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FLOLAN (epoprostenol) – Two different sterile diluents 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**
- **FLOLAN solution prepared with Sterile Diluent (pH12) must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG).**

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 pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity and for use in renal dialysis 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 diluent for reconstituting the active drug to produce the final solution for intravenous infusion.

GlaxoSmithKline (GSK) would like to inform you that a reformulated diluent, Sterile diluent (pH12), for FLOLAN is now available. Reconstituted FLOLAN solution is more stable when prepared with Sterile diluent (pH12) which eliminates the need for use of a cold pouch during administration.

GSK is alerting prescribers to the launch of the reformulated Sterile diluent (pH12) and differences in storage and administration to ensure proper use of each of the diluents during the period when patients should be transitioned from FLOLAN prepared with Sterile diluent (pH10.5) to FLOLAN prepared with Sterile Diluent (pH12).

Finally, GSK is writing to you because we have recently received reports in some countries of leakage of administration materials used with FLOLAN prepared with Sterile Diluent (pH12) due to cracking or damage. The leakage occurred in components containing polyethylene terephthalate glycol (PETG) that were being used in renal dialysis. Polyethylene terephthalate (PET) is not considered to be compatible with highly alkaline solutions, based on reports of administration set damage when used with highly alkaline medications. PETG is thought to be similarly susceptible to alkaline solutions.

Key Messages

- Storage and administration conditions when using FLOLAN to treat PAH

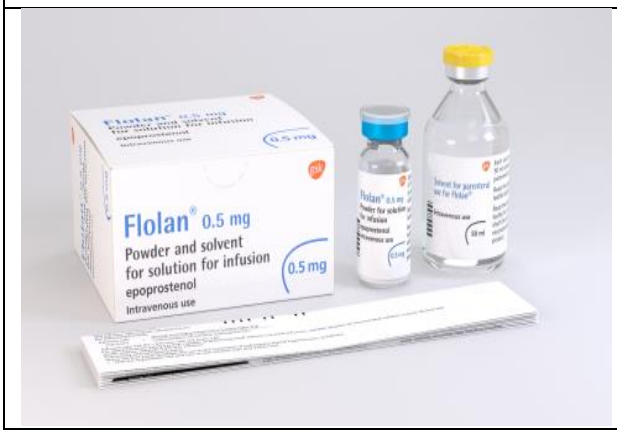
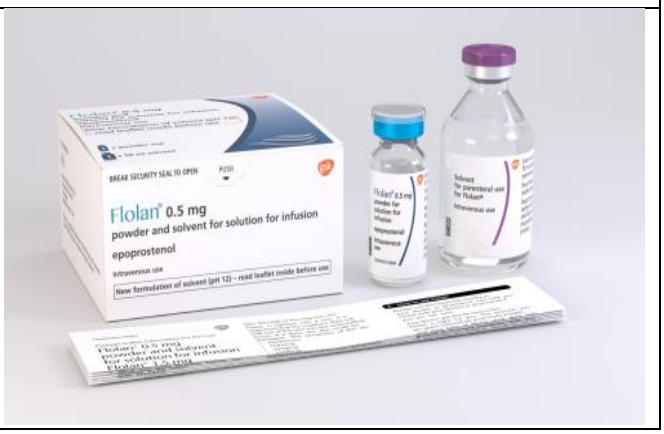
FLOLAN solution prepared with Sterile diluent (pH10.5):	***FLOLAN solution prepared with Sterile diluent (pH12):***
Should be used within 12 hours at 25°C if freshly prepared, OR May be stored for up to 40 hours between 2°C and 8°C and then used within 8 hours at 25°C, OR May be stored for up to 24 hours 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.	<u>For solutions ≤150,000 ng/ml:</u> 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 30ºC or • 24 hours at up to 35 ºC or • 12 hours at up to 40 ºC Discard any unused solution after this time. For solutions >150,000ng/mL and ≤300,000ng/mL: Reconstituted solutions that have been stored at 2 to 8°C for up to 7 days can be administered for up to 24 hours at 25°C. Freshly prepared Reconstituted solutions, or solutions that have been stored at 2 to 8°C for no longer than 5 days can be administered for up to: • 48 hours at up to 25°C • 24 hours at up to 35°C Discard any unused solution after this time.

