Team Beyond the IV

Title: Milrinone alternative delivery system

Product Design Specification

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Project title: Milrinone Delivery Alternative Solution

BME 200/300 | Lab 310

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Function

The device shall provide a non-invasive alternative delivery system for milrinone therapy in congestive heart failure (CHF) patients, enabling outpatient and long term self management without the need for intravenous administration. The system shall consist of two complementary components: a rapid- onset formulation(e.g., nebulized/inhaled, oral liquid or nasal spray) for fast daytime symptom control, and a longer-acting oral formulation for sustained, steady state dosing overnight. Together these formulations shall deliver Milrinone with pharmacokinetic and pharmacodynamic profiles that are therapeutically equivalent to existing IV administration, while reducing adverse side effects, simplifying the dosing regimen and improving patient adherence and overall quality of life.

Client requirements

- Target population: Address the needs of patients with stage D congestive heart failure who require milrinone pumped IV therapy, including patients who are not eligible for heart transplant.
- Delivery method: Prioritize evaluation of an oral pouch for milrinone delivery if possible, reflecting the client's report that his brother, who is a patient receiving milrinone through pumped IV, prefers a pouch over a nasal spray. Nasal and other delivery methods remain alternatives pending feasibility assessment.
- Duration of action: Aim to provide sustained delivery that is suitable for overnight use and reduce the need for frequent administration of milrinone. Investigate whether sustained-release pouches or a daytime pouch

combined with an extended-release nighttime formulation could meet this need. Required duration and administration frequency will be established with the client and clinical specialists.

- Ease of use and replacement: Design for convenient routine administration by the patient or caregiver, with a clearly defined pouch replacement schedule. Determine whether any delivery-system components can be reused without compromising hygiene.
- Patient comfort and material safety: Select pouch material for contact with the oral lining and evaluate potential irritation effects on teeth, and ingredient-related allergy risks.

Design requirements

1. **Physical and Operational Characteristics**

a. **Performance requirements**

i. The milrinone delivery system product is targeted towards patients with stage D cognitive heart failure that currently require a constant IV infusion of milrinone. However, the alternate milrinone administration system should deliver the medication to the patient in a safe route that allows for patient mobility and activity, eliminates the risk of infection, and be more affordable. The correct milrinone dosage should be administered in short acting formulations during the day and long acting dosage at night. The dosage of milrinone delivered to the patient should work to increase cardiovascular functions and manage heart failure.

b. **Safety**

i. The device must comply with pharmaceutical and medical device safety regulations, likely requiring FDA review under an NDA and if paired with delivery hardware such as a nebulizer, inhaler, or nasal applicator regulation as a drug device combination product under 21 CFR Part 4, as well as device quality standards, relevant device specific standards, and biocompatibility requirements for any patient contacting components. Chemically, because Milrinone has a narrow therapeutic index, the formulation must ensure consistent, reproducible dosing to avoid arrhythmia, hypertension, or thrombocytopenia from overdose, with validated stability and preservative safety over shelf life. Mechanically, delivery hardware must minimize choking, breakage, or aspiration risk and require minimal actuation force for elderly or weakened patients; if electrically powered the device must meet electrical safety and EMC standards and battery safety standards, with any heating elements maintaining drug safe, non-injurious temperatures. Finally, clear labeling and warnings must distinguish the fast acting daytime formulation from the long acting nighttime formulation to prevent dosing confusion, specify overdose symptoms and emergency guidance and provide storage, handling and device cleaning instructions.

c. **Accuracy and Reliability**

i. The device must deliver Milrinone within a validated dose accuracy range across its full intended dosing range, with repeatability maintained within a similarly tight tolerance across the device’s rated number of actuations/uses, given Milrinone's narrow therapeutic index and the risk of arrhythmia or hypotension from over or underdosing.

d. **Life in Service**

i. If implementing the capsule version of mirinone, the life in service is one capsule per dosage. The frequency of dosage is currently undetermined however it is expected to be 2-3 capsules per day. The specific frequency will be determined once an effective dosage of milrinone administered has been determined

ii. If implementing the nasal spray solution, the life in service will be a few dosages per container. The specific dosage and number of dosages per nasal spray container will be determined with the formulation of a nasal spray as well as the chamber design for the nasal spray mechanism. The solution will be sealed, non-refillable, and able to be disposed of by standard means.

e. **Shelf Life**

i. The product will have a shelf life of up to 3 years while sealed and in standard room temperature conditions. After being unsealed or opened, the shelf life will fall to 72 hours.The product will not have any light sensitivity, oxygen sensitivity, or strong temperature sensitivity as long as it stays at or under 25 degree celsius climates. Outside of shelf life, the product must be disposed of.

f. **Operating Environment**
   i. The product is intended to be administered to the patient in a typical indoor environment without any specialized environmental conditions or restraints during administration. Normal variations in temperature, humidity, lighting, and patient surroundings are expected during use. The product shall be designed to function as intended under the environmental conditions reasonably anticipated during administration and use.

g. **Ergonomics**
   i. The product will be designed to be used by the patient itself. The oral capsule version will be designed so that the patient can easily swallow with minimal discomfort.
   ii. The nasal version will have two flaps on the side to anchor the nasal spray and a push bottom in the middle for administering the medicine. The product will also be designed to be used for the patient by others in case of emergency, similar to an Epipen but a nasal version.

h. **Size**
   i. The oral capsule version will be designed to maximize the effectiveness of the medicine, further research will be required for the exact capsule type.
   ii. The nasal version will hold 15 mL of medicine in a bottle with a tip for administration. The product should be easy to fit within a pocket or a small medicine pouch allowing ease of transport. The tip should be able to be removed for cleaning.

i. **Weight**
   i. The milrinone delivery system should be lightweight and portable. The patient should be able to have easy access to the milrinone dosage throughout the day. Additionally, the overall weight of the product should not interfere with the patient's mobility and daily activities.

j. **Materials**
   i. The product would include a safe dosage of milrinone that can be administered to the patient throughout the day.
      1. If implementing a capsule version of milrinone, the proposed device would require an extended release tablet that can be made out of either a gelatin or polymer. The specific capsule type would need to be determined based on the dosage of milrinone that needs to be administered to the patient over a specific period of time.
      2. If the proposed device is a nasal spray, the final product would be a liquid dosage form of milrinone. The spray should come in a device that is ergonomic and allows patients to easily administer the drug while on their own.

k. **Aesthetics, Appearance, and Finish**
   i. The milrinone delivery system should have a simple compact appearance that allows for patient comfort and ease of use. Due to the fact that this device may be used multiple times throughout the day, the product should be portable and allow for the patients to administer the prescribed dosage. Furthermore, the product exterior should be easy to clean and durable, withstanding daily wear and tear.
   ii. If the deceive consists of a capsule or tablet, it should be a reasonable shape and size and have a smooth finish to allow for ease of swallowing. For a nasal spray product, the deceive should be user-friendly and allow for a controlled administration of the milrinone.

2. **Production Characteristics**

a. **Quantity**
   i. The client called for a short-acting and a long-acting prototype for the project. The team will focus on the short-acting version for this semester with the goal of producing 1 final prototype for demonstration at the