Dear Healthcare Professional,

A Safety Warning for Preparations Containing Metoclopramide (Pramin®)
New Restrictions to Reduce the Risk of Side Effects

The Ministry of Health wishes to update Healthcare Professionals regarding restrictions on the usage of Metoclopramide preparations, in accordance with recent warnings released in Europe. The new restrictions are primarily intended to reduce the known risk for extra-Pyramidal side effects. On analysis of side effect reports in Europe, it was found that there is significantly elevated risk for extra-pyramidal side effects in children, as well as elevated risk for Tardive Dyskinesia in the elderly, mainly when applied for chronic treatment. In addition, very rare instances of cardiac adverse events were reported, primarily when administered intravenously. In most medical conditions requiring chronic treatment, the risk exceeds the benefit. The main points are as follows:

- Metoclopramide should only be prescribed for short term use (up to 5 days) excluding exceptional cases (e.g. diabetic gastroparesis), in accordance with the physician’s discretion.
- Metoclopramide should not be used in children under one year of age. Over the age of one year, it shall not be given as a first line of treatment.
- For adults and children, the maximum dose per day (24 hours) is 0.5 mg per kg body weight.
In adults, the recommended dosage is 10 mg, one to three times per day (all routes of administration).

In children, the recommended dosage is 0.1-0.15 mg per kg body weight (per dose), one to three times per day.

The marketing of Pramin 20 mg suppositories for adults will be stopped, in accordance with Europe (attached is the notification from Rafa Laboratories Ltd.).

Rapid intravenous administration of Metoclopramide has been linked to an increased risk of side effects. Intravenous Metoclopramide should be given by slow intravenous administration. When administrated as a bolus dose, it should be given over at least 3 minutes.

The product leaflets will be updated accordingly

**Background**

On 24th October 2013, the European Medicines Agency (EMA) publicized new restrictions for preparations containing Metoclopramide. The new restrictions were introduced after an extensive review was performed to assess the efficacy versus safety profile of Metoclopramide preparations. In view of this, discussions were held in the Ministry of Health in the framework of the Advisory committee for Drug Safety, as well as with Rafa Laboratories Ltd., the manufacturer and distributer of Pramin ®. The MOH decided to adopt the majority of the restrictions added in Europe, and the leaflets will be updated accordingly.

**Main Safety Issues**

**Extra-Pyramidal Side Effects (EPS)**

The findings of the review emphasized the known risk of extra-pyramidal side-effects with Metoclopramide. By December 2011, 1,749 reports of extra-pyramidal side effects have been received by the manufacturers of the preparations in Europe.

**Analysis of the Reports from Europe:**

- The reporting rate for EPS was calculated to be 6 times higher in children than in adults.
• Extra-pyramidal side effects were more likely to occur after several doses, although usually at the beginning of treatment.

• Rapid intravenous administration of Metoclopramide was linked to a higher risk of adverse effects.

• Elderly patients seemed to be more at risk of potentially irreversible tardive dyskinesia with prolonged use.

Cardiac Side Effects

There are very rare reports of severe cardiac adverse events during Metoclopramide treatment, including reduced blood pressure, syncope, bradycardia, QT prolongation, AV block and cardiac arrest, mainly with intravenous administration. Caution should be exercised in administration to at-risk populations, such as: elderly patients, patients with arrhythmias, uncorrected electrolytic disorders, bradycardia and patients taking other medications that are known to prolong QT interval.

Steps for Reducing Side Effects with Administration of Metoclopramide:

• Metoclopramide should only be prescribed for short term use (up to 5 days) excluding exceptional cases (e.g. diabetic gastroparesis), in accordance with the physician’s discretion

• Treatment of diabetic gastroparesis shall be given for 3 months, with prolongation of treatment in accordance with the physician’s discretion.

• For adults and children, the maximum dose per day (24 hours) is 0.5 mg per kg body weight.

• In adults, the recommended dosage is 10 mg, one to three times per day (all routes of administration).

• The marketing of Pramin 20 mg suppositories for adults will be stopped, in accordance with Europe (attached is the notification from Rafa Laboratories Ltd.).

• Rapid intravenous administration of Metoclopramide has been linked to an increased risk of side effects. Intravenous Metoclopramide should be given by slow
intravenous administration. When administrated as a bolus dose, it should be given over at least 3 minutes.

**Additional Points to be emphasized in reducing Side Effects and avoiding dosage errors in Administration of Metoclopramide to Children:**

- **Metoclopramide preparations should not be given for the treatment of children under one year of age** (note: in children under the age of one year, when the benefits exceeds the risks,, Metoclopramide may be administered in a hospital framework after approval on an institutional Form 29c).

- In children over the age of one year, treatment with Metoclopramide shall be administered as per dosage restrictions, and not as a first line of treatment.

- In children, the recommended dosage is 0.1-0.15 mg per kg of body weight (per dose), one to three times per day, and shall not exceed 0.5 mg per kg of body weight per day (24 hours).

- Pediatric suppositories contain Metoclopramide 5 mg, and are intended for the treatment of children who weigh **over 30 kg**.

- Since September 2006, Pramin syrup has not been marketed in Israel, and currently, liquid Metoclopramide is available for preparation in a pharmacy by physician’s prescription. **Cases of overdoses in children have occurred due to dosage errors in the administration of liquid formulations of Metoclopramide.** In cases that liquid preparation is necessary, please follow the instructions bellow in order to avoid dosage errors in children:
  - **Metoclopramide liquid formulation** should be prepared at a **standard concentration of 1 mg/ml only**.
  - The required dosage should be clearly recorded.
  - Together with the dispensing of the liquid formulation, an appropriate syringe for measuring the volume required for treatment should be dispensed.
  - It is necessary to provide appropriate instructions at the time of dispensing to ensure the administration of an exact dosage of the formulation.
The current measures are being taken in order to reduce the risk of side effects, and harmonize Israeli and European guidelines for use of Metoclopramide

Link to the EMA notification:

Pharmacovigilance and Drug Information Department is continuing to monitor side effects and safety information from Israel and the world. Please report side effects using the online form at the following link:
http://forms.gov.il/globaldta/getsequence/getsequence.aspx?formType=AdversEffe ctMedic%40moh.health.gov.il or to ADR@MOH.health.gov.il

Yours sincerely,

Dr. Dorit Dil Nahlieli, Pharm.D
Head of PV and Risk management department
Pharmaceutical division, Ministry of Health, ISRAEL