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Worldwide Biopharmaceutical Businesses

Date: 01 October 2020

INFORMATION FOR HEALTHCARE PROFESSIONALS

To: Healthcare Professionals

Re: Temporary supply of a different presentation and changes to the instructions for Ativan 4mg/ml Solution for Injection (Lorazepam) (PL 00057/1279)

Due to supply disruption we are temporarily managing the supply of Ativan (Lorazepam) 4mg/ml from early October 2020 with alternative Canadian licensed product – LORAZEPAM injection USP, sterile solution 4mg/ml glass vials.

Whilst the strength and excipients of the Canadian formulation being supplied on a temporary basis are very similar to the licensed UK Ativan (Lorazepam) 4mg/ml there are differences in presentation and prescribing information. Please read the following information carefully and ensure all healthcare professionals involved in the administration of lorazepam solution for injection are familiar with the details and the process for administering the medicine.

A summary of the key points are as follows:

- To help mitigate the national shortfall in supply against demand, Pfizer has obtained agreement from the Medicines and Healthcare products Regulatory Agency (MHRA) to import Pfizer stock of LORAZEPAM injection USP, sterile solution 4mg/from Canada.
- LORAZEPAM injection USP, sterile solution 4mg/ml glass vials are considered an unlicensed medicine in the UK.
- See table for differences in presentation, dilution and preparation between products.
- The constituents/excipients of UK and Canadian formulations are identical, and the benefit-risk profile is consistent with the UK formulation.
- Canadian LORAZEPAM injection USP, sterile solution 4mg/ml is supplied in multi-dose glass vials with latex-free stoppers whereas UK Ativan 4mg/ml Solution for Injection (Lorazepam) is supplied in 2ml ampoules (Type I glass) with a one-point-cut opening
- Please note the expiry of the Canadian lorazepam solution 4mg/ml is 01-Dec-2021.

The UK Summary of Product Characteristics and Patient Information Leaflet for Ativan 4mg/ml Solution for Injection (Lorazepam) can be found at: https://www.medicines.org.uk/emc/product/5473

The Canadian Summary of Product Characteristics and Patient Information Leaflet for LORAZEPAM injection USP, sterile solution 4mg/ml can be found at: https://www.pfizer.ca/lorazepam-injection-usp

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

DIFFERENCES IN PRESENTATION:

For your awareness the key differences between Ativan 4mg/ml Solution for Injection (Lorazepam) (PL 00057/1279) and LORAZEPAM injection USP, sterile solution 4mg/ml have been highlighted in the table below.

Table 1. Notable differences between the Canadian and UK product

Marketing Authorisation Holder	**Pfizer Canada ULC,** **17300 Trans-Canada Highway,** **Kirkland,** **Quebec** **H9J 2M5**	**Pfizer Limited** **Ramsgate Road,** **Sandwich,** **Kent,** **CT13 9NJ** **United Kingdom**
Product Name	LORAZEPAM injection USP, sterile solution 4mg/ml	Ativan 4mg/ml Solution for Injection (Lorazepam)
Licensed Indication	**Anxiety**: Lorazepam Injection USP is useful for the short-term relief of manifestations of severe anxiety in people with anxiety neurosis. It is also useful for the relief of excessive anxiety that might be present prior to surgical interventions. **Status epilepticus**: Lorazepam Injection USP is useful to help control severe seizures	Pre-operative medication or premedication for uncomfortable or prolonged investigations, e.g. bronchoscopy, arteriography, endoscopy. The treatment of acute anxiety states, acute excitement or acute mania. The control of status epilepticus.
Solution strength/dose	Each vial contains 1ml of 4mg/ml solution for a full dose of 4mg	Each ampoule contains 1ml of 4mg/ml solution for a full dose of 4mg
Primary Container	Multi-dose glass vials with latex-free stoppers	2ml ampoules (Type I glass) with a one-point-cut opening
No. of Packs	10 vials of 1ml; Each vial contains 1ml of solution for injection	10 ampoules of 1ml; Each ampoule contains 1ml of solution for injection
Administration	When given intramuscularly, Lorazepam Injection USP, undiluted, should be injected deep into a muscle mass. Immediately prior to intravenous use, Lorazepam Injection USP must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing intravenous infusion. The rate of injection should not exceed 2 mg/minute. **Refer to the Canadian Summary of Product Characteristics for full administration guidance and solution compatibilities.**	Ativan Injection can be given intravenously or intramuscularly. However, the intravenous route is to be preferred. Care should be taken to avoid injection into small veins and intra-arterial injection. **Intramuscular administration:** A 1:1 dilution of Ativan Injection with normal saline or Sterile Water for Injection BP is recommended in order to facilitate intramuscular administration. **Intravenous administration:** For intravenous administration, Ativan Injection should always be diluted with saline or Sterile Water for Injection BP as a 1:1 dilution. Ativan Injection is presented as a 1ml solution in a 2ml ampoule to facilitate dilution. **Refer to the UK Summary of Product Characteristics for full administration guidance and solution compatibilities.**

Dosing	**Excessive Anxiety Prior to Surgical Procedure:** **Adults -** Usually 0.05 mg/kg to a maximum of 4 mg total, given intramuscularly (2 to 3 hours before surgery). **Status Epilepticus: Adults** - The usual recommended initial dose of Lorazepam Injection USP is 0.05 mg/kg up to a maximum of 4 mg given by slow intravenous injection. If seizures are terminated, no additional Lorazepam Injection USP is required. If seizures continue or recur after a 10 to 15 minute observation period, an additional intravenous dose of 0.05 mg/kg may be administered. If the second dose does not result in seizure control after another 10 to 15 minute observation period, other measures to control status epilepticus should be employed. A maximum of 8 mg total only, of Lorazepam Injection USP, should be administered during a 12 hour period.	**Premedication**: Adults: 0.05mg/kg (3.5mg for an average 70kg man). By the intravenous route the injection should be given 30-45 minutes before surgery when sedation will be evident after 5-10 minutes and maximal loss of recall will occur after 30-45 minutes. By the intramuscular route the injection should be given 1-11/2 hours before surgery when sedation will be evident after 30-45 minutes and maximal loss of recall will occur after 60-90 minutes. Paediatric population: Ativan Injection is not recommended in children under 12. **Acute Anxiety** Adults: 0.025-0.03mg/kg (1.75-2.1mg for an average 70kg man). Repeat 6 hourly. Paediatric population: Ativan Injection is not recommended in children under 12. **Status epilepticus** Adults: 4mg intravenously Paediatric population: 2mg intravenously
Contraindications	Lorazepam Injection USP (lorazepam) is contraindicated in patients with myasthenia gravis or acute narrow angle glaucoma, and in those with known hypersensitivity to benzodiazepines. Lorazepam Injection USP is also contraindicated in patients with known hypersensitivity to benzodiazepines or the vehicle (polyethylene glycol, propylene glycol and benzyl alcohol). Lorazepam Injection USP should not be injected intra-arterially and care should be taken to prevent its extravasation into tissue adjacent to an artery because of the danger of producing arteriospasm resulting in gangrene which may require amputation.	• Acute pulmonary insufficiency • Hypersensitivity to benzodiazepines, including lorazepam or to any of the excipients listed in section 6.1. • Sleep apnoea syndrome • Myasthenia gravis • Severe hepatic insufficiency Ativan Injection is not recommended for out-patient use unless the patient is accompanied. NB: Section 4.4 Special warnings and precautions for use states: *"Caution should be used in the treatment of patients with acute narrow-angle glaucoma"*
Precautions/ Warnings	Refer to Appendix 1 for list of differences in Precautions/Warnings across UK & Canadian SPCs	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard, by searching for MHRA Yellow Card in the Google Play or Apple App Store, or via some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals. Suspected side effect can also be reported by calling 0800 731 6789 for free

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Further Information

LORAZEPAM injection USP, sterile solution 4mg/ml which is the alternative to Ativan 4mg/ml Solution for Injection (Lorazepam) can be ordered through the new PIP code **802-5132** via Alliance Healthcare. Please see batch details below:

Batch Number	**Expiry Date**
18213EV	01-Dec-2021
18245EV	01-Dec-2021

Please note expiry of the LORAZEPAM injection USP, sterile solution 4mg/ml is 01-Dec-2021

If you have any questions about this letter, please contact Pfizer Medical Information at the following address:

Medical Information, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. United Kingdom. Telephone: **01304 616161** or visit https://www.pfizermedicalinformation.co.uk/

For questions concerning the supply and order quantities of Lorazepam injection, please contact the Pfizer Customer Contact Centre on **0845 608 8866**.

