תאריך : יולי 2021

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 עדכון העלון לרופא של התכשירים: Flolan Infusion of Epoprostenol 500&1500 mcg.

- **ההתוויה הרשומה לתכשירים בישראל:**

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 to conventional therapy.

לשימת ליבכם, עדכון העלון לרופא כולל מכלול רב של שינויים. בהודעה זו מצויינים השינויים המהותיים בלבד. למידע נוסף יש לעיין בעלון לרופא המעודכן.

<u>מקרא לעדכונים המסומנים:</u>
תוספת החמרה - כתב **כחול**

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

4.3 Contraindications

Flolan is contraindicated in patients:
- with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- with congestive heart failure arising from severe left ventricular dysfunction.
- Flolan must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.

Flolan is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 min of the end of administration.
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If excessive hypotension occurs during administration of Flolan, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see section 4.9).

Blood pressure and heart rate should be monitored during administration of Flolan.

Flolan may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the concentration of Flolan administered.

The effects of Flolan on heart rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

Extreme caution is advised in patients with coronary artery disease.

Elevated serum glucose levels have been reported (see section 4.8).

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Sodium content
This medicinal product contains sodium, which should be taken into consideration by patients on a controlled sodium diet.

The amount of sodium present in the reconstituted concentrate solution equals 73 mg approximately, equivalent to approximately 4 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

The amount of sodium present in the powder for solution for infusion equals 3 mg approximately per vial, equivalent to approximately 0.2 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

The amount of sodium present in the solvent for parenteral use equals 70 mg approximately per vial, equivalent to approximately 4 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

Some patients with pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Flolan must not be used chronically in patients who develop pulmonary oedema during dose initiation (see section 4.3).

Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death (see section 4.2).

Flolan is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with Flolan requires commitment by the patient to sterile drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education.

Sterile technique must be adhered to in preparing the drug and in the care of the catheter. Even brief interruptions in the delivery of Flolan may result in rapid symptomatic deterioration. The decision to administer Flolan for pulmonary arterial hypertension should be based upon the patient's understanding that there is a high likelihood that therapy with Flolan will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent i.v. catheter and infusion pump should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

When Flolan is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable.

The vasodilator effects of Flolan may augment or be augmented by concomitant use of other vasodilators.

As reported with other prostaglandin analogues, Flolan may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding.

Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with Flolan, which although transient, may be clinically significant in patients prone to digoxin toxicity.

4.6 Fertility, pregnancy,and lactation

Breast-feeding

It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan.

4.7 Effects on ability to drive and use machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

4.8 Undesirable effects

Infections and Infestations	
Common	septicaemia (mostly related to delivery system for Flolan)[1]
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Endocrine Disorders	
Very rare	Hyperthyroidism
Psychiatric Disorders	
Very rare	Agitation
Cardiac Disorders	
Common	bradycardia[3]
Vascular Disorders	
Very common	Facial flushing (seen even in the anaesthetised patient)
Very rare	Pallor
Not known	Ascites
Respiratory, thoracic and mediastinal disorders	
Unknown	Pulmonary oedema
Gastrointestinal Disorders	
Common	Abdominal colic, sometimes reported as abdominal discomfort
Uncommon	Dry mouth
Skin and Subcutaneous Tissue Disorders	
Uncommon	Sweating
Musculoskeletal and Connective Tissue Disorders	
Common	Arthralgia
General Disorders and Administration Site Conditions	
Common	Pain at the injection site*, chest pain
Rare	Local infection*
Very rare	Erythema over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness
Investigations	
Unknown	Blood glucose increased
* Associated with the delivery system for Flolan	
[1] Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.	
[3] Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of Flolan greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of Flolan equivalent to 30 nanograms/kg/min in healthy conscious volunteers.	

4.9 Overdose

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If overdose occurs reduce the dose or discontinue the infusion and initiate appropriate supportive measures as necessary; for example plasma volume expansion and/or adjustment to pump flow.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

בברכה,
עינת טל
רוקחת ממונה