VELETRI® (epoprostenol)
Transitioning Patients From Epoprostenol for Injection (eg, Flolan®) or Generic Epoprostenol to VELETRI for Injection

SUMMARY

- Two phase 3 open-label studies, EPITOME-2 and EPITOME-4, assessed the safety and efficacy of switching patients from epoprostenol for injection (eg, Flolan®) to VELETRI for injection.[1,2]
- Epoprostenol for injection (eg, Flolan®), VELETRI, and generic epoprostenol sodium all contain the same active ingredient, epoprostenol sodium. The package inserts for all 3 products contain similar information regarding indications and usage, clinical studies, and adverse reactions.[3-5]
- This letter should not be seen as a comprehensive reference on this patient, or as a recommendation or endorsement for transitioning patients from epoprostenol for injection (eg, Flolan®) to VELETRI for injection. Publications mentioned should be consulted for full information.

BACKGROUND/GUIDELINES

Epoprostenol arginine and sucrose (AS) is the only formulation of VELETRI for injection currently available in countries where VELETRI for injection has been approved. In the United States, an earlier formulation of VELETRI, epoprostenol arginine and mannitol (AM), was made available in 2010.[6] The AM formulation was replaced with AS in June 2012.

As outlined in the Prescribing Information, epoprostenol for injection (eg, VELETRI®) is stable only when reconstituted as directed using Sterile Water for Injection, United States Pharmacopeia (USP), or Sodium Chloride 0.9% Injection, USP.[4] Epoprostenol for injection (eg, VELETRI®) must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration. Importantly, VELETRI for injection should not be reconstituted or diluted with sterile diluent for epoprostenol for injection (eg, Flolan®) or pH 12 Sterile Diluent for epoprostenol for injection (eg, Flolan®). VELETRI for injection has a distinct excipient formulation from epoprostenol for injection (eg, Flolan®) and generic epoprostenol sodium, as summarized in Table: Product Characteristics of VELETRI for Injection Compared to Epoprostenol for Injection (eg, Flolan®) and Generic Epoprostenol.[3-5]

Product Characteristics of VELETRI for Injection Compared to Epoprostenol for Injection (eg, Flolan®) and Generic Epoprostenol[3-5]

	VELETRI for Injection	Flolan® for Injection	Generic Epoprostenol Sodium
Chemical name	(5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid sodium salt		
Molecular formula	$C_{20}H_{31}NaO_5$		
Molecular weight	374.45		
Vial contents	Epoprostenol sodium equivalent to 0.5 mg or 1.5 mg epoprostenol, 100 mg sucrose, 50 mg arginine, NaOH to adjust pH	Epoprostenol sodium equivalent to 0.5 mg or 1.5 mg epoprostenol, 3.76 mg glycine, 2.93 mg NaCl, and 50 mg mannitol. NaOH may have been added to adjust pH	Epoprostenol sodium equivalent to 0.5 mg or 1.5 mg epoprostenol, 100mg sucrose, 5 mg glycine, NaOH to adjust pH
Reconstitution	• Sterile water for injection, USP or	• pH 12 sterile diluent (plastic vials, 50 mL) containing 94 mg glycine,	• Sterile water for injection, USP (5 mL) or

	VELETRI for Injection	Flolan® for Injection	Generic Epoprostenol Sodium
	• Sodium chloride 0.9% injection, USP	73.3 mg NaCl, NaOH to adjust pH, and water for injection	• Sodium chloride 0.9% injection, USP (5 mL)
pH of reconstituted solution	• pH 11-13 • Solution is increasingly unstable at a lower pH	• pH 12 sterile diluent: pH 11.7-12.3 • Solution is increasingly stable at higher pH	• pH 12-13.2 • Increasingly unstable at a lower pH
Abbreviations: NaOH, sodium hydroxide; NaCl, sodium chloride; USP, United States pharmacopeia.			

CLINICAL DATA

Phase 3 Studies

EPITOME-2: Open Label Study Assessing the Transition of Epoprostenol for Injection (eg, Flolan®) to VELETRI for Injection

EPITOME-2 was a multicenter, single-arm, open-label, prospective phase 3b study designed to assess the effects of switching PAH patients from epoprostenol for injection (eg, Flolan®) (epoprostenol GM: epoprostenol sodium containing excipients glycine and mannitol) to VELETRI for injection (epoprostenol AS: epoprostenol sodium containing excipients arginine and sucrose).[1] Forty-one PAH patients ≥18 years treated for ≥12 months with epoprostenol for injection (eg, Flolan®) and on a stable dose for ≥3 months prior to enrollment were eligible. Concomitant PAH-specific therapies (including bosentan, ambrisentan, sitaxsentan, sildenafil and tadalafil) were permitted if patients were already receiving these therapies for 90 days and on a stable dose for 30 days prior to enrollment. Calcium channel blockers, diuretics, oxygen (if on a stable dose 30 days prior to enrollment), and oral anticoagulants were permitted. Select exclusion criteria included: known or suspected veno-occlusive disease, use of intravenous (IV) inotropic agents, prostacyclin treatment other than Flolan®, tachycardia >120 beats/minute at rest, history of myocardial infarction, left-sided heart disease or a chronic bleeding disorder. Please visit http://www.clinicaltrials.gov for more information on the inclusion and exclusion criteria for EPITOME-2 (identifier NCT01431716).[7]

