statistically significantly higher incidence of use among patients with post-injection syndrome compared with patients who did not experience post-injection syndrome. Statistically significant differences were noted with respect to 3 specific medications: escitalopram (n=19, p=.026), fluvoxamine (n=3, p=.040), and oxaprozin (n=1, p=.014). However, the authors stated that these may be the result of very small numbers of patients receiving treatment with those medications in the total sample and are likely spurious.

A pooled analysis of 7 olanzapine LAI clinical trials (conducted March 2001 to December 2010) reported that, among 1752 patients with schizophrenia or schizoaffective disorder who received at least 1 olanzapine LAI injection (45 to 405 mg at intervals of 2, 3, or 4 weeks), 92 patients (5.3%) experienced ≥1 injection site AE (Atkins, 2014). Most of the injection site AEs were injection site pain and were classified as mild. The percentage of patients who experienced a post-injection syndrome event (n=37) was significantly greater among those who reported an injection site AE at some time during the study (5/92 or 5.4%) than those who did not (32/1660 or 1.9%; p=.041). A limitation noted by the authors that might have impacted this finding was that some other AEs in the database could have been related to the injection but were excluded because the location of the reaction was not specified. Additional information regarding injection site AEs during treatment with olanzapine LAI is available upon request.

OLANZAPINE LAI BENEFIT-RISK

A post hoc analysis of 1192 patients with schizophrenia or schizoaffective disorder treated for at least 2 years with olanzapine LAI from long-term treatment studies (McDonnell, 2014; Detke, 2014b) evaluated frequency versus duration of benefits and risks (Detke, 2014a). The most common dose regimens of olanzapine LAI were 405 mg/4 weeks and 300 mg/2 weeks. Mean daily olanzapine dose equivalent for all patients in the analysis was 14.1 mg/day. The most frequent benefits at 2 years were remaining free of relapse (88.4% of patients for a mean of 546 days) and symptomatic remission (84.1% of patients for a mean of 438 days). The most frequently reported AEs at 2 years were clinically significant weight gain (≥7% of body weight) in 42% of patients and hyperlipidemia in 30% of patients. Post-injection syndrome occurred in 1.5% of patients. The authors noted that the analysis methodology had limitations that included subjective value of efficacy outcome versus safety outcome. The assessment of duration could be influenced by infrequency of certain measures or limited by a patient's early discontinuation. The authors concluded that, in this analysis, the remission days and relapse-free days benefits of olanzapine LAI appeared to outweigh lower-probability events (eg, post-injection syndrome), but higher probability events (eg, weight gain) remained a significant clinical concern for many patients treated for up to 2 years. Overall, the authors stated that the benefit-risk balance was within an acceptable range.

POTENTIAL MECHANISM

Although the exact mechanism of post-injection syndrome is unknown, it most likely involves accidental entry of olanzapine into the bloodstream following blood vessel injury during the injection process (occurring even with proper injection technique) (McDonnell, 2010). Olanzapine LAI consists of an olanzapine pamoate salt, which has greater solubility in blood and plasma than in muscle tissue. Contact with a substantial volume of blood would therefore lead to a more-rapid-than-intended dissolution of a portion of the olanzapine LAI dose as the olanzapine disassociates from the pamoic acid. Plasma samples taken from patients experiencing olanzapine LAI post-injection syndrome revealed higher-than-intended olanzapine plasma concentrations during the post-injection period. Although intended for IM injection only, contact between olanzapine LAI and blood could occur through various mechanisms, but most likely as a result of accidental intravascular injection or blood vessel injury during the IM injection process.

INFORMATION ON ADMINISTRATION AND POST-INJECTION PRECAUTIONS

When administering olanzapine LAI, the syringe should be aspirated for several seconds prior to injection to ensure that no blood is visible (Detke, 2010a). The injection should not proceed if blood is visible. If this does occur, the syringe should be discarded, and a new vial should be reconstituted and injected into the alternate buttock, deep into the gluteal muscle. The ventrogluteal site is preferred for IM injections to decrease risk of accessing the sciatic nerve or major blood vessel (Beyea, 1995; Workman, 1999). Administration at this site also maximizes the likelihood of achieving an IM injection, as opposed to an accidental subcutaneous injection.

It is important to note that proper injection technique does not guarantee that a blood vessel injury has not occurred during the injection (Detke, 2010a). Therefore, following each injection of olanzapine LAI, appropriately qualified healthcare professionals should observe the patient at the healthcare facility for at least 3 hours for signs and symptoms consistent with olanzapine overdose, and immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose (Zyprexa Relprevv Package Insert, 2016; ZypAdhera Summary of Product Characteristics, 2016). Patients should also be advised to be vigilant for symptoms of post-injection adverse reactions, should be able to obtain medical assistance if needed, and should not drive or operate machinery for the remainder of the day after injection (Detke, 2010a; Data on file).

