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GLAXOSMITHKLINE SAFETY ADVISORY

Date: 23 January 2017

Flolan 0.5 mg Powder and Solvent for Solution for Infusion (PA 1077/058/002)

Flolan 1.5 mg Powder and Solvent for Solution for Infusion (PA 1077/058/001)

Flolan (epoprostenol) – Introduction of new sterile solvent with different pH; stock of current formulation to be phased out in 2017, at which stage the new formulation will be made available to order in Irish market (available from 20th March 2017)

PLEASE ENSURE ALL HEALTHCARE PROFESSIONALS WHO PRESCRIBE, ADMINISTER OR DISPENSE FLOLAN IN YOUR UNIT/HOSPITAL/PHARMACY ARE AWARE OF THE INFORMATION OUTLINED IN THIS LETTER

Dear Healthcare Professional,

A new formulation of Flolan (with solvent pH 12) will be available with differences in storage and administration from the current formulation (with solvent pH 10.5). Stock of the current formulation (with solvent pH 10.5) will be phased out over the next couple of months, with the new formulation of Flolan (with solvent pH 12) being introduced to the Irish market on 20th March 2017. GSK is alerting healthcare providers to the launch of the reformulated (pH 12) Solvent for Solution for infusion and differences in storage and administration to ensure proper use during the period when both solvents are available for the transition of patients from Flolan prepared with the reformulated (pH 12) Solvent for Solution for infusion.

Reconstituted Flolan with pH 12 Solvent (the new formulation) is more thermostable, which eliminates the need for use of a cold pouch/ice pack during administration.

Key Messages

- Storage and administration conditions when using FLOLAN

	CURRENT FOMULATION (with Solvent pH 10.5)	**NEW FORMULATION** (with Solvent pH 12)
Storage (PAH)	Should be used within 12 hours at 25°C if freshly prepared, OR May be stored for up to 40 hours between 2°C and 8°C and then	Freshly prepared solutions for infusion 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

	used within 8 hours at 25°C, OR May be stored for up to 24 hours between 2°C and 8°C and then used over 24 hours between 2°C and 8°C with use of a cold pouch changed to as necessary throughout the day.	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.
Storage (Renal)	Reconstituted solutions, prepared in real time, must not be administered over more than 12 hours when they are used at room temperature (between 15°C and 25°C). They should be kept under 25°C and protected from light. It is possible to refrigerate Flolan reconstituted solutions, before they are used at room temperature, ranging between 2°C and 8°C and without exceeding 40 hour storage. In this case, the solutions should not be used over more than 8 hours when administered at room temperature.	Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered for up to 12 hours at up to 25°C.

- Accidental use of Solvent for Solution for Infusion in place of the reformulated (pH 12) Solvent for Solution for Infusion without concurrent use of a cold pouch for the FLOLAN solution could result in possible decrease in efficacy due to drug degradation. Decreased drug delivery could result in rebound of PAH symptoms resulting in dizziness and dyspnoea.
- Flolan (with solvent pH 10.5) should continue to be used with a cold pouch/ice pack. Failure to do so may result in possible decrease in efficacy due to drug degradation.
- It is recommended that when healthcare professionals are writing a Flolan prescription for a patient, they should make it clear to the pharmacist, which formulation they are requesting for the patient (as it is likely pharmacies may have both formulations in stock from March 2017)
- It is recommended that if a pharmacist receives a prescription, where it is unclear whether it should be dispensed as the pH 10.5 or pH 12 formulation, this should be clarified with the prescribing physician
- There will be a period of time in which both the Solvent for Solution for Infusion and the reformulated (pH 12) Solvent for Solution for Infusion will be on the market simultaneously while existing Solvent for Solution for Infusion supplies are transitioned to the reformulated (pH 12) Solvent for Solution for Infusion.

- It is important that you are aware of this solvent reformulation to ensure that the correct instructions for reconstitution, storage and administration of FLOLAN are given to your patients who are receiving FLOLAN for the treatment of PAH.
- The change in the solvent formulation does not affect the reconstitution or administration of FLOLAN solution for use in renal dialysis.
- Please ensure patients receiving Flolan for their PAH receive advice and information on the changes in storage/administration and that their dose should be unchanged.