Patients were transitioned from epoprostenol for injection (eg, Flolan®) to VELETRI for injection via direct exchange of the medication cassette containing the drug solution in the infusion pump. The mean dose of VELETRI for injection at baseline was 29.9±15.1 ng/kg/min and 30.2±15.0 ng/kg/min at month 3. The majority of patients (n=35) remained at the initial dose throughout the 3-month study. Four patients required dose increases due to relapse or worsening of PAH, dyspnea, dyspnea upon exertion, chest discomfort, and/or fatigue. Two patients required dose decreases, 1 due to a high cardiac output (CO) and the other due to increased skin sensitivity, jaw pain, flushing and foot pain. During the 90-day follow-up, the primary outcome was change from baseline to month 3 in hemodynamics and clinical parameters including: pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), CO, World Health Organization Functional Class (WHO FC), as well as safety and tolerability of VELETRI. Hemodynamics did not change over the study period and WHO FC remained stable. Please refer to Table: Change in Hemodynamic and Clinical Parameters and Vital Signs From Baseline to Month 3 After Switch From Epoprostenol GM to VELETRI for a summary of parameters.[1]

Change in Hemodynamic and Clinical Parameters and Vital Signs From Baseline to Month 3 After Switch From Epoprostenol GM to VELETRI[1]

Parameter	Change From Baseline		% Ratio, Month 3/ Baseline (95% CI)
	Mean±SD	Median (Range)	
Hemodynamics			
RAP (mmHg)	-0.8±3.6	0.0 (-9.0 to 6.0)	86.0 (70.3 to 105.1)
mPAP (mmHg)	-0.2±7.0	0.0 (-20.0 to 17.0)	98.6 (94.2 to 103.3)
mPCWP (mmHg)[a,b]	-0.2±3.4	-1.0 (-9.0 to 7.0)	100.3 (84.9 to 118.6)
Cardiac index (L/min/m^2)	0.0±0.5	0.0 (-1.0 to 1.4)	100.4 (95.9 to 105.0)
PVR (dyn•sec/cm^5)[a,b]	-8.0±116.8	13.7 (-225.0 to 232.7)	98.0 (91.3 to 105.2)
Clinical parameters			
6MWD (m)[c]	-5.3±29.1	-7.5 (-62.0 to 69.0)	99.1 (97.0 to 101.3)
Borg dyspnea score[c]	-0.7±1.1	-0.3 (-4.0 to 1.0)	80.1 (67.9 to 94.3)
NT-proBNP (ng/L)[a]	13.6±318.6	-3.5 (-679.0 to 1217.0)	97.8 (83.1 to 115.1)
Vital signs			
Heart rate (beats/min)	1.5±11.0	0.0 (-20.0 to 35.0)	101.6 (97.3 to 106.1)
Systolic/diastolic blood pressure (mmHg)	4.0±14.3 /-0.9±11.2	5.0 (-37.0 to 34.0) /0.0 (-31.0 to 26.0)	103.5 (99.5 to 107.7) /98.0 (92.6 to 103.7)

Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation.
[a]n=36.
[b]mPCWP as PVR could not be measured in 5 patients.
[c]n=40.

The most common adverse events (AEs) occurring in >5% of patients included headache (29.3%), nasopharyngitis (17.1%), jaw pain (14.6%), flushing/hot flush (14.6%), dyspnea/dyspnea upon exertion (12.2%), device connection issue (7.3%), epistaxis (7.3%), extremity pain (7.3%), and palpitations (7.3%). Six serious adverse events (SAEs) occurred during the study, but none were considered to be related to VELETRI treatment.[1]

EPITOME-2 Extension

Patients that completed the EPITOME-2 core study could enroll in the extension study to continue on VELETRI for injection (eg, VELETRI®) until it became commercially available in their country or until they discontinued the study.[8] During the extension phase, patients were followed up by monthly telephone calls to inquire about AEs and by site visits as part of routine care. For more information on the EPITOME-2 extension, please visit http://www.clinicaltrials.gov (Identifier: NCT01470144).[9]

Forty-one patients from the EPITOME-2 core study entered the extension phase. The median exposure to VELETRI in the extension study was 892 days. The median dose of VELETRI for injection at transition was 25.0 ng/kg/min (range 7-76), which was identical to the median dose of epoprostenol for injection (eg, Flolan®) prior to the transition. At the end of the extension study, the median dose of VELETRI for injection was 31.0 ng/kg/min (range 0-79). Ten patients prematurely discontinued treatment during the extension phase. One patient experienced syncope and died at home after 11.6 months of treatment, 1 patient discontinued treatment per physician/patient decision after 10.6 months of treatment and 8 patients discontinued due to AEs (lung transplantation [n=6], RV failure [n=1], and thrombocytopenia [n=1]).[8]