Please refer to your local product labeling for further detailed information on instructions regarding administration of olanzapine LAI and post-injection precautions.

CLINICAL MANAGEMENT OF POST-INJECTION SYNDROME EVENTS

The following provides information on clinical management when signs and symptoms of olanzapine overdose consistent with post-injection syndrome are observed.

If an overdose is suspected at any time, close medical supervision and monitoring should be instituted until examination indicates signs and symptoms have resolved (Detke, 2010a; Data on file). The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose (ZypAdhera Summary of Product Characteristics, 2016).

In clinical trials, most patients who experienced a post-injection syndrome event during olanzapine LAI therapy were hospitalized (Detke, 2010a; Detke, 2010b; Data on file). The majority of patients either recovered with no treatment or were managed only with observation and hydration with fluids (Appendix 1 – Table 1). Pharmacologic therapy was initiated in some patients to manage specific symptoms (related or unrelated to post-injection syndrome) such as EPS, agitation, elevated blood glucose, hypertension, infection, or seizure.

In the postmarketing setting, most patients who experienced a post-injection syndrome event during olanzapine LAI therapy were hospitalized (Detke, 2010b; Bushe, 2015; Data on file). In an analysis of 338 postmarketing cases (66 events from 2 postmarketing studies and 272 spontaneously reported events among 333 patients; total 499 921 injections administered to an estimated 65 000 patients) from 01 March 2009 through 01 March 2014, of the 316 cases where the patient received an injection outside of the hospital, 65%

(206/316) were hospitalized as a result of the event (Bushe, 2015). Of the 193 cases with known number of injections before the post-injection syndrome event occurred, the event was most commonly reported after 1 to 3 injections (43% [83/193]; range 1 to 94). Of the 243 cases where outcomes and treatment were available, 19% patients required no treatment, 46% were treated with fluids and/or monitoring, 31% were treated with medication (including beta-agonists, benzodiazepines, diuretics, and anticholinergics), 19% received potentially sedative medication (benzodiazepine or antipsychotic), 5% were given oxygen. Thirteen patients (5%) were intubated or ventilated: 7 due to respiratory distress and 6 prophylactically). Forty-four patients (18%) were admitted to an intensive care unit. Of the 318 patients with recovery status available, 98% (311/318) had a full recovery (88% [273/311] of those within 72 hours).

Similar to the clinical management of oral olanzapine overdose, there is no specific antidote for olanzapine LAI overdose (Data on file). Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation. If parenteral benzodiazepines are required for the management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended (Data on file). In the event of hypotension and circulatory collapse, the patient should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents; do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade; respiratory support may be required (Zyprexa Relprevv Package Insert, 2016; ZypAdhera Summary of Product Characteristics, 2016; Data on file).

POST-RECOVERY TREATMENT

The majority of patients in clinical trials who experienced a post-injection syndrome event continued olanzapine LAI therapy and did not experience further post-injection syndrome events (Detke, 2010a; Data on file). However, 1 patient did experience a second post-injection syndrome event and discontinued olanzapine LAI therapy thereafter. Also, 5 patients in a postmarketing study and 9 patients in spontaneous reports experienced a second post-injection syndrome event. Two patients continued olanzapine LAI after the second post-injection syndrome event, five patients discontinued olanzapine LAI therapy thereafter, and continuation information was unknown for 7 patients (Data on file). In the aforementioned analysis of 338 postmarketing cases from 01 March 2009 through 01 March 2014, among the 210 cases where continuation information was available, 55% (116/210) of patients continued olanzapine LAI treatment (Bushe, 2015).

If olanzapine LAI therapy is continued, the dose and timing of the next injection may occur as previously scheduled or earlier if clinically indicated for exacerbation of schizophrenia symptoms (Data on file). Alternatively, oral olanzapine supplementation may be considered. The combined total dose of olanzapine from both formulations should not exceed the maximum dose allowed per local product labeling.

If olanzapine LAI therapy is discontinued, treatment efficacy and/or treatment-emergent AEs may continue for some time (Data on file). The systemic half-life of olanzapine LAI is approximately 30 days. Treatment with alternative antipsychotic medication(s) may be initiated when clinically indicated.

