VELETRI® (epoprostenol)
VELETRI - Compatibility of Solutions at High Concentrations with Intravenous Administration Equipment

SUMMARY

- The administration of VELETRI should be done in accordance with the product label. Manufacturer guidelines of the intravenous (IV) access systems used to administer VELETRI for injection should also be followed.
- In-house studies[1-4] have been performed to assess the compatibility of epoprostenol solutions at different concentrations with IV administration equipment including different IV access systems, in addition to an extractables/leachables study[5] designed to assess the leaching of organic compounds when an IV administration system is exposed to VELETRI solutions. Details of these studies are provided in this letter.
- Based on the results of these studies:[1-5]
  - The specific IV administration equipment tested (including the CADD-Legacy Plus infusion pump, the 100 mL CADD medication cassette reservoir, the CADD extension tubing set, different IV access systems (Clave, Bionector, or BD-Q Syte), and the single lumen central venous Groshong or Hickman catheters is compatible with epoprostenol solutions up to 300,000 ng/mL (ie, up to 90,000 ng/mL with the Clave IV access system and up to 300,000 ng/mL with the Bionector and BD-Q Syte IV access systems), provided that VELETRI solution does not come into contact with the exterior of the IV access system, and in particular, does not come into contact with the interstitial space of the housing of the male Luer lock at the distal end of the CADD extension tubing. If such exposure is allowed to occur, there may be an increased risk of breakage of the IV access system and leakage of VELETRI solution. For this reason, consideration should be given to providing appropriate training and advice to patients and caregivers about the importance of shaking or wiping off any drops that may emerge during the priming of the extension tubing and prior to connection to the IV access system.
  - No significant toxicological concerns emerged, when the administration system components (stopper, CADD cassette, and CADD tubing set) were exposed to epoprostenol 75,000 ng/mL stored in the cassette for 24 hours at 5°C followed by 24 hours at 40°C.
- Compatibility (integrity of, and potential for contamination with molecules leaching from components of, the infusion apparatus) cannot be assumed if other types of infusion apparatus and equipment are used to administer VELETRI.
- For current status of availability of any infusion equipment used to administer VELETRI, please refer to the manufacturer of that equipment.
- A search of the scientific literature did not identify any additional information of relevance.

CLINICAL DATA

Overview of Identified Information from In-house Studies

The following in-house studies[1-5] were performed to assess:

1. the compatibility of epoprostenol solution at different concentrations with the complete IV administration equipment set-up (pump and related disposable accessories, details below);
2. the effect of exposing both the lumen and the exterior of the IV access systems to epoprostenol solution at different concentrations;
3. the effect of VELETRI solution inside the interstitial space of the male Luer lock (as well as solution inside the lumen of the apparatus) at the distal end of the extension tubing on the connection with the IV access system;

4. the leaching of organic compounds when the pump disposable accessories are exposed for 2 days (ie, 24 hours at 5°C followed by 24 hours at 40°C) to epoprostenol diluted at a concentration of 75,000 ng/mL.

Details of these studies are described in the corresponding sections below.

1. Compatibility Studies with IV Administration Equipment Including 3 Different IV Access Systems (Clave, Bionector, BD-Q Syte)

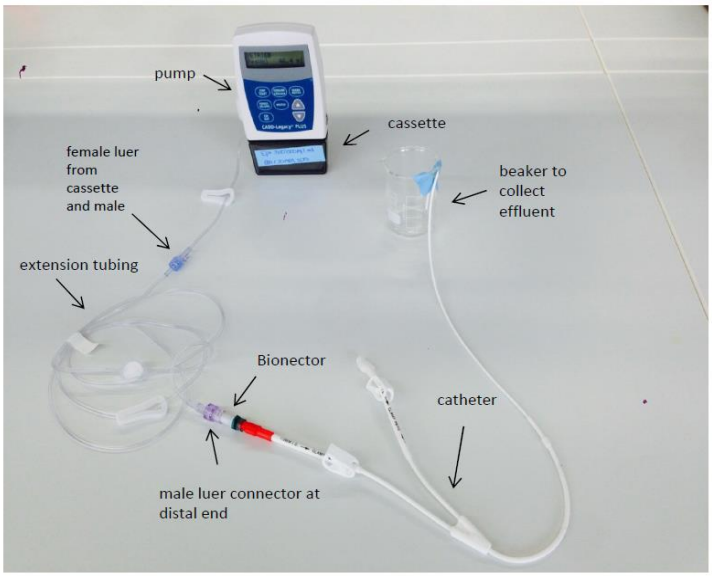
Set-up

Three compatibility studies[1-3] were performed in which different IV administration equipment set-ups were continuously flushed with epoprostenol at different concentrations. The tested IV administration equipment set-ups consisted of the following parts:

