Saudi Public Assessment Report

(Summary Report)

Brinavess®

Type of Application: New drug application.

Type of Product: New chemical entity.

Active Pharmaceutical Ingredient(s): Vernakalant hydrochloride

ATC code: C01BG11.

Dosage Form: Concentrate for solution for infusion.

Dosage Strength: 20 mg/ml.

Shelf life: 48 months.

Storage Conditions: Do not store above 30°C.

Reference Product in SA (if applicable): NA.

Marketing Authorization Holder: Cardiome UK Limited.

Manufacturer: Hameln Pharmaceuticals GmbH, Germany. (bulk manufacturer)

Geodis Logistics Netherlands B.V. Netherlands. (final release).

Registration No.: NA (rejected).

Decision and Decision Date: Rejected.

Proposed Indications: Rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults

- For non-surgery patients: atrial fibrillation ≤ 7 days duration.
- For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration.

Product Background

This product is considered as a new chemical entity for Saudi regulatory purposes. Furthermore, this product is qualified to follow the SFDA's regulatory pathway regular submission.

The SFDA rejection of Brinavess® (vernakalant hydrochloride 20 mg/ml) is based on the review of the quality, safety and efficacy, which is summarised hereinafter:

Quality Aspects

Drug Substance

- **General information:**
  Vernakalant hydrochloride is a white-to-beige powder. It is highly soluble in water. It does have chirality. Polymorphism has not been observed. The structure has been fully elucidated using several spectroscopic techniques.

- **Manufacture, characterization and process controls:**
  Vernakalant hydrochloride is manufactured by Merck & Cie, Switzerland, through a multiple-step chemical synthesis. Data on manufacturing process validation has been provided.
  A list of reagents and solvents used in the manufacturing process with identification of ICH classification for solvents, as well as the respective specifications has been submitted. The specifications for raw materials are acceptable. Potential and actual impurities were identified and assessed according to international guidelines and references on impurities.

- **Control of the drug substance:**
  The DS specification includes tests for assay, appearance, identification, related substances, water determination, colour of solution, PH, residual solvents, bacterial endotoxins and microbiological examination tests. All methods and acceptance criteria included in the drug substance specifications have been described, justified, and accepted. Batch analysis data and CoA have been presented by the DS manufacturer, demonstrating compliance of three validation batches with the DS specification. The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the international guidelines. The reference standards used for assay and impurities testing have been presented with satisfactory information.

- **Container closure system:**
  The primary packaging is low-density polyethylene (LDPE) bags closed with a plastic tie. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the product's intended use. The secondary packaging is aluminum compound foil bags.

- **Stability:**

  Stability data was provided on five commercial and validation scale batches of the DS from the proposed manufacturer stored in the intended commercial package for 36,48 and 60 months under long-term conditions 25°C/60% RH, and on five commercial and validation scale batches for 6 months under accelerated conditions (40 ºC / 75% RH) according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. The following parameters were tested: assay, appearance, identification, related substances, water determination, color of solution, clarity of solution, specific rotation, pH, residual solvents, bacterial endotoxins and microbiological examination tests. All batches remained stable at long-term conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the DS manufactured by Merck & Cie, Switzerland is sufficiently stable. The stability results justify the proposed re-test period in the proposed container.

Drug Product

- **Description of the product and pharmaceutical development:**

  Vernakalant hydrochloride concentrate for solution for infusion is a sterile, isotonic, buffered solution of vernakalant hydrochloride at a concentration of 20 mg/ml (equivalent to 18.1 mg/ml vernakalant free base). Vernakalant concentrate is manufactured as 200 mg and 500 mg presentations. Each single-use vial contains 200 mg or 500 mg of vernakalant hydrochloride in 10 ml or 25 ml of 40 mMcitrate buffer at pH 5.5, the solution is clear and colourless to pale yellow in appearance. Prior to intravenous infusion into the patient, vernakalant concentrate is diluted with either of the recommended diluents (0.9% Sodium Chloride Injection, Lactated Ringers Injection, or 5% Dextrose Injection). All excipients are well known pharmaceutical ingredients and their quality complies with the international standards. “There are no novel excipients used in the DP formulation.” The list of excipients is included in section 6.1 of the SPC. The compatibility of the DS with the excipients has been adequately demonstrated. The development of the formulation composition including the formulation design, choices of product components (e.g., properties of the drug substance, excipients, container closure system), and manufacturing process has been adequately described.

- **Manufacture of the product:**

  The manufacturing process of the DP consists of six main steps: compounding, filtration, filling, capping, terminal sterilization, inspection and packaging. The process is considered to be a standard manufacturing process. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Process controls with their control limits for the finished product manufacturing process have been provided and accepted.