PUBLISHED LITERATURE

A search of the published literature has identified some case reports describing post-injection syndrome in adult patients (Steinmann, 2011; Duran-Sindreu, 2013; Sobanski, 2013; Buts, 2014; Lukasik-Glebocka, 2014; Wilms, 2014; Panzavolta, 2015; Petrolini, 2016). These cases met post-injection syndrome criteria and were included in the spontaneous report data summary above. An additional case report identified as meeting criteria for post-injection syndrome received after 30 August 2016 cutoff was not included in the spontaneous report data summary above (Sarangula, 2016).

A review of data from patients who were admitted to a hospital clinical ward and received olanzapine LAI (every 2 to 4 weeks) revealed 3 cases consistent with post-injection syndrome (2 cases in the same patient) among 300 consecutive olanzapine LAI injections (between 2011 and 2013) (Preve, 2014). Symptoms included tachycardia and hypotension, hyperventilation and a progressive respiratory depression, dysarthria, and reduced level of consciousness. One patient had an olanzapine plasma concentration of 254 ng/mL on the day after the injection. The authors noted that low BMI and the presence of calcification at the injection site in the gluteus might be potential causes of the onset of post-injection syndrome.

In 1 pharmacokinetic study, a 31-year-old man experienced symptoms consistent with post-injection syndrome 45 minutes after the second injection of olanzapine LAI prescribed at 300 mg every 4 weeks (Mitchell, 2013) (Note: The clinical features of this case are described in greater detail in Table 1 [Case 1] of Appendix 1). Olanzapine concentrations were 172.75 ng/mL at 6 hours after the second injection and returned to the typical range during the next 24 to 48 hours. The patient received 4 more injections of olanzapine LAI at a reduced dose (200 mg every 4 weeks), where concentrations were in the typical range (see published article for a figure showing the concentration-time profile of olanzapine LAI concentrations for this patient over the course of the study). He completed the study without experiencing any other injection-related AEs. The authors noted that "because overall exposure values calculated for the first and second injections in this patient were similar, the incident was considered to reflect an inadvertent intravenous injection of a portion of the dose." Limitations noted by the authors included the following: lack of a placebo group or comparator arm, study design flexibility for regimen, dosage, and frequency, the restriction that did not allow patients in the single-dose study to participate in the multiple-dose study, and the use of oral olanzapine supplementation in the multiple-dose 3-week study.

A literature review on post-injection syndrome in patients treated with olanzapine LAI, including incidence, management, and potential mechanism, has been published (Luedecke, 2015).

ADDITIONAL INFORMATION REGARDING OLANZAPINE LAI: US FDA DRUG SAFETY COMMUNICATIONS – 18 JUNE 2013 AND 23 MARCH 2015

The US Food and Drug Administration (FDA) published a Drug Safety Communication on June 18, 2013, indicating that the FDA is investigating 2 unexplained deaths in patients who received an IM injection of the antipsychotic drug olanzapine LAI (known as Zyprexa Relprevv in the United States) (FDA Drug Safety Communication, 2013 [WWWa]). According to the FDA communication, the patients died 3 to 4 days after receiving an appropriate dose of the drug, well after the 3-hour post-injection monitoring

period required under the Zyprexa Relprevv Risk Evaluation and Mitigation Strategy (REMS). Both patients were found to have very high olanzapine blood levels after death (both 1000 ng/mL) (McDonnell, 2013).

Following the 2 deaths in patients treated with olanzapine LAI with high post-mortem olanzapine blood concentrations, a review was conducted to examine all olanzapine LAI cases with available post-mortem assessments of olanzapine concentrations to determine whether a post-injection syndrome event may have occurred (McDonnell, 2013). Of the 4 identified olanzapine LAI cases (2 cases in addition to the 2 cases discussed in the FDA Drug Safety Communication), all 4 had received standard doses (300 mg/2 weeks or 405 mg/4 weeks). One death occurred as a result of hanging and another as a result of multiple drug overdose (post-mortem olanzapine blood concentrations of 116 ng/mL and 600 ng/mL, respectively). Of the 2 cases with concentrations of 1000 ng/mL, 1 patient drowned in the bathtub 3 to 4 days after the injection but did not show symptoms of a post-injection syndrome event at any time prior to his death; the other patient left the healthcare facility sometime after 45 minutes post injection, was not observed for the required time period, and was found dead 4 days later with no witnesses.

Following consultation with the FDA, Lilly conducted a study in dogs to investigate the potential for postmortem redistribution of olanzapine following biweekly intramuscular administration of olanzapine LAI, which might explain the very high blood levels of olanzapine in the 2 patients that died (Data on file). The overall design of the study was intended to mimic the real life forensic situation in which patients may be found deceased at room temperature, from hours to days after death, and a subsequent autopsy is performed. An increase in blood concentration of olanzapine after death was observed in all but 1 animal, suggesting that postmortem redistribution may occur in dogs following biweekly intramuscular administration of olanzapine LAI. These study results suggest that the very high blood levels of olanzapine in the 2 patients who died may be the result of postmortem redistribution, but this has not been established.

