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The content of this letter has been agreed with the European Regulatory Authorities.

Dear Dr Spooner,

IMPORTANT SAFETY INFORMATION
ON THE ASSOCIATION OF ZYPADHERA (olanzapine powder and solvent for prolonged release suspension for injection) AND POST INJECTION SYNDROME

Summary
ZYPADHERA (olanzapine powder and solvent for prolonged release suspension for injection) was approved for maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine on 19th November 2008.

This communication is being provided by Eli Lilly and Company to inform you of important safety information regarding ZYPADHERA and its association with a **post injection syndrome** characterized primarily by signs and symptoms of sedation and/or delirium consistent with olanzapine overdose. **This syndrome does not apply to any other formulation of olanzapine.**

When prescribing ZYPADHERA, it is important for healthcare professionals to follow all **recommended conditions for safe use and to inform patients of this potential risk.**

- ZYPADHERA should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique, and given in locations where observation and access to appropriate medical care can be assured following dose administration in case of symptoms of olanzapine overdose.
- Patients should be advised about this potential risk and the need to be observed for 3 hours following dose administration in a healthcare facility each time ZYPADHERA is administered.
- Prior to giving the injection, the healthcare professional should determine that the patient will not travel alone to their destination.
- After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

- It should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of olanzapine overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved.
- For the remainder of the day following ZYPADHERA dose administration, patients should be advised to be vigilant for signs and symptoms of olanzapine overdose secondary to post injection adverse reactions, be able to obtain assistance if needed and not drive or operate machinery.

Further Information on Post Injection Syndrome

Signs and Symptoms: During pre-marketing clinical studies, events that presented with signs and symptoms consistent with olanzapine overdose were reported in some patients following injection of ZYPADHERA. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms included extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.

Rate of Occurrence and Timing of Events: These events occurred in <0.1% of injections and approximately 1.4% patients in clinical trials. In most cases, initial signs and symptoms appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 to 72 hours after injection. Events occurred rarely (<1 in 1,000 injections) between 1 and 3 hours after injection, and very rarely (<1 in 10,000 injections) after 3 hours following injection.

Mechanism: The exact mechanism of post injection syndrome is unknown. However, higher than expected systemic olanzapine concentrations have been observed in patients with post injection syndrome. The clinical manifestations are consistent with those of oral olanzapine overdose and therefore, may be associated with accidental intravascular injection of ZYPADHERA.

Further Information for Healthcare Professionals

The clinical trial database of ZYPADHERA is comprised of eight studies involving more than 2,000 patients. Analyses of these data demonstrate that the effectiveness of ZYPADHERA in the treatment and maintenance treatment of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine.

Please consult the Summary of Product Characteristics (SPC) for complete information on the efficacy and safety of ZYPADHERA as well as recommendations on the appropriate clinical monitoring for hyperglycemia, diabetes, and lipid alterations in patients treated with antipsychotic agents, including ZYPADHERA, in accordance with utilized antipsychotic guidelines.

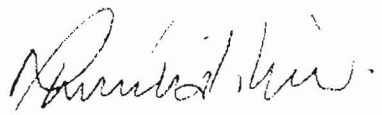
Call for Reporting

Healthcare professionals are reminded of the need to report adverse reactions in accordance with the national spontaneous reporting system. The primary contact is Lilly (+44(0) 1256 315999), however the IMB (Pharmacovigilance Unit) may also be contacted.
If you wish to report an adverse drug reaction to the Irish Medicines Board please do so using the "on-line reporting" section of the IMB website at www.imb.ie or contact the IMB at 01 6764971.

Communication Information

The safety of patients is Lilly's highest priority and we greatly value your collaboration. Please contact the Medical Information Department at +44 (0) 1256 315 999 if you have any questions or if you wish to receive further information or training.

Yours sincerely,



Dr Maurício Silva de Lima M.D., Ph.D.
UK & ROI Medical Director
Eli Lilly and Company

Appendix: ZYPADHERA Summary of Product Characteristics