Epoprostenol
Important information about change in formulation of *Flolan*
October 2016

What has changed?

GlaxoSmithKline (GSK) has reformulated *Flolan* (epoprostenol). The company issued a 'Dear Healthcare Professional' safety advisory notice stating there will be two formulations of *Flolan* on the market until April 2017, one with a solvent pH of 10.5 (old) and one with a solvent pH of 12 (new). The packaging has changed to help distinguish between formulations (see letter at http://www.medicines.org.uk/emc/RMM.667.pdf for pictures). Both 0.5mg and 1.5mg strengths have been reformulated.

There is also a difference between old and new formulations in their licensed indications, final concentrations, shelf life and storage. See Table 1 below and letter for further details.

The old formulation is thermolabile; it is stable for only 12 hours at 25°C. When used as a continuous infusion over 24 hours, a cold pouch/ice pack is used to prevent/delay degradation. The new formulation is more stable and a cold pack is not needed. The new formulation is also stable for longer once reconstituted.

To increase the stability of epoprostenol it is necessary to increase the pH. However, this introduces other issues that need to be considered notably effects on administration devices.

How is epoprostenol used in the NHS?

Pulmonary arterial hypertension (PAH): This is a licensed indication for all epoprostenol products.

Renal dialysis: This is a licensed indication for all epoprostenol products (except the new 1.5mg *Flolan* formulation).

Other indications: Critical care units use epoprostenol for a range of off-label indications.

What are the risks?

Epoprostenol is already categorised as a high risk drug using NPSA 20 risk scoring criteria due to risks associated with reconstitution, dilution and administration. The following are additional risks associated with the reformulation:

- Medication error by diluting the old or new formulation incorrectly (resulting in under or overdose if inappropriate flow rates are used).
- Medication error through administering the old or new formulation at the wrong rate (see below for examples).
- Medication error through administering the new 1.5mg pH 12 formulation to a patient with renal dialysis (unlicensed).
- Medicine degradation due to storing the old or new formulation incorrectly once reconstituted or diluted.
- Medicine degradation due to administering the old formulation over 24 hours without using a cold pack.
- Microbiological contamination due to preparation in an uncontrolled environment (e.g. clinical area, patient's home). Current NHS guidance is that any IV medicine prepared in an uncontrolled environment should be administered immediately and not stored for later use. NB NHS Pharmacy aseptic units can extend the shelf life of chemically stable IV preparations to allow advance preparation.
- Degradation of administration sets and lines. Infusions with a higher pH are more likely to interact with certain plastics especially those containing polyethylene terephthalate (PET). GSK do not recommend the use of PET containing administration devices. It is known that administration compatibility issues exist with *Veletri* which also has a pH of 12. See appendix 1 for a list of giving sets and preparation devices *Flolan* pH 12 is compatible with.

Examples of risk of administration at the wrong rate

After reconstitution, *Flolan* can be administered as a concentrated solution or as a more dilute solution. Advice in the new pH 12 formulation SmPCs as to which dilutions are commonly used has changed:

- **In renal dialysis**, the new pH 12 formulation SmPC states that a commonly used concentration is 3,000nanograms/mL. The Intensive Care Society recommends a standard infusion concentration of 2,000nanograms/mL, and the old pH 10.5 SmPC gives advice on preparing a 2,000nanograms/mL solution. There is currently no stability data to support a 2,000nanograms/mL concentration using the new pH 12 formulation but there is data supporting this concentration using the old, less stable formulation (stability is directly related to pH). GSK has advised that diluting the new pH 12 formulation to a concentration of 2,000nanogram/mL is unlikely to cause stability problems as it is inherently more stable than the old formulation due to the higher pH.[2] However, GSK have indicated they will undertake stability studies to confirm this.[2]

  If a 2,000nanogram/mL solution has been prepared but the new pH 12 SmPC is used as a guide to flow rate (which recommends a 3,000nanogram/mL solution), a 33% underdose will occur.

- **In PAH**, the old pH 10.5 SmPC states that a commonly used concentration is 15,000nanograms/mL. In the new pH 12 SmPC and a concentration of 5,000nanograms/mL and 10,000nanograms/mL are used as examples.