The FDA published an updated Drug Safety Communication on March 23, 2015 (FDA Drug Safety Communication, 2015 [WWWb]). The FDA stated that it had concluded a review of a study conducted by Lilly to further evaluate elevated levels of olanzapine LAI in the 2 patients who died. The FDA further stated that it is unable to exclude the possibility that the deaths were caused by rapid, but delayed, entry of the drug into the bloodstream following intramuscular injection of olanzapine LAI. The FDA acknowledged, however, that the dog study conducted by Lilly suggested that much of the drug level increase could have occurred after death, a finding that could explain the extremely high blood levels found in the 2 patients who died 3 to 4 days after receiving injections of appropriate doses of olanzapine LAI.

On the basis of all of the information reviewed, the FDA is not recommending any changes to the prescribing information or use of olanzapine LAI. Compliance with the required post-injection observation period and labeled safety precautions should be ensured at every olanzapine LAI injection. Lilly continuously monitors safety reports for all of our medications, including for reports of post-injection syndrome in patients treated with olanzapine LAI. Further information regarding the FDA Drug Safety Communications is available upon request. Additional information regarding olanzapine and postmortem redistribution is also available in a separate summary.

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APPENDIX 1

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
1	31/M	300 mg/ 4 wks	45 min (2)	No	Biperiden	45 min after injection, experienced severe sedation, moderate tension (akathisia) in legs, mild dizziness, and weakness. Disoriented, spoke briefly, fell asleep. 6 hrs after injection, still sleepy, but felt better. **Recovered in approx. 48 hrs; continued in study.**
2	32/M	405 mg/ 4 wks	10 min (1)	Yes	Fluids, mannitol, lucetam (piracetam), cerebrolysin, glucose, infesol	10 min after injection, experienced dizziness and bad general state. Speech progressively altered and somnolence appeared. After 1.5 hrs, stopped responding to verbal stimuli. After 2 hrs, profound sedation, bilateral miosis with no photomotor reflex, automatic movements, Babinski on left side, no response to pain or verbal stimuli. CT scan negative. Able to speak next morning, but with difficulty. **Recovered in approx. 60 hrs; discontinued study.**
3	63/M	405 mg/ 4 wks	15-20 min (2)	Yes	Midazolam, ranitidine, diazepam, haloperidol, promethazine; ventilated	15-20 min after injection, appeared pale, yellowish, not standing steady, a little confused. 30 min after injection, felt bad, disoriented, with "seizures in hands and legs" which appeared as clonic movements of limbs without loss of consciousness. Disoriented with psychomotor agitation. Ventilated as preventive measure after benzodiazepines. **Recovered in approx. 60 hrs; discontinued drug; completed study.**
4	30/M	405 mg/ 4 wks	~60 min (4)	Yes	Unknown	Appeared to have presented self at hospital. Approx. 1 hr after injection, experienced sedation. Became drowsy, irritable, disoriented to time, place, and person. Felt stiff and weak in legs. Stated that he passed out for a while, was very confused, slightly febrile (100.6°F). **Recovered in approx. 24 hrs; continued in study.**
5	50/M	250 mg/ 2 wks	Within 60 min (22)	Yes	None	Returned to site about 1 hr after injection; appeared in drunken-like state. Speech was slurred, gait unsteady. Sent to hospital; all tests negative. Difficulty ambulating, incontinent of urine while at hospital. Reported drinking ¾ pint of whiskey the evening before the injection. **Recovered in approx. 48 hrs; continued in study.**
6	52/M	300 mg/ 2 wks	Within 50 min (24)	Yes	Fluids	Pt left site 10 min after injection. Was found in "coma" approx. 50 min later. According to investigator, pt was riding on a bus when he began to feel unwell. He got off the bus and was later found on a bench in a public plaza. Pt was hospitalized; remained unconscious/unresponsive to verbal stimuli for approx. 12 hrs. **Recovered in approx. 22 hrs; continued in study.**
7	32/F	300 mg/ 3 wks	30 min (11)	Yes	None	30 min after injection, experienced drowsiness and "washy speech." Admitted to psychiatric hospital. Also experienced slight confusion. **Recovered in approx. 24 hrs; continued in study.**
8	50/M	250 mg/ 2 wks	15 min (35)	Yes	None	15 min after injection, began to have slurred speech and unsteady gait. Progressed to point where could not speak clearly or ambulate without assistance. Taken to hospital for evaluation. All tests negative. This was the second event for this pt (see Case 5). **Recovered in approx. 72 hrs; discontinued study.**

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013) (continued)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
9	34/M	300 mg/ 4 wks	5 min (29)	Yes	Insulin, haloperidol, omeprazole, alprazolam, fluids	Pt with diabetes. 5 min after injection, became increasingly sedated. In and out of consciousness. Site assumed low glucose and gave pt Coke to drink. Pt confused, ataxic (as if drunk). 30 min after injection, glucose was 275 mg/dL. Site laid pt down in ward, where he was in and out of sleeping state. When he would try to get up, was restless and had slurred speech. Next day pt was still sleepy and disoriented, delirious, with slight rigidity in extremities, high glucose with slight hypokalemia. Tests indicated hepatic steatosis. **Recovered in approx. 72 hrs; continued in study.**
10	45/M	405 mg/ 4 wks	30 min (20)	Yes	None	Pt returned to work soon after injection. Within 30 min after injection, felt bad. Approx. 60 min after injection, pt noted to have somnolence, dysarthria, irritability. Coworkers contacted site and returned pt to site. Pt had difficulty walking, became sedated. Sent to hospital for observation. **Recovered in approx. 24 hrs; continued in study.**
11	45/F	100 mg/ 2 wks	10 min (27)	Yes	None	10 min after injection, pt experienced weakness, dizziness, slurred speech, "profound sedation" (described as slightly decreased level of consciousness). **Recovered in approx. 48 hrs; continued in study.**
12	58/M	210 mg/ 2 wks	Unspecif. (within 3 hrs) (2)	No	None	3 hrs after injection, felt weak. Wife contacted site, reported that pt was experiencing profound sedation, weakness, slurred speech. Not unconscious. Remained at home. **Recovered in approx. 3 hrs; continued in study.**
13	25/M	270 mg/ 4 wks	Immediate-ly post-injection (18)	Yes	None	Immediately after injection, pt complained of weakness, dizziness, headache. Stated that he had been working outside all day in warm weather without eating or drinking. Stayed at site 45 min but then left per investigator instructions to get something to eat. Pt got sandwich on street; felt unwell as started to eat. Began staggering; attempted to go into bar but was turned away as appeared drunk. Shopkeeper called emergency services. 3 hrs after injection, admitted to hospital confused and dizzy. All tests negative. **Recovered in approx. 21 hrs; continued in study.**
14	58/F	210 mg/ 4 wks	Unspecif. (within 75 min) (25)	Yes	IV midazolam, sufentanil, enoxaparin, furosemide, fluids; ventilated	Pt refused to stay at site; left 20-25 min after injection. Experienced malaise 75 min after injection; admitted to hospital with loss of consciousness (duration <1 hr). Experienced agitation, somnolence, dysarthria, sweating, mild tachycardia (114 bpm). Due to persistence of agitation, given IV midazolam and intubated and ventilated to perform tests. Pt extubated and released. **Recovered in approx. 60 hrs; continued in study.**
15	41/M	300 mg/ 3 wks	15 min (7)	Yes	Urinary catheterization	15 min after injection, became confused and weak. 1 hr 30 min after injection, condition worsened; pt appeared stunned, with deep sedation, loss of consciousness (duration unknown, but <3 hrs). **Recovered in approx. 3 hrs; discontinued study.**
16	37/M	405 mg/ 4 wks	75-105 min (17)	Yes	None	75-105 min after injection, experienced somnolence. 60-90 min later, experienced fatigue, inconsistent speech, mumbling, and automatism (picking up invisible things on the floor – pseudo-delirium). Hospitalized overnight for confusional state. Pt later reported drinking 1 L of beer prior to injection. **Recovered in approx. 24 hrs; continued in study.**