- CADD-Legacy Plus infusion pump (Smiths Medical)
- CADD medication cassette reservoir (Smiths Medical)
- CADD extension tubing set (Smiths Medical)
- Clave (ICU Medical Inc), Bionector (Vygon), or BD-Q Syte (Becton Dickinson) IV access systems
- Single lumen or double lumen central venous Groshong or Hickman catheter

A representative administration set-up[2] is shown in Figure: Representative Set-up of the Compatibility Studies Showing a Cassette with Diluted VELETRI Solution and Bionector IV Access System and includes the CADD-Legacy Plus infusion pump, a CADD 100 mL medication cassette reservoir connected to the CADD extension tubing set. In this example, the extension set was connected to the Bionector IV access devices and then to a single lumen central venous catheter.

Representative Set-up of the Compatibility Studies Showing a Cassette with Diluted VELETRI Solution and Bionector IV Access System[2]



Objective

The objective of the compatibility studies[1-3] was to determine whether VELETRI solution, under conditions that mirror routine clinical use, ie, contact of the solution inside the lumen of the connected pieces only and no external contact, could cause leakage, fractures of the IV access system or any other undesired results, eg, precipitation.[1]

Experimental Conditions

The first compatibility study tested IV administration equipment that included all 3 IV access systems by continuously flushing them with epoprostenol at a concentration of 90,000 ng/mL for 2 weeks.[1]

Two additional compatibility studies tested the effect of continuously flushing epoprostenol, at concentrations ranging from 15,000 ng/mL to 300,000 ng/mL, through IV administration equipment that included the Bionector and BD-Q Syte IV access systems, for a period of 3 weeks.[2,3]

In each experiment, 0.9% NaCl was used as diluent. Care was taken to avoid VELETRI solution coming into contact with the exterior of the equipment. This was accomplished by always connecting all pieces together first and then flushing out the air through the catheter.[2,3]

Results

At all epoprostenol concentrations tested (ie, up to 90,000 ng/mL for the Clave IV access system and up to 300,000 ng/mL for the Bionector and BD-Q Syte IV access system) no fractures, cracks, obstruction or leakage on visual or microscopic assessment of the respective complete IV administration equipment were reported (Table: Results of the Visual and Microscopical Assessment of Complete Administration Equipment With Either Clave, Bionector or BD-Q Syte IV Access System After Flushing With Epoprostenol Solutions at Different Concentrations for 2-3 Weeks).[1-3]

Results of the Visual and Microscopical Assessment of Complete Administration Equipment with Either Clave, Bionector or BD-Q Syte IV Access System After Flushing with Epoprostenol Solutions at Different Concentrations for 2-3 Weeks[1-3]

Epoprostenol Concentration Tested	Clave IV Access System	Bionector IV Access System	BD-Q Syte IV Access System
15,000 ng/mL	N/A	N/A	No cracks, fractures or leakage
90,000 ng/mL	No cracks, fractures or leakage	No cracks, fractures or leakage	No cracks, fractures or leakage
180,000 ng/mL	N/A	No cracks, fractures or leakage	No cracks, fractures or leakage
300,000 ng/mL	N/A	No cracks, fractures or leakage	No cracks, fractures or leakage
Abbreviations: IV, intravenous; N/A, not available			

2. Immersion Study

Set-up

The compatibility studies were supplemented by an immersion study[2] to assess the effect of exposing both the lumen and the exterior of the IV access systems to epoprostenol solutions at different concentrations. The following IV administration equipment parts were tested by their submersion in epoprostenol solutions at different concentrations:

- Individual unconnected IV access systems (Clave, Bionector, and BD Q-Syte)
- IV access systems (Clave, Bionector, and BD Q-Syte) connected to the distal male Luer locks of the CADD extension tubing
- Male Luer locks from both the proximal and distal ends of the CADD extension tubing

The above items were immersed in glass beakers containing VELETRI solutions diluted from 1.5 mg epoprostenol vials with 0.9% NaCl to concentrations of 45,000, 90,000, 180,000 and 300,000 ng/mL, respectively.

Visual and microscopic assessment for any cracks or fractures was performed after between 2 and 15 days, depending on the item being tested.

