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FLOLAN *(epoprostenol)* – Two different sterile solvents for FLOLAN will be temporarily available, each with different instructions for reconstitution, storage and administration of FLOLAN solution.

Dear Healthcare Professional,

GlaxoSmithKline (GSK) would like to inform you of the following:

SUMMARY

- **A reformulated (pH 12) Solvent for Solution for Infusion for FLOLAN is now available.**
- **Two different sterile solvents for FLOLAN will be temporarily available, each with different instructions for reconstitution, storage and administration of FLOLAN solution**

This information is being sent in agreement with the European Medicines Agency and the Malta Medicines Authority.

FURTHER INFORMATION ON THE SAFETY CONCERN AND THE RECOMMENDATIONS

Therapeutic Indication

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. FLOLAN is administered via continuous intravenous infusion and is supplied as two vials, one containing freeze-dried active drug and the other containing specialized solvent for reconstituting the active drug to produce the final solution for intravenous infusion.

GSK would like to inform you that a reformulated (pH 12) Solvent for Solution for Infusion for FLOLAN is now available. Reconstituted FLOLAN solution is more stable when prepared with the reformulated (pH 12) Solvent for Solution for Infusion which eliminates the need for use of a cold pouch during administration.

GSK is alerting health care 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 Solvent for Solution for Infusion to FLOLAN prepared with the reformulated (pH 12) Solvent for Solution for Infusion.

Key Messages

- Storage and administration conditions when using FLOLAN to treat PAH

FLOLAN solution prepared with Solvent for Solution for Infusion:	***FLOLAN solution prepared with reformulated (pH 12) Solvent for Solution for Infusion:***
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 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.	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 solution for infusion should be used within: • 72 hours at up to 25°C or • 48 hours at up to 30°C or • 24 hours at up to 35°C or • 12 hours at up to 40°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.
- 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.
- The change in the solvent formulation does not affect the dosing of FLOLAN solution for treatment of PAH or use in renal dialysis.

Action being taken by GlaxoSmithKline

GSK has clearly distinguished the reformulated solvent with a statement on the external carton of FLOLAN highlighting the change to the solvent, “New formulation of solvent (pH 12) - see leaflet inside for use”. This statement will be present on the external carton for approximately 6 months following introduction of the reformulated (pH) solvent.

The predominant label colour and flip-top lid colour have also been changed to purple from yellow to ensure that the reformulated (pH 12) Solvent for Solution for Infusion looks different from Solvent for Solution for Infusion.

The reformulated Solvent for Solution for Infusion can be further distinguished as it is contained in a plastic vial compared to the glass vial of Solvent for Solution 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.

Flolan solution for injection prepared with solvent (pH 10.5):	FLOLAN solution prepared with reformulated (pH 12) Solvent for Solution for Infusion:
	

GSK has updated the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for FLOLAN to include information regarding use of the reformulated (pH 12) Solvent for Solution for Infusion.

Action required by Healthcare Professionals

- 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.
- 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.

Revised SmPC

Full SmPC and PIL including information for FLOLAN solution reconstituted with reformulated (pH 12) Solvent for Solution for Infusion is enclosed for your information and reference.

FURTHER INFORMATION

All adverse events should be reported directly to:
GSK (Malta) Limited, 1, 1st floor, de la Cruz Avenue, Qormi, QRM 2458 (phone: +356 21238131).

Any suspected adverse reaction and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 Malta, or sent by email to postlicensing.medicinesauthority@gov.mt.

When reporting please provide as much information as possible, including information about medical history, concomitant medications, onset and treatment dates.

Contact(s) for Further Information/Questions:

Should you have any questions or require additional information, please contact Ruth Gatt (Medical Manager) at GSK (Malta) Limited (Tel: +356 21238131)

Yours sincerely

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