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013) (continued)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
17	61/F	300 mg/ 2 wks	2 hrs 45 min (27)	Yes	None	2 hrs 45 min after injection, experienced significant somnolence. Pt took 4 mg of unprescribed clonazepam 8 hrs prior to injection (but did not appear drowsy when arrived at site). Approx. 3 hrs after injection, experienced difficulty in speech but still alert and oriented; displayed motor restlessness. 6-7 hrs after injection, presented with profound sedation; unarousable for 8 hrs. Responsive to pain. Awoke next morning. **Recovered in approx. 15 hrs; continued in study.**
18	27/M	345 mg/ 4 wks	30 min (17)	Yes	Fluids	30 min after injection, experienced dizziness, "gummy legs," insecurity while standing. Symptoms slowly increased, progressing to deep sedation, reported to be like deep sleep but pt could always be aroused by speaking to him loudly. Hospitalized for monitoring and hydration. **Recovered in approx. 24 hrs; discontinued study.**
19	39/F	390 mg/ 4 wks	5 min (16)	No	None	5 min after injection, experienced somnolence that worsened gradually; pt was oriented and able to communicate although had dysarthria. Event was described as nonserious by investigator. At end of 3-hr observation, pt was sent home with a friend in an improved but still slightly somnolent state. **Recovered in approx. 72 hrs; discontinued study.**
20	50/F	405 mg/ 4 wks	20 min (15)	No	None	20 min after injection, experienced dizziness. 45 min after injection, was severely sedated but always conscious; was disoriented to place and time, with dysarthria and confusion. All nonserious AEs. Site was attached to psychiatric unit where pt lived for social reasons; pt was able to be observed by staff there until recovered. **Recovered in approx. 16 hrs; continued in study.**
21	52/M	210 mg/ 4 wks	15 min (35)	Yes	Fluids	15 min after injection, became confused, somnolent, with blurred vision, dizziness. All events considered nonserious. 2.5 hrs after injection, sent to hospital for monitoring. Remained conscious throughout. **Recovered in approx. 12 hrs; continued in study.**
22	52/M	360 mg/ 4 wks	10 min (20)	Yes	Urinary catheterization	10 min after injection, became somnolent, confused, developed cramps. Slept for 30 min. Arousable but couldn't answer questions correctly. Disoriented with altered consciousness but not unconscious. Experienced retention of urine. Sent to hospital after 4 hrs of observation. Pt did not urinate despite attempts, so was catheterized. Cramps of moderate severity localized in arms and legs. **Recovered in approx. 24 hrs; discontinued study.**
23	47/M	405 mg/ 3 wks	Within 30 min (17)	Yes	None	Pt complained of dizziness prior to injection, probably due to fasting. Symptoms worsened. Pt ate 15-30 min after injection; while eating began to feel nervous and experienced abnormal movements like tonic convulsion in arms, sporadic at first and then increasing. 2 hrs after injection, began to present somnolence and dysarthria but nervous and with abnormal movements so unable to fall asleep. Given 1 mg lorazepam (his usual daily dose). No loss of consciousness at any time. Sent to hospital 4 hrs after injection due to continued symptoms. **Recovered in approx. 24 hrs; discontinued study.**

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013) (continued)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
24	55/M	330 mg/ 4 wks	30 min (40)	Yes	Captopril, enalapril, paracetamol, IV antibiotics, IV diazepam	Pt's medical history revealed untreated hypertension for the year prior to the event. BP prior to injection was 140/90 mm Hg. 30 min after injection, BP increased to 180/90 mm Hg. 45 min after injection, complained of headache and stomachache. 60 min after injection was confused, ataxic, restless. Highest BP was 210/110 mm Hg, managed and resolved with enalapril and captopril. Because of restlessness, given IV diazepam; slept. Diagnosed with UTI. **Recovered in approx. 60 hrs; discontinued study.**
25	36/M	405 mg/ 4 wks	15 min (36)	Yes	IV fluids	15 min after injection, started experiencing dizziness, dysarthria, gait disturbance. With progressive deepening of sedation over the next 10 min. Pt sent to ER 6 hrs 40 min after injection, where remained sedated, disoriented, confused. **Recovered in approx. 48 hrs; continued in study**
26	73/F	195 mg/ 2 wks	11 min (68)	No	None	Approx. 11 min after injection, complained of generalized weakness, palpitations, heaviness sensation in head. ECG showed a right bundle branch block secondary to long-standing arterial hypertension. Pt gradually presented with sedation, slurred speech, and somnolence approx. 30-45 min after injection. Was observed for 7 hrs after injection and discharged in stable condition. **Recovered in approx. 12 hrs; continued in study.**
27	28/M	300 mg/ 2 wks	60 min (66)	No	$MgSO_4$	Pt reported feeling "constrained" just after injection. 60 min after injection became sleepy, confused, disoriented, weak. BP at 60 min after injection recorded at 160/100 mm Hg and managed with IV $MgSO_4$, with consequent decrease in BP reading. Pt was released from observation same day; reported as recovered by the following day. **Recovered in approx. 22 hrs; continued in study.**
28	45/M	405 mg/ 4 wks	Unknown (reported at 300 min) (44)	Yes	IV fluids, KCl, $MgSO_4$, IV diazepam, oral propranolol, glibenclamide, lorazepam, IV ranitidine, aspirin, chloramphenicol optic drops, Foley catheter	Pt found on hospital grounds with confusion, ataxia, and apparent remains of vomit approx. 5 hrs after injection. Approx. 5.5 hrs after injection, pt experienced apparent tonic-clonic convulsions for 10-15 sec. Admitted to ER for observation. Reported with tachycardia, dehydration, disorientation, confusion, incoherence, altered states of consciousness, with fluctuations of aggressiveness, agitation, and sleepiness. Administered benzodiazepines and IV fluids. EEG normal, CPK increased. Pt had limited recollection of event; discharged 5 days later with diagnosis of delirium. **Recovered in approx. 72 hrs; continued in study.**
29	45/M	300 mg/ 2 wks	90 min (64)	No	None	90 min after injection, pt presented with mild to moderate somnolence, dizziness, confused consciousness state, difficulty speaking, weak legs while standing. Pt showed resolution of all events 1.5 hrs later. Pharmacokinetic samples taken during event revealed elevated olz concentrations. **Recovered in approx. 1.5 hrs; continued in study.**