Results

Individual Unconnected IV Access Systems

There were no fractures observed in the unconnected Bionector IV access system (after up to 15 days of immersion), nor in the BD-Q Syte IV access system (after up to 7 days of immersion), at any of the epoprostenol concentrations tested, ie, up to 300,000 ng/mL.[2]

No fractures were observed in the Clave IV access system after immersion for 7 days in epoprostenol at concentrations from 45,000 to 180,000 ng/mL. However, it was found to be fractured when inspected after 7 days (the second time point of inspection following inspection after 3 days) of immersion in epoprostenol solution at a concentration of 300,000 ng/mL (Table: Visual Assessments From the Immersion Testing of IV Access Systems at Different VELETRI Concentrations).[2]

IV Access Systems Connected to the Distal Male Luer Locks of the Extension Tubing

Fractures were observed for both the Clave and Bionector IV access system connected to male Luer locks at the first time point of testing (2 days of immersion for the Bionector connected to male Luer locks and 3 days of immersion for the Clave connected to male Luer locks) at all epoprostenol concentrations tested.[2]

The BD-Q Syte IV access system connected to the male Luer lock was found to be fractured on inspection after 7 days (the second time point of inspection following inspection after 3 days) of immersion in epoprostenol solution diluted to 300,000 ng/mL. No fractures were observed in the BD-Q IV access system connected to male Luers after 7 days (the last time point of inspection) of immersion in any of the lower epoprostenol concentrations tested (Table: Visual Assessments From the Immersion Testing of IV Access Systems at Different Epoprostenol Concentrations).[2]

Male Luer Locks from Both the Proximal and Distal Ends of Extension Tubing

No fractures occurred in the single male Luer locks after up to 15 days of immersion in epoprostenol at any of the concentrations tested, ie, up to 300,000 ng/mL (Table: Visual Assessments From the Immersion Testing of IV Access Systems at Different Epoprostenol Concentrations).[2]

Visual Assessments from the Immersion Testing of IV Access Systems at Different Epoprostenol Concentrations[2]

Test Item	N° of Items	Concentration ng/mL	Visual Appearance
Bionector	3 or 5	300,000/180,000/90,000/45,000	Up to day 15: No fractures
Bionector+Luer[a]	3	300,000/180,000/90,000/45,000	Day 2-4: All Luer fractured
	3	180,000/90,000	Day 10: All Luer fractured+2 Bionectors (at 180,000)
	3	45,000	Day 7: All Luer+1 Bionector fractured
BD-Q Syte	2	300,000/180,000/90,000/45,000	Day 3 and day 7: No fractures
BD-Q Syte+Luer[a]	3	300,000	Day 3: No fracture, day 7: 1 Luer fractured
	3	180,000/90,000/45,000	No fractures day 3 and day 7

Test Item	N° of Items	Concentration ng/mL	Visual Appearance
Clave	2	300,000	Day: 3: No fractures, day 7: All Clave fractured
	2	180,000/90,000/45,000	No fractures at day 3 and day 7
Clave+Luer[a]	3	300,000	Day 3: All luer fractured, day 7: All Luer+2 Clave fractured
	3	180,000/90,000/45,000	Day 3 and day 7: All Luer fractured
Male Luer distal end	2 or 3	300,000/180,000/90,000/45,000	Up to day 15: no fractures
Male Luer proximal end	2 or 3	300,000/180,000/90,000/45,000	Up to day 15: no fractures

Abbreviation: IV, intravenous
[a]"Luer" refers to Luer lock from the distal end of the Smith Medical extension tubing (the distal end is the end to be connected to the IV access system whereas the proximal end is connected to the medication cassette)

3. Supplemental Compatibility Study With Bionector and BD-Q Syte IV Access Systems at an Epoprostenol Concentration of 300,000 ng/mL