- Accidental use of Sterile diluent (pH10.5) in place of the reformulated Sterile diluent (pH12) 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 Sterile diluent (pH10.5) and the reformulated Sterile diluent (pH12) will be on the market simultaneously while existing Sterile diluent (pH10.5) supplies are transitioned to the reformulated Sterile diluent (pH12).
- It is important that you are aware of this diluent 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 diluent formulation does not affect the preparation of FLOLAN solution for use in renal dialysis.
- The change in the diluent formulation does not affect the dosing of FLOLAN solution for treatment of PAH or use in renal dialysis.
- FLOLAN solution prepared with Sterile Diluent (pH12) must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG).

Action being taken by GlaxoSmithKline

GSK has clearly distinguished the reformulated diluent with changes to the description of the diluent on the vial, Sterile diluent (pH12) in place of Sterile diluent (pH10.5) as well as changing the predominant packaging color and flip-top lid to purple from yellow to ensure that the reformulated diluent looks different from the predecessor diluent. Sterile diluent (pH12) can be further distinguished from Sterile diluent (pH10.5) as it is contained in a plastic vial compared to the glass vial of the predessor. This change eliminates potential for interaction between the glass vial container and FLOLAN diluent that may result in the presence of glass particles in some vials of diluent.

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 product labeling for FLOLAN to include information regarding use of both the reformulated Sterile diluent (pH12) and Sterile diluent (pH10.5).

GSK is reviewing the product labeling for FLOLAN and Sterile Diluent (pH12) to establish whether an update is warranted to highlight the incompatibility of FLOLAN solution prepared with Sterile Diluent (pH12) and preparation and administration materials containing PET or PETG.

Action required by Healthcare Professionals

- You are advised to read the revised product labeling related to use of Sterile diluent (pH12) 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 Sterile diluent (pH12) as well as appropriate instructions for reconstitution, storage and administration of FLOLAN with Sterile diluent (pH12).
- Should a patient be transitioned from FLOLAN prepared with Sterile diluent (pH12) 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.
- You should confirm if your patients who are receiving FLOLAN solution use any preparation or administration materials that contain PET or PETG.
- If you are unsure of the materials that are used by your patients for preparation or administration of FLOLAN solution, you should consult the manufacturer of the sets to confirm if they are considered compatible with highly alkaline solutions.

Revised Labeling

Full product labeling including information for FLOLAN solution reconstituted with either the Sterile diluent (pH10.5) or reformulated Sterile diluent (pH12) is enclosed for your information and reference.

Supporting Information

During development of Sterile Diluent (pH12) for FLOLAN, GSK performed physical compatibility tests with preparation and administration materials that were reported to be used during preparation or administration of FLOLAN. These tests assessed the potential for an interaction between epoprostenol reconstituted with Sterile Diluent (pH12) and contact materials used during reconstitution and administration of epoprostenol solutions.

In addition, for some materials, compatibility testing with sodium hydroxide solutions is reported in published literature. These test conditions are frequently at higher pH, higher temperature and longer duration than administration components would be exposed during preparation or administration of FLOLAN solution prepared with Sterile Diluent (pH12). It is therefore likely that a material compatible with these extreme conditions will be generally compatible with FLOLAN solution prepared with Sterile Diluent (pH12).

Based on GSK testing with Sterile Diluent (pH12) or published literature with sodium hydroxide solutions, the following materials are likely to be compatible with FLOLAN solution prepared with Sterile Diluent (pH12):

- Modified Acrylic
- Acrylonitrile butadiene styrene (ABS)
- Cyclic olefin polymer
- Polyamide
- Polyethersulfone
- Polyethylene
- Polyisoprene
- Polyolefin
- Polypropylene
- Polytetrafluoroethylene (PTFE)
- Polyurethane
- Polyvinyl chloride (PVC) (plasticised with bis(2-ethylhexyl) phthalate [DEHP])
- Polyvinylidene fluoride (PVDF)
- Silicone

GSK did not test all administration sets that contain the above materials. The use of components of similar composition to those that were tested constitutes a lower risk of incompatibility. Manufacturers of administration sets may sometimes change the components or materials. You should consult the manufacturer of the sets to confirm if they are considered compatible with highly alkaline solutions, such as FLOLAN solution prepared with Sterile Diluent (pH12), if you are unsure of the materials that are used by your patients for preparation or administration of FLOLAN.
FLOLAN solution prepared with Sterile Diluent (pH12) must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG).

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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