  In practice concentrations and flow rates are tailored to dose required to control symptoms and size of available home administration devices.[1]

How do epoprostenol products compare?

There are several licensed epoprostenol formulations (see Table 1). The formulation on Commercial Medicines Unit (CMU) frameworks may differ around the country and changes over time, and so hospital pharmacies may purchase various combinations of the brands detailed in the table below.

Table 1.

Company	*Brand name*	*SmPC links*	*Licensed indications*	*Notes*
GSK	*Flolan* *pH 10.5* ***OLD formulation***	0.5mg, 1.5mg	PAH (0.5mg and 1.5mg) Renal dialysis (0.5mg and 1.5mg) **NB**. SmPCs state indicated for dialysis but only 0.5mg pack is available for this indication.	• This *Flolan* formulation will not be available after April 2017, however, as it will no longer be manufactured it will only be available until stocks are exhausted, which may be sooner[2]. Both formulations could be supplied on contract. • Flow rate recommendations based on infusion concentration of 2,000nanograms/mL (dialysis) and 15,000nanograms/mL (PAH). • Powder and solvent for solution for infusion shelf life is 3 years.
GSK	*Flolan* *pH 12* ***NEW formulation***	0.5mg, 1.5mg	PAH (0.5mg and 1.5mg) Renal dialysis **(0.5mg strength ONLY)**	• This is available from 14 October 2016, and will be the only *Flolan* formulation available after April 2017. Both formulations could be supplied on contract. • Flow rate recommendations based on infusion concentration of 3,000nanograms/mL (dialysis),and 5,000nanograms/mL and 10,000nanograms/ml (PAH).

				• Reconstituted concentrate contains about 30% more sodium than the old formulation. • Powder for solution for infusion shelf life is 3 years, and solvent shelf life is 2 years. The new formulation solvent is presented in plastic, which is less likely to react with higher pHs than glass. So far, the company only have stability data for 2 years in plastic. • Incompatible with some administration devices (see appendix 1)
Concordia International - formerly AMCo		0.5mg, 1.5mg	PAH (0.5 and 1.5mg) Renal dialysis (0.5 and 1.5mg)	• Details as for *Flolan* pH 10.5.
Sandoz		0.5mg, 1.5mg	PAH (0.5 and 1.5mg) Renal dialysis (0.5 and 1.5mg) **NB**. SmPCs state indicated for dialysis but only 0.5mg pack is available for this indication.	• No mention of cold pouch use. • Shelf life of powder for solution for infusion and solvent is 2 years. • All other details as for *Flolan* pH 10.5.
Actelion Pharma-ceuticals	*Veletri*	0.5mg, 1.5mg	PAH (0.5 and 1.5mg) Renal dialysis (0.5 and 1.5mg) **NB**. SmPCs state indicated for dialysis but only 0.5mg pack is available for this indication.	• Very low sodium content. • Storage temperatures and stability as for *Flolan* pH 12. • No need for cold pouch use. • SmPC includes flow rate guidance using 2,000nanograms/mL as standard infusion concentration in renal dialysis. • Shelf life is 3 years. • Incompatible with some administration devices – see alert

What needs to happen in my organisation?

Advice below is only applicable if your organisation uses *Flolan*, all other epoprostenol products remain the same. However, be aware that available generic formulations are based on *Flolan* pH 10.5. *Flolan* pH 12 is similar to the epoprostenol *Veletri* brand in terms of stability. The potential for risks associated with generic substitution may occur after full transition to *Flolan* pH 12.

The Injectable Medicines Guide is in the process of being updated to reflect the changes.

Pulmonary arterial hypertension services:

- For homecare patients receiving *Flolan*, make the homecare company and patients aware of the formulation change. GSK have materials to help with the transition including a checklist. This can be accessed via the eMC *Flolan* pH 12 monograph risk materials.

- Make *Flolan* prescriptions clear by stating which formulation (pH 10.5 or pH 12) should be supplied. The new formulation will be on the market from 14th October 2016. Query all prescriptions not stating pH. It is likely patients will be transitioned over to the new formulation in a staged manner. Once patients have transitioned to the new formulation they should stay on it.
- Check compatibility of administration devices when using *Flolan* pH 12 (see appendix 1).
- Make prescribers aware of the higher sodium content of the new formulation which could have a clinical impact.