All patients experienced ≥1 treatment-emergent AE with the most common AEs being typical of IV prostacyclin therapy or PAH progression. The majority of AEs were mild (n=203, 45%) or moderate (n=182, 40.4%) intensity. Overall, 36 patients (87.8%) reported ≥1 SAE with 25 being related to the IV administration system (functional complication of the device [n=22], cutaneous complication at the catheter site [not infection, n=6], local infection at the catheter site [n=9], systemic infection [n=9]) and 21 not associated with the IV administration system (PAH [n=7], lung transplant and RV failure [n=6 each], angina pectoris, diverticulitis, road traffic accident, syncope, and transplant evaluation [n=2 each]).[8]

EPITOME-4: Open-label Study Assessing the Transition From Epoprostenol for Injection (eg, Flolan®) to VELETRI for Injection

EPITOME-4 was a two-site, open-label, single-arm, phase 3b study. Eight adult Japanese PAH patients (7 females) ≥20 years old treated with a stable dose of Flolan® (epoprostenol GM) for ≥30 days were switched to VELETRI for injection (epoprostenol AS) and followed for 12 weeks. Select inclusion criteria included: patients with WHO Group 1 PAH, and treatment with epoprostenol for injection (eg, Flolan®) for ≥3 months prior to enrollment and at a stable dose for ≥30 days before the start of study treatment. Select exclusion criteria included: diagnosis of respiratory or cardiovascular disorder requiring immediate surgery, pulmonary vein occlusion, history of myocardial infarction or a resting pulse rate ≥120 beats/minute.[2]

VELETRI for injection was started at the same dose of epoprostenol for injection (eg, Flolan®), with a mean dose of 40.13 ng/kg/min (range 17.0-61.0). The mean duration of exposure to VELETRI for injection during the 12-week treatment period was 86.9 days (range 78.4-91.6). There were no dose adjustments in any patient.[2]

Outcomes included safety, changes from baseline to 12 weeks in pulmonary hemodynamic factors (PVR, mPAP, CO), and treatment satisfaction, assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM-9). There were no unexpected safety or tolerability concerns after switching formulations. There were no significant changes in pulmonary hemodynamic factors from baseline to week 12 (Table: Changes in Hemodynamic Parameters From Baseline to Week 12 After Switching Epoprostenol Formulations below). Regarding treatment satisfaction, there were improvements in effectiveness, global satisfaction, and particularly convenience at week 12 (P=0.03).[2]

Changes in Hemodynamic Parameters From Baseline to Week 12 After Switching Epoprostenol Formulations[2]

Parameter	Baseline (n=8) Mean±SD, Median, [Min, Max]	After Minute 60 (n=8) Mean±SD, Median, [Min, Max]	Change From Baseline Mean±SD, Median, [Min, Max]	*P*-Value
Systolic PAP, mmHg	50.6±12.4, 46.0, [34, 69]	49.8±14.1, 44.5, [29, 70]	-0.9±3.5, -1.0, [-5, 4]	0.4375
Diastolic PAP, mmHg	17.1±2.2, 17.0, [14, 22]	18.8±4.6, 19.0, [11, 24]	1.6±3.7, 2.0, [-3, 7]	0.4844
mPAP, mmHg	31.1±5.1, 31.5, [22, 40]	31.4±7.2, 32.0, [18, 41]	0.3±2.8, 0.5, [-4, 4]	0.8906
PCWP, mmHg	8.4±1.8, 8.0, [5, 11]	7.3±1.2, 7.5, [6, 9]	-1.1±2.3, -2.0, [-4, 3]	0.2344
CO, L/min	4.829±1.057, 4.440, [2.72, 5.99]	4.499±1.005, 4.095, [3.25, 5.98]	0.210±0.790, 0.310, [-0.91, 1.35]	0.4609
mRAP, mmHg	4.8±1.8, 4.5, [3, 8]	4.8±1.8, 4.5, [3, 7]	0.0±1.7, 0.0, [-3, 3]	1.0000

Parameter	Baseline (n=8) Mean±SD, Median, [Min, Max]	After Minute 60 (n=8) Mean±SD, Median, [Min, Max]	Change From Baseline Mean±SD, Median, [Min, Max]	*P*-Value
Mixed venous oxygen saturation, %	73.43±5.50, 73.20, [63.4, 83.2]	72.10±3.28, 72.75, [67.1, 76.3]	-1.33±4.64, -0.50, [-8.4, 4.7]	0.5469
Cardiac input, L/min/m^2	2.98±0.86, 2.80, [2.0, 4.3]	3.11±0.72, 3.00, [2.4, 4.3]	0.14±0.52, -0.25, [-0.6, 0.9]	0.6563
PVR, dyn•sec/cm^5	448.3±158.1, 429.5, [201, 676]	453.6±175.3, 424.5, [154, 686]	5.4±78.3, -25.0, [-61, 182]	0.5469
PVR index, dyn•sec/cm^5/m^2	646.5±223.1, 598.0, [338, 1000]	648.5±239.6, 640.5, [251, 992]	2.4±98.4, -15.5, [-87, 212]	0.7109

Abbreviations: CO, cardiac output; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase, BIOSIS Previews®, Derwent Drug File (and/or other resources, including internal/external databases) was conducted on the 8 April 2024.

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