Action Being Taken by GlaxoSmithKline

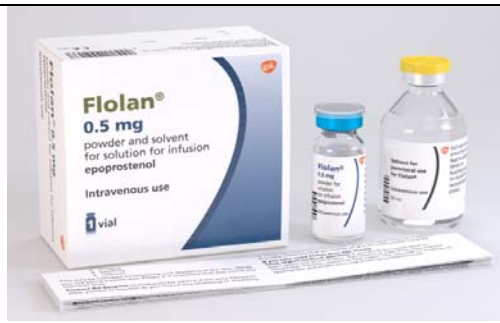
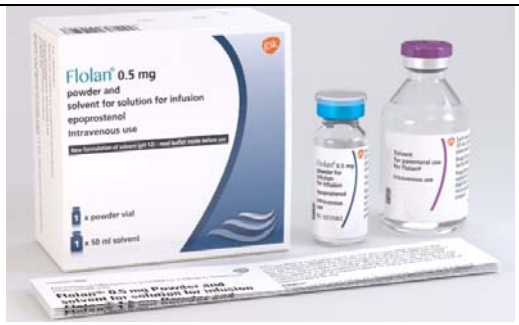
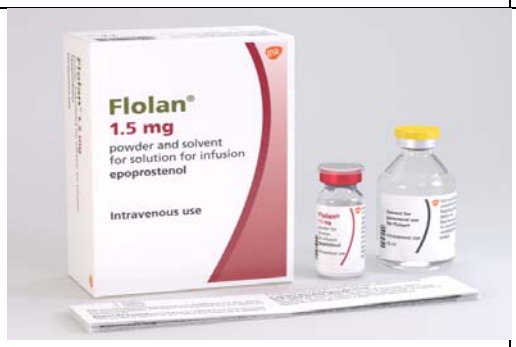
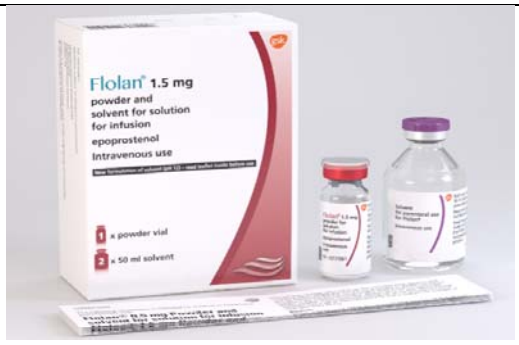
Packaging:

- The packaging has changed and you will be able to clearly distinguish the reformulated solvent with a statement on the external carton of Flolan highlighting the change to the solvent, "**New formulation of solvent (pH 12) - read leaflet inside before use**". This statement will be present on the external carton for approximately 6 months following introduction of the reformulated (pH 12) solvent.

- The flip-top lid colour on the solvent bottle has also been changed from yellow to purple to ensure that the reformulated (pH 12) Solvent for Solution for Infusion looks different from Solvent for Solution for Infusion (pH 10.5). The reformulated Solvent for Solution (pH 12) for Infusion can be further distinguished as it is contained in a plastic vial compared to the glass vial of Solvent for Solution (pH 10.5) for Infusion.

- These changes are intended to minimize any potential for medication errors given the different instructions related to storage and administration of the two formulations.

- The Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for Flolan have been updated to include information regarding use of the reformulated (pH 12) Solvent for Solution for Infusion.

PACKAGING		
	Flolan solution prepared with Solvent for Solution for Infusion (pH 10.5)	**Flolan solution prepared with Solvent for Solution for Infusion (pH 12)**
0.5 mg pack	 Note: Yellow cap on glass bottle containing solvent	 Note: Purple cap on plastic bottle containing solvent
1.5 mg pack	 Note: Yellow cap on glass bottle containing solvent	 Note: Purple cap on plastic bottle containing solvent

AVAILABILITY INFORMATION		
	CURRENT FOMULATION (with Solvent pH 10.5)	**NEW FORMULATION** (with Solvent pH 12)
Name on ordering system	Flolan Inj 0.5mg 1_+ 50ml Dil Flolan FD Inj 1,5mg 1_+2Dil	Flolan Dil 1 FD Inj 0.5mg 1x17ml Flolan Dil 2 FD Inj 1.5mg 1x17ml
Availability	Stock levels to be phased out in Q1 2017. Based on current demand, it is expected that supplies will be exhausted by approximately March/ Apr 2017.	Will be available to Irish market from 20th March 2017

Therapeutic Indications

Flolan (epoprostenol) 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 and

- For use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated*

*Note – Only the 0.5 mg pack is suitable for use in renal dialysis.

Action required by Health Care Providers

- You are advised to read the revised SmPC relating to use of the reformulated (pH 12) Solvent for Solution for Infusion for preparation of FLOLAN solution. The new version is attached to this communication. Please share this information with relevant health care personnel under your supervision.
- You are advised to ensure patients being treated for PAH with FLOLAN are aware of the reformulated (pH 12) Solvent for Solution for Infusion as well as appropriate instructions for reconstitution, storage and administration of FLOLAN prepared with the reformulated (pH 12) Solvent for Solution for Infusion.
- Please note that given that both formulations will be available on the market, both sets of SmPC and PIL (pH 10.5 and pH 12) will be available at www.medicines.ie until the 20th September 2017 (a period of six months post launch of pH 12).

- Should a patient be transitioned from FLOLAN prepared with the reformulated (pH 12) Solvent for Solution for Infusion to another intravenous prostanoid therapy in the future, please ensure that the patient understands any differences in reconstitution, storage, and administration occurring as a result of that change.

Adverse event reporting:

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website: *www.hpra.ie*; Email: *medsafety@hpra.ie*. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.

Please note, the formulation of diluent which is used at the time of the event should be specified at the time of reporting.

Contact(s) for Further Information/Questions:

Should you have any questions or require additional information, please contact *Medical Information on 1800 244 255.*

With regards,
Martijn Akveld

Director of Medical Affairs

GSK

IE/ESM/0008/16

Date of Preparation: December 2016 .