# VELETRI® (epoprostenol)
# Pharmacokinetics of VELETRI for Injection Compared to Epoprostenol for Injection (e.g., Flolan®)

## SUMMARY


- VELETRI for injection was approved by the Food and Drug Administration (FDA) in June 2008 utilizing the 505(b)(2) approval process, and contains the same active ingredient (epoprostenol sodium) as epoprostenol for injection (e.g., Flolan®) and generic epoprostenol.[1-5]
- In a single-center, open-label, prospective, phase 1 study, epoprostenol AM (VELETRI®, first generation), epoprostenol AS (VELETRI®, second generation) and epoprostenol GM (Flolan®) were shown to have highly comparable pharmacokinetic parameters, hemodynamic effects, and safety profiles.[6]


## BACKGROUND/GUIDELINES

### Information From Prescribing Information and the FDA VELETRI Medical Review

VELETRI contains the same active ingredient as epoprostenol for injection (e.g., Flolan®).[1-5] The excipients of VELETRI for injection differ from those of epoprostenol for injection (e.g., Flolan®), principally by the substitution of L-glycine with L-arginine for the purpose of increasing the pH of the reconstituted solution. During the medical review of VELETRI for injection by the FDA, it was concluded that no differences in the pharmacokinetics between epoprostenol for injection (e.g., VELETRI®) and epoprostenol for injection (e.g., Flolan®) were anticipated.[3]

## CLINICAL DATA

### Pharmacokinetics of Ascending Doses of VELETRI and Flolan: Study AC-066-102[6]

A single-center, open-label, two-period, two-treatment, crossover, ascending dose study in healthy male subjects was conducted to assess the pharmacokinetics of three different formulations of epoprostenol sodium: VELETRI (first generation, epoprostenol AM), VELETRI (second generation, epoprostenol AS) and Flolan (epoprostenol GM).

Forty healthy male subjects, divided into 2 groups of 20 subjects each, received either (1) epoprostenol AM or epoprostenol AS followed by a crossover of the medications or (2) epoprostenol AS or Flolan followed by a crossover of the medications in 2 separate treatment periods separated by a washout period of 7 days. Epoprostenol AS, epoprostenol AM, and Flolan were administered as sequential intravenous (IV) infusions of 2, 4, 6, and 8 ng/kg/min for 2 hours at each dose, followed by a 40-hour observation period.

The plasma concentrations of the 2 primary metabolites of epoprostenol, 6-keto-prostacyclin F1α (kPF) and 6,15-diketo-13,14-dihydro-prostacyclin F1α (ddPF) were measured. Results from this study showed that the plasma concentration curves of epoprostenol AM, epoprostenol AS, and Flolan were essentially superimposable, suggesting that the pharmacokinetics of the 2 formulations are comparable. Please refer to the full publication for the figure: Arithmetic Mean Plasma Concentration-Time Profiles of (a) 6-keto-prostacyclin F1α and (b) 6,15-diketo-13,14-dihydroprostacyclin F1α After 2-Hour Sequential Infusions of 2, 4, 6, and 8 ng/kg/min Epoprostenol AM, Epoprostenol AS, or Flolan (epoprostenol GM).

Epoprostenol AM, epoprostenol AS, and Flolan had comparable treatment-emergent adverse event profiles with no serious adverse events experienced. The most frequently occurring adverse events were headache, flushing, pain in jaw, nausea, and vomiting. There were no clinically relevant changes observed in vital signs, electrocardiographic parameters, and safety laboratory data (hematologic and blood chemistry).

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, Derwent® (and/or other resources, including internal/external databases) was conducted on 14 March 2024.

## REFERENCES


1. VELETRI (epoprostenol) [Prescribing Information]. Titusville, NJ: Actelion Pharmaceuticals US, Inc;https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/VELETRI-pi.pdf.

2. Food and Drug Administration. Veletri (eporpostenol) NDA 022260. Drug Approval Package. 2008.

3. Food and Drug Administration. Veletri (epoprostenol) NDA 022260. Medical Review(s). 2008.

4. Flolan (epoprostenol sodium) [Prescribing Information]. Durham, NC 27701: GlaxoSmithSline;https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Flolan/pdf/FLOLAN-PI-PIL.PDF.

5. Epoprostenol sodium for injection [Prescribing Information]. USA: Teva Pharmaceutical Industries Ltd;http://www.tevagenerics.com.

6. Nicolas LB, Gutierrez MM, Dingemanse J. Comparative pharmacokinetic, pharmacodynamic, safety, and tolerability profiles of 3 different formulations of epoprostenol sodium for injection in healthy men. *Clin Ther*. 35(4):440-449.