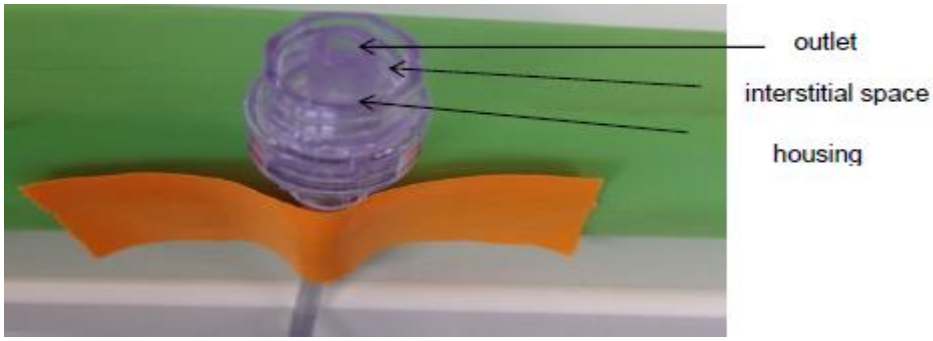
Set-up

The objective of this supplemental compatibility study[4] was to assess whether epoprostenol solution at a concentration of 300,000 ng/mL inside the interstitial space of the male Luer lock (as well as solution inside the lumen of the apparatus) could cause leakage or fractures at this connection. Assessment of compatibility in the context of this study constituted of visual and microscopic observation of potential leakage or fractures at the connection between the male Luer lock of the CADD extension tubing and the IV access system.[4]

Unlike the previous compatibility studies already described above, in this study, the IV Bionector or BD Q Syte IV access system was connected to the extension tubing only after priming the extension tubing. Moreover, the priming was conducted in such a way that a defined number of drops (1, 2, or 3 drops) was allowed to fall into the interstitial space of the Luer lock of the extension tubing prior to connecting the Luer lock to the IV access system (Figure: Male Luer Lock at the Distal End of CADD Extension Tubing. The Drops Are Exiting the Outlet During Priming and, Instead of Wiping Them off, They Fell into the Interstitial Space).[4]

Note that apart from during priming, no flow through the system was applied, ie, the IV administration set-up was not continually flushed as was the case with the prior compatibility studies; rather, epoprostenol solution diluted to 300,000 ng/mL remained stagnant within the system for the duration of the experiment.[4]

Male Luer Lock at the Distal End of CADD Extension Tubing. The Drops Are Exiting the Outlet During Priming and, Instead of Wiping Them off, They Fell into the Interstitial Space[4]



Results

- Bionector IV access system: fractures were seen 2 hours after 2 or 3 drops had been allowed to enter the interstitial space of the male Luer locks. After 1 drop had been allowed to enter the interstitial space of the male Luer lock, no fractures were observed for 24 hours. However, after 7 days (next time point of observation) fractures of the male Luer locks and/or the Bionector IV access system were evident.
- BD-Q Syte IV access system: After either 1, 2, or 3 drops had been allowed to enter the interstitial space of the male Luer lock, fractures in the male Luer lock and/or the BD-Q Syte IV access system were observed after 24 hours.[4]

4. Extractables/Leachables Study

A leachables study[5] was performed to characterize the leaching behavior of the following administration system components (including stopper) when exposed to contact with epoprostenol diluted to a concentration of 75,000 ng/mL:

- Infusion cassette; CADD medication cassette reservoir 50 or 100 mL, Smiths Medical
- Extension tubing set; CADD extension tubing set, with male Luer, clamp, 0.2 µm filter, and anti-siphon valve with male Luer, Smiths Medical

Epoprostenol 75,000 ng/mL was stored in the cassette for 24 hours at 5°C followed by 24 hours at 40°C. The cassette was emptied at ambient temperature through the extension tubing set, making use of the pump that is also used by the patient during administration in order to mimic the contact of the solution with the tubing set. The minimal flow rate of 2 mL/hour was used to have the maximal exposure time of 50 hours of the solution when passing through the tubing.[5]

Results

The main leachable compound identified was bisphenol A. Bisphenol A is a known impurity of polycarbonate, which was used in the manufacture of one of the components of the tubing set. A toxicological risk assessment of the leachables arising from the administration system (stopper, cassette and tubing set) was performed. This assessment did not identify any additional toxicological risk due to chemical compounds identified and quantified.[5]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 01 August 2024.

REFERENCES

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2. Data on File. Compatibility of diluted epoprostenol for injection EFI2 solutions with the administration device including a Bionector i.v. access system. Actelion Pharmaceuticals Ltd. COMR23-77B; 2015.

3. Data on File. Compatibility of diluted epoprostenol for injection EFI2 solutions with the administration device including a BD-Q Syte i.v. access system. Actelion Pharmaceuticals Ltd. COMR23-77C; 2015.

4. Data on File. Compatibility of diluted epoprostenol for injection EFI2 solutions with the administration device: dripping study with Bionector- and BD-Q Syte i.v. access systems. Actelion Pharmaceuticals Ltd. COMR23-77E; 2015.

5. Data on File. 3.2.P.2.6 COMPATIBILITY (ALL, MONZA). Actelion Pharmaceuticals Ltd. TPL-128-GQM-GL_v2-280809.