CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-260

OTHER REVIEW(S)

NDA 22-260 Epoprostenol for Injection
RHPM Overview
June 27, 2008

Sponsor: GeneraMedix, Inc.
Type: 505(b)(2)/5S
Receipt Date: August 27, 2007
Goal Date: June 27, 2008

Action: Approval
Action Date: June 27, 2008

Background
This 505(b)(2) application is for a new formulation of epoprostenol for injection, slightly different than the reference listed product, Flolan for Injection. The new formulation includes omission of sodium chloride, substitution of arginine for glycine, and a higher pH. In addition, this formulation can be reconstituted with sterile water for injection or 0.9% sodium chloride, while Flolan requires a special diluent. These changes provide for improved stability of the reconstituted and fully diluted products compared to Flolan.

No clinical studies were performed to support this application. During a pre-NDA meeting the sponsor agreed to conduct a safety study to investigate the potential for phlebitis. The issue was discussed both internally and with the sponsor during the review cycle, and it was determined that they safety study would not be required.

The labeling, while similar to the RLP, has been formatted into the new PLR format. The sponsor did not submit a tradename. Most of the labeling differences compared to the Flolan label are the result of the differences in stability of the reconstituted and fully diluted solutions.

Division Director's Memo (1/20/08)
Reviewer: Norman Stockbridge, M.D., Ph.D.
Recommendation: Approval
Summary: This is a new generic formulation of epoprostenol for intravenous use, differing from Flolan by substitution of arginine as a [redacted] agent instead of Flolan's glycine, but this difference suffices to have the NDA reviewed in OND rather than OGD. b(4)

There are no CMC issues (McLamore; 10 June 2008), no microbiology issues (Lolas; 28 January 2008, 8 May 2008). There are no pharmacology/toxicology, carcinogenicity, clinical pharmacology, or statistical reviews.

There are no clinical studies. The medical review (Williams; 11 May 2008) recommended withholding approval pending a study to assess the potential for phlebitis, a theoretical concern arising because the reconstituted drug has a pH >11. This issue was discussed internally and with the sponsor. I concluded that this was not a valid concern based on the very low infusion rate, even compared with blood flow in a peripheral vein (100-fold larger than infusion rate), and much less for the usual use in a central vein.

I conclude that this application should be approved.

Medical Review (5/11/08)
Medical Reviewer: Akinwole Williams, M.D.
Recommendation: Approvable
Summary: It is recommended that the proposed formulation be approvable, subject to submission of a safety study that will characterize any adverse events, particularly the potential for phlebitis. [This issue was

discussed both internally, and with the sponsor, (after the medical review was finalized) and it was determined that the safety study would not be required.]

The product that is the subject of this submission is a new formulation of Epoprostenol Sodium for Injection. This formulation is deemed by the sponsor to be an advantage for the patient population because it is substantially more stable upon reconstitution and administration than the currently marketed epoprostenol product, Flolan®, made by GlaxoSmithKline.

The rationale for the development of a new epoprostenol injection formula is to minimize the shortcomings of the currently marketed product, Flolan.

In particular:

- The formula should have a better stability profile both during the manufacturing process and upon reconstitution. An improved stability profile would make the use easier for the patient.
- The lyophilized product should be able to be reconstituted with commercially available IV fluids such as sterile Water for Injection, rather than a specially made diluent.
- Upon dilution for delivery, the drug solution should be able to be infused under ambient conditions, rather than requiring ice packs for prolonged delivery.
- The formula should be self-preserving without the addition of antimicrobial agents, to allow for extended shelf life after reconstitution.

The proposed formulation is not identical to the Flolan for Injection currently on the market; however, both formulations are solutions at the time of use and both are injected via the central venous catheter. However, the pharmacokinetics are expected to be identical.

Chemistry Review (12/19/07)
Reviewer: Sherita McLamore, Ph.D.
Recommendation: Approval
Summary: No outstanding issues.

Microbiology Review (1/28/08, 5/8/08)
Reviewer: Anastasia Lolas
Recommendation: Approval
Summary: No outstanding issues.

DSI
N/A

Pediatric Rule
PREA does not apply to this application.

Labeling
Labeling has been discussed and agreed upon. While the labeling is very similar in content to the RLP, it has been formatted in the PLR format.

Advisory Committee
N/A

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/s/

Russell Fortney
6/30/2008 03:10:31 PM
CSO