The supply of Canadian LORAZEPAM injection is being implemented in order to mitigate stock shortages brought about by supply disruption to the licensed UK Ativan 4mg/ml Solution for Injection (Lorazepam).

Kind regards,

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Greg Coates
Medical Affairs, Internal Medicine, Pfizer Ltd

Appendix 1

Content of the Canadian Precautions/Warnings which is not reflected in the UK Precautions/Warnings:

- Lorazepam Injection USP is not recommended for use in patients less than 18 years of age
- Excessive sedation has been observed with lorazepam at standard therapeutic doses. Therefore, patients on Lorazepam Injection USP should be warned against engaging in hazardous activities requiring mental alertness and motor coordination, such as operating dangerous machinery or driving motor vehicles.
- PRIOR TO INTRAVENOUS USE, LORAZEPAM INJECTION USP SHOULD BE DILUTED WITH AN EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). INTRAVENOUS INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CARE SHOULD BE TAKEN TO DETERMINE THAT ANY INJECTION WILL NOT BE INTRA-ARTERIAL AND THAT PERIVASCULAR EXTRAVASATION WILL NOT TAKE PLACE. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. INTRAVENOUS LORAZEPAM INJECTION USP, WHEN GIVEN ALONE IN GREATER THAN THE RECOMMENDED DOSE, OR AT THE RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING THE ADMINISTRATION OF ANESTHESIA, MAY PRODUCE HEAVY SEDATION, THEREFORE EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY AND TO SUPPORT RESPIRATION/VENTILATION SHOULD BE AVAILABLE.
- Clinical trials have shown that patients over the age of 50 years may have a more profound and prolonged sedation with intravenous lorazepam. Ordinarily an initial dose of 2 mg may be adequate, unless a greater degree of lack of recall is desired.
- There is no evidence to support the use of lorazepam in coma, shock or acute alcohol intoxication at this time.
- As is true of other similar CNS-acting drugs, patients receiving Lorazepam Injection USP should not operate machinery or engage in hazardous occupations or drive a motor vehicle for a period of 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, concomitant use of other drugs, stress of surgery or the general condition of the patient.
- Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines. Infants of lactating mothers should be observed for pharmacological effects
- Use in Children: Lorazepam Injection USP is not intended for use in children under 18 years of age. The safety and effectiveness of Lorazepam Injection USP (lorazepam) in children less than 18 years of age has not been established.
- Use in Mental and Emotional Disorders: Lorazepam Injection USP is not recommended for the treatment of psychotic or depressed patients. Since excitement and other paradoxical reactions can result from the use of these drugs in psychotic patients, they should not be used in ambulatory patients suspected of having psychotic tendencies.
- As with other anxiolytic-sedative drugs, Lorazepam Injection USP should not be used in patients with nonpathological anxiety. These drugs are also not effective in patients with characterological and personality disorders or those with obsessive-compulsive neurosis.
- When using Lorazepam Injection USP, it should be recognized that suicidal tendencies may be present and that protective measures may be required.

Content of the UK Precautions/Warnings which is not reflected in the Canadian Precautions/Warnings:

- It is recommended that patients receiving Ativan Injection should remain under observation for at least eight hours and preferably overnight. When Ativan Injection is used for short procedures on an outpatient basis, the patient should be accompanied when discharged.
- It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimise anxiety should they occur.
- There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.
- When benzodiazepines with a long duration of action are being used, it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.
- Anxiety or insomnia may be a symptom of several other disorders. The possibility should be considered that the complaint may be related to an underlying physical or psychiatric disorder for which there is more specific treatment.
- As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.
- Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.
- Although hypotension has occurred only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.