- **Product control:**

  The DP specifications (release and shelf life) include appropriate tests for this kind of dosage form: identification, appearance, assay, degradation products, clarity, degree of colouration, pH, osmolality, particulate contamination, extractable volume, sterility and bacterial endotoxins. All methods and acceptance criteria included in the DP specifications have been described, justified, and accepted. The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the international guidelines. The reference standards used for assay and impurities testing have been presented with satisfactory information.

- **Batch analysis:**

  Batch analysis data and CoA have been presented by the DP manufacturer demonstrating compliance of 18 primary/commercial scale batches with the DP specification.

- **Container Closure System:**

  The primary packaging is a 10 ml or 30 ml, Type I ISO 8362 part 1 a clear glass tubing vial with ready-to-sterilize FluroTec® chlorobutyl rubber stopper and aluminum overseal with red plastic Flip-Off® cap. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product. The secondary packaging is a cardboard carton.

- **Stability of the product:**

  Stability data was provided on six commercial/primary scale batches of DP from the proposed manufacturer stored in the intended commercial package for 36 and 48 months under long-term conditions 25ºC/60% RH and 30ºC /65% RH, and on six commercial/primary scale batches for 6 months under accelerated conditions (40 ºC / 75% RH) according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. Photostability and stress testing have been performed. The following parameters were tested: identification, appearance, assay, degradation products, clarity, degree of colouration, pH, osmolality, particulate contamination, extractable volume, sterility and bacterial endotoxins. All batches remained stable at long-term, photostability, and stress conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the DP manufactured by Hameln Pharmaceuticals GmbH, Germany is sufficiently stable. The stability results justify the proposed shelf life of 48 months in the proposed container.

Clinical Aspects

The clinical development program for Brinavess consisted of three clinical studies to support two therapeutic indications. Atrial Conversion Trial "ACT I, ACT III", and ACT II phase three efficacy studies which expand the efficacy profile to include post-cardiac surgery atrial fiblirration (AF) patients. In addition, supportive safety and/or efficacy from phase II study in patients with AF, Cardiome Recent onset of AF "CRAFT", and a phase III open-label study in patients with AF "ACT IV".

Other studies included in the new drug application (NDA) included the following:

- Phase III "Scene 2"- Efficacy and safety of Vernakalant in patients with atrial flutter: a randomized, double-blind, placebo-controlled trial.
- Phase III "AVRO"-Amiodarone vs Vernakalant in recent onset AF – randomized, prospective, multi-center study.

The evalution of the submitted studies showed that the product's efficacy is positive but the safety profile is unfavorable and the benefit/risk balance is undetermined or likely to be negative for use in AF. Following the rejection, the applicant submitted the first appeal and SFDA's clinical assessors concluded that the safety concern remained and the appeal was rejected. The rejection letter of SFDA was sent to the applicant on 11th of February 2019, highlighting the following safety concerns: increased rates of serious cardiac disorders, QT interval prolongation and unsatisfactory hypotensive. The applicant filled a second appeal against the decision on 10th of May 2019, stating that additional information on clinical safety from a post-marketing safety study (SPECTRUM) supports approval. Therefore, the applicant was requested to submit the full clinical study report, an updated periodic safety report (PSUR), and a systematic review of published literature on the clinical effectiveness and safety of vernakalant injection in adults with recent-onset AF in the post-marketing setting. Upon the applicant response to the request on December 2020, a reassessment of the safety concerns of Brinavesss in light of the newly submitted safety data was conducted.

<u>Summary of the clinical studies presented hereafter:</u>

- SPECTRUM (EUPAS2078), observational cohort post-authorization safety study (PASS), including overall 1,778 unique patients with a total of 2,009 vernakalant IV treatment episodes included in the registry. The primary endpoint is to estimate the incidence of the following medically significant health outcomes of interest (HOIs) reported during treatment and during the first 24 hours after the last infusion of vernakalant IV or until discharge/end of the medical encounter, whichever occurred earlier: significant hypotension, significant ventricular arrhythmia, significant atrial flutter (AFL), and significant bradycardia. Also, the endpoint included an investigation of the potential risk of overdose and medication error and an evaluation of the effectiveness of the risk minimization activities.

The clinical pharmacology, efficacy and safety results from the aforementioned studies were assessed by the SFDA efficacy and safety department. Based on the review of the submitted evidence, the benefit/risk balance of Brinavess is considered negative due to the safety risk identified. Therefore, we recommend againest the approval of the marketing authorization of Brinavess.

Product Information

In light of the negative recommendation, the summary of product characteristics, labelling and package leaflet are not available at this stage.

The date of revision of this text corresponds to that of the Saudi PAR. The Saudi public assessment report (Saudi PAR): provides information for public about the evaluation of medicines submitted to have marketing authorization in Saudi Arabia and the considerations that led the SFDA to approve or not approve medicine authorization. For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa