תאריך : מאי 2023

הנדון:

<u>פלולן אפופרוסטנול 1500 מק"ג לעירוי / Flolan Infusion of Epoprostenol 1500 mcg</u>
<u>פלולן אפופרוסטנול 500 מק"ג לעירוי / Flolan Infusion of Epoprostenol 500 mcg</u>
<u>Epoprostenol (as sodium) 0.5 mg / vial</u>
<u>Epoprostenol (as sodium) 1.5 mg / vial</u>
<u>Powder for solution for infusion</u>
<u>I.V</u>

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עלון חדש לצרכן ועדכון העלון לרופא של התכשירים: Flolan Infusion of Epoprostenol 500&1500 mcg.

עד כה לתכשירים היה עלון לרופא בלבד.
העלון לצרכן יחליף את העלון לרופא שנמצא כעת בתוך אריזות התכשירים.

<u>לשימת לבכם, חל שינוי בסעיפי ההתוויה ומשטר המינון</u> של התכשירים, לצורך הלימה לרישום האירופאי.

- **ההתוויה הרשומה לתכשירים בישראל:**

Flolan is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III-IV symptoms to improve exercise capacity.

<u>מקרא לעדכונים המסומנים:</u>
תוספת טקסט - כתב **כחול**
מחיקת טקסט – כתב ~~אדום~~

- **<u>עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא:</u>**

4.1 Therapeutic indications

~~FLOLAN is indicated for the long term intravenous treatment of primary arterial pulmonary hypertension and arterial pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.~~
Flolan is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III-IV symptoms to improve exercise capacity (see section 5.1).

4.2 Posology and method of administration

~~**Reconstitution**~~

~~Each vial is for single use only; discard any unused diluent or unused reconstituted solution. Select a concentration for the solution of FLOLAN that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed below *[see Administration]*.~~

~~Using aseptic technique, reconstitute FLOLAN only with pH 12 STERILE DILUENT for FLOLAN. Table 1 gives directions for preparing several different concentrations of FLOLAN. See Table 2 for storage and administration time limits for the reconstituted FLOLAN.~~

~~**Table 1. Reconstitution and Dilution Instructions for FLOLAN Using pH 12 STERILE DILUENT for FLOLAN.**~~

To make 100 mL of solution with final concentration of:	Directions:
3,000 ng/mL	Dissolve contents of **one 0.5-mg vial** with 5 mL of sterile diluent. Withdraw 3 mL and add to sufficient sterile diluent to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of **one 0.5-mg vial** with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of **two 0.5-mg vials** each with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.
15,000 ng/mL[a]	Dissolve contents of **one 1.5-mg vial** with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.

[a] Higher concentrations may be prepared for patients who receive FLOLAN long-term.

Table 2. Storage and Administration Limits for Reconstituted FLOLAN

	When Using pH 12 STERILE DILUENT for FLOLAN
Stability	Freshly prepared reconstituted solutions or reconstituted solutions that have been stored at 2°C to 8°C for no longer than 8 days can be administered up to: • 72 hours at up to 25°C. • 48 hours at up to 30°C. • 24 hours at up to 35°C. • 12 hours at up to 40°C.
• Reconstituted solutions can be used immediately. Refrigerate at 2°C to 8°C if not used immediately. • Protect from light. • Do not freeze reconstituted solutions.	

Dosage

Initiate intravenous infusions of FLOLAN at 2 ng/kg/min. Alter the infusion by 1- to 2 -ng/kg/min increments at intervals sufficient to allow assessment of clinical response. These intervals should be at least 15 minutes.

During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output may occur. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated.

Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse vasodilatory reactions. In general, expect progressive increases in dose.

If dose-related adverse reactions occur, make dose decreases gradually in 2 -ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve *[see section 4.8 Undesirable effects]*. Avoid abrupt withdrawal of FLOLAN or sudden large reductions in infusion rates *[see section 4.4 Special warnings and precautions for use]*.

Following establishment of a new chronic infusion rate, measure standing and supine blood pressure for several hours.

Taper doses of FLOLAN after initiation of cardiopulmonary bypass in patients receiving lung transplants.

Administration

Initiate FLOLAN in a setting with adequate personnel and equipment for physiologic monitoring and emergency care.

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, do not use.

Administer continuous chronic infusion of FLOLAN through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Do not administer bolus injections of FLOLAN.

The ambulatory infusion pump used to administer FLOLAN should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion, end-of-infusion, and low-battery alarms, (4) be accurate to ±6% of the programmed rate, and (5) be positive-pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver FLOLAN. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. Use a 60-inch microbore non- di-(2-ethylhexyl)phthalate (DEHP) extension set with proximal antisyphon valve, low priming volume (0.9 mL), and in-line 0.22-micron filter.

Preparation and administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG) may become damaged when used with FLOLAN prepared with pH 12 STERILE DILUENT for FLOLAN and therefore must not be used.

Consult the manufacturer of the sets to confirm that they are considered compatible with highly alkaline solutions, such as FLOLAN prepared with pH 12 STERILE DILUENT for FLOLAN.

To avoid interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets.
Do not administer or dilute reconstituted solutions of FLOLAN with other parenteral solutions or medications.
Consider a multi-lumen catheter if other intravenous therapies are routinely administered.

Select a concentration for the solution of FLOLAN that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. When administered chronically, prepare FLOLAN in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL, using 2 vials of pH 12 STERILE DILUENT for FLOLAN.

Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of FLOLAN.

Infusion rates may be calculated using the following formula:

$$\textbf{Infusion Rate (mL/h)} = \frac{\textbf{[Dose (ng/kg/min) x Weight (kg) x 60 min/h]}}{\textbf{Final Concentration (ng/mL)}}$$

Example calculations for infusion rates are as follows:

Example 1: for a 60-kg person at the recommended initial dose of 2 ng/kg/min using a 3,000-ng/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{\textbf{[2} \text{ (ng/kg/min)} \textbf{ x 60} \text{ (kg)} \textbf{ x 60 (}\text{min/h)}\textbf{]}}{\textbf{3,000} \text{ (ng/mL)}} = \textbf{2.4} \text{ (mL/h)}$$

Example 2: for a 70-kg person at a dose of 16 ng/kg/min using a 15,000-ng/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{\textbf{[16} \text{ (ng/kg/min)} \textbf{ x 70} \text{ (kg)} \textbf{ x 60 (}\text{min/h)}\textbf{]}}{\textbf{15,000} \text{ (ng/mL)}} = \textbf{4.48} \text{ (mL/h)}$$

Posology

Epoprostenol is only indicated for continuous infusion by intravenous route.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Short-term (acute) dose ranging:

This procedure should be conducted in a hospital with adequate resuscitation equipment.

A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 min or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.
If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified.

Long-term continuous infusion:

Long-term continuous infusion of Flolan should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanograms/kg/min.

Dosage adjustments:

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reaction due to excessive doses of Flolan.

In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms of pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 min. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse reactions may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect (see section 4.4). Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Flolan should be adjusted only under the direction of a physician.

Elderly
There is no specific information on the use of Flolan in patients over 65 years for pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other medicine therapy.

Paediatric population
The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within 72 hours at up to 25°C, or 48 hours at up to 30ºC, or 24 hours at up to 35 ºC, or 12 hours at up to 40 ºC.

Epoprostenol solution prepared with solvent (pH 11.7-12.3), must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG; see section 6.2 and 6.6).

The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Epoprostenol must not be administered as a bolus injection.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#!/byDrug וניתן לקבלם מודפס על-ידי פניה לחברת גלקסוסמיתקליין: רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,

טניה רשקובן
רוקחת ממונה