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013) (continued)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
30	42/F	300 mg/ 4 wks	15 min (45)	Yes	Clonazepam, haloperidol	Prior to injection, appeared anxious and restless, with possible akathisia. 15 min after injection experienced increased anxiety, restlessness, which progressed to moderate agitation. Treated with clonazepam, developed somnolence. 30 min after injection, experienced dizziness, weak legs, appearance of drunken state, dysarthria, difficulty walking, agitation, and mental confusion. 1 hr after injection, pt was unintelligible with increased sedation in combination with restlessness, confusion, delirium-type behavior and ataxia. Sent to ER at 90 min after injection and treated with IM haloperidol for agitation. Significantly improved 24 hrs later. Of note, prior to visit, pt took single dose of naproxen due to pain in legs. **Recovered in approx. 72 hrs; continued in study.**
31	45/M	225 mg/ 3 wks	3-5 min (58)	Yes	None	3-5 min after injection, pt experienced odd sensation in tongue, slurred speech, feeling slightly unwell, tired. 1 hr after injection, pt hospitalized for closer supervision. At admission, showed amnestic aphasia, somnolence, complained of dry mouth and heavy sensation in tongue, which caused problems with speech. Pt remained conscious and oriented at all times. Examination indicated dyspnea and vesicular respiratory sound but with no diagnosis of respiratory abnormalities. BP was elevated prior to admission (diastolic 100 mm Hg) and at admission (150/97 mm Hg); no other increased BP measurements noted. **Recovered in 24 hrs; continued in study.**
32	56/F	210 mg/ 4 wks	30 min (62)	Yes	None	30 min after injection, pt experienced weakness, dizziness, pallor. After 1 hr, pt felt stronger but complained of leg cramps. Developed mild sedation and slept for approx. 1 hr. Refused hosp. for observation; was released from site at 7 hrs post-injection. 11.5 hrs after injection, pt complained of stomachache and was taken to ER 2 hrs later, by which time stomachache had resolved. Laboratory results normal. **Recovered in approx. 24 hrs; continued in study.**
33	53/M	405 mg/ 4 wks	1.5 hrs (61)	Yes	None	30 min after injection, pt was noted pale; 1 hr after injection, complained of appetite loss; 1.5 hrs after injection, experienced sedation with drowsiness, moderate dizziness, not feeling well, weakness, unable to speak clearly. Gradually became slightly confused, disoriented. Fell asleep twice for periods of 10-15 min each. Showed improvement 3.5 hrs after injection but hospitalized 6 hrs post-injection as still not completely recovered and as pt lived alone. Pt ate and went to bed 10.5 hrs after injection. ECG normal. **Recovered in approx. 24 hrs; continued in study.**
34	40/M	210 mg/ 4 wks	3 hrs (63)	Yes	None	3 hrs after injection, pt left site with caregiver but became somnolent and disoriented while leaving the facility. Fell asleep on the way home. Caregiver contacted the site and took pt to ER. Admitted to ER 4 hrs after injection mildly somnolent and disoriented with fluctuating consciousness but otherwise in good condition. All tests normal. Discharged next morning feeling sleepy and tired, but recovered during the day. **Recovered in approx. 24 hrs; discontinued study.**

Table 1. Summary of Post-Injection Syndrome Cases in Clinical Trials through Final Clinical Trial Datalock (Detke, 2010a; Detke, 2010b; Data on file; Mitchell, 2013) (concluded)