Renal services:

- Renal services are only likely to use the 0.5mg strength (even though both of the pH 10.5 strengths are licensed). Therefore the fact that the new *Flolan* 1.5mg (pH 12) formulation is not licensed for use in renal dialysis patients has few practical implications.
- Establish which infusion concentration is used in dialysis units and ensure the correct flow rate recommendations are followed. In practice, epoprostenol is infrequently used[3] so could be managed on a case by case basis.
- Check compatibility of administration devices when using *Flolan* pH 12 (see appendix 1).
- Make prescribers aware of the higher sodium content of the new formulation which could have a clinical impact.

Critical care use:

- Check what final concentrations and recommended flow rates are used locally. The SmPCs for the old and new *Flolan* 0.5mg strength differ in their recommendations on what constitutes a commonly used infusion for renal dialysis; 2,000nanograms/mL (old pH 10.5 formulation) vs. 3,000nanograms/mL (new pH 12 formulation). The Intensive Care Society recommends a standard epoprostenol infusion concentration of 2,000nanograms/mL. There is currently no stability data to support a 2,000nanograms/mL concentration using the new pH 12 formulation but there is data supporting this concentration using the old, less stable formulation (stability is directly related to pH).[2] Make sure the correct flow rates are used for the infusion concentration used.
- Check compatibility of administration devices when using *Flolan* pH 12 (see appendix 1).
- Make prescribers aware of the higher sodium content of the new formulation which could have a clinical impact.

Aseptic services:

- If pharmacy aseptic services provide a reconstitution and dilution service for epoprostenol, review dilution required and storage recommendations.

Pharmaceutical procurement and storage:

- Implement processes to minimise risks associated with inadvertent procurement, storage and supply of the incorrect formulation. The new formulations have different order codes.

References

1. Personal communication, Specialist PAH pharmacist, Papworth hospital 18/10/16
2. Personal communication, GSK, 18/10/16
3. Personal communication, Specialist renal pharmacist, Royal Liverpool and Broadgreen University Hospitals NHS Trust, 19/10/16

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October 2016

Appendix 1

Epoprostenol pH 12 diluent physical compatibility with commonly used pulmonary arterial hypertension administration sets

Due to the potential for incompatibility with high pH solutions, GlaxoSmithKline (GSK) performed compatibility studies with pH 12 Sterile Diluent used for reconstitution of epoprostenol with the following products to assess the potential for interaction:

Preparation

- *Becton Dickinson Plastic Syringe, 50mL, Luer Lok (reference 300865)*
- *Millipore MillexGV 0.22µm PVDF filter unit (reference SLGUGSK33)*

Administration

- *CADD-Legacy Plus and CADD-Legacy 1 ambulatory pumps (Smiths Medical)*
- *CADD Medication Cassette Reservoir with clamp, female Luer and nonvented stopper (Smiths Medical, reference 21–7001 (50ml) and 21–7002 (100ml))*
- *CADD Extension Set with male Luer, clamp, 0.2µm air-eliminating filter and anti-siphon valve with male Luer (Smiths Medical, reference 21–7040, 21–7052 and 21–7106)*
- *Hickman 9.6 Fr. Single-Lumen CV Catheter (Bard access systems, reference 0600560)*
- *Groshong 8 Fr. Single-Lumen CV Catheter (Bard access systems, reference 7711800)*
- *Port-a-Cath Power P.A.C. 7.8 Fr. Single-Lumen CV Catheter (Smiths Medical, reference 21–4423–24)*

These preparation and administration components have been demonstrated to be compatible with epoprostenol infusion reconstituted in pH12 Sterile Diluent during normal use as defined in the product labelling.

Use of administration components from alternative suppliers using similar construction materials is a decision for Healthcare Professionals.

Some administration sets use polyethylene terephthalate (PET) as a component which is known to be incompatible with high pH solutions, and as such GSK cannot recommend the use of these sets.

If you are using a set other than those mentioned above and are unsure of the construction materials, please consult the manufacturer.

Please report all adverse events associated with epoprostenol, including events associated with the administration set or central line used to administer epoprostenol, to GSK.

If a problem has occurred with the administration set, this should be returned to the manufacturer for further evaluation.

Source: GSK, received 26/10/16