Case #	Age/ Gender	Olz LAI Dose	Onset (Injection #)	Hosp	Treatment	Description/Duration/Disposition
35	65/M	405 mg/ 4 wks	20 min (41)	No	None	20 min after injection, pt started to feel somnolent, sedated, said he felt as if "drunk." Experienced dizziness, slowness walking, slight discoordination of inferior limbs, somnolence, and slurred speech. 1 hr after injection, experienced high somnolence but did not fall asleep. Pt was released after 3 hrs of observation. **Recovered in approx. 2 hrs; continued in study.**
36	34/M	405 mg/ 4 wks	80 min (67)	Yes	Serum physiologic, serum glucose	80 min after injection, pt experienced deep sedation, could not walk, and was hospitalized for observation. The study investigator reported that, in the first 12 hrs, pt had only answered to painful stimulus. Conflicting information was also reported that pt was eating and sedation was improving at 7 hrs after injection. Pt recovered completely and was discharged from the hospital the next morning. **Recovered in 23.5 hrs; continued in study.**
37	23/M	405 mg/ 4 wks	15 min (42)	Yes	Not reported	15 min after injection, pt experienced dizziness; 30 min after injection, pt experienced motor restlessness (especially right arm), agitation, somnolence, and an increase in BP (148/80 mm Hg), HR (98 bpm), and RR (20/min) (pre-injection: 128/76 mm Hg, 76 bpm, and 18/min, respectively). Developed confusion, visual and tactile hallucinations, and was disoriented 90 min after injection. Symptoms continued and at 200 min after injection, pt was taken to ER. Nine days prior to the injection, pt had elevated WBC count (18 200). **Recovered in 13.5 hrs; continued in study.**
38	54/M	405 mg (frequency unknown)	2 min (75)	Yes	Serum physiologic, lorazepam	2 min after injection, pt lost consciousness and was hospitalized. Vital signs were normal; pt was responsive to pain stimuli. No other symptoms were reported prior to loss of consciousness. Received 500 mL of physiological serum. Woke up confused and agitated approx. 10 hrs post-injection. Olz plasma concentrations support a clinical diagnosis of post-injection syndrome. **Recovered in 12.5 hrs; continued in study.**
39	67/F	210 mg/ 4 weeks	45 min (66)	Yes	Saline infusion	45 min after injection, pt developed somnolence and slurred speech and was subsequently hospitalized. Pt was observed in the psychiatric ER and continuously monitored. Pt given saline infusion and responded very shortly to external stimuli. Pt was not sedated but was delirious. Approx. 5 hrs later, pt had not improved and was transferred to the ICU for continuous monitoring. Relevant diagnostic findings included delirium, elevated HR (result not provided), and complete amnesia for the event. No corrective treatments were administered in the ICU. Pt transferred to psychiatric department for 3 days of further observation. **Recovered in 22.5 hrs; discontinued study.**

Abbreviations: AEs = adverse events; approx. = approximately; BP = blood pressure; bpm = beats per minute; CPK = creatine phosphokinase; CT = computerized tomography; ECG = electrocardiogram; EEG = electroencephalogram; ER = emergency room; F = female; Hosp = hospitalization; HR = heart rate; hr(s) = hour(s); ICU = intensive care unit; IM = intramuscular; IV = intravenous; KCl = potassium chloride; LAI = long-acting injection; M = male; $MgS0_4$ = magnesium sulfate; min = minutes; Olz = olanzapine; pt = patient; RR = respiratory rate; Unspecif. = Unspecified; UTI = urinary tract infection; WBC = white blood cell; wks = weeks.

APPENDIX 2

Case Definition of Olanzapine LAI Post-Injection Syndrome (Detke, 2010a)

Criteria 1 through 4 must be met for a clinical diagnosis of post-injection syndrome.

1. One or both of the conditions listed in (a) and (b):
    a. A minimum of 1 sign or symptom from at least 3 of the following symptom clusters consistent with olanzapine* overdose with 1 or more of at least moderate severity.
        i. Sedation/somnolence
        ii. Delirium/confusion/disorientation/other cognitive impairment
        iii. Dysarthria/other speech impairment
        iv. Ataxia/other motor impairment
        v. EPS
        vi. Agitation/irritability/anxiety/restlessness
        vii. Dizziness/weakness/general malaise
        viii. Seizure
    b. Any of the following signs and symptoms such that patient is:
        - Unarousable/unconscious/stuporous/comatose

    *Other signs and symptoms listed under 1a may occur with olanzapine overdose, but are not considered criteria for post-injection syndrome. Please refer to your local olanzapine product labeling.
2. Condition develops within 24 hours of an olanzapine long-acting injection.
3. Condition cannot be explained by a significant dose increase of olanzapine LAI, initiation or addition of oral olanzapine or other sedating medication, or new exposure to olanzapine LAI.
4. Underlying medical conditions have been ruled out, including concomitant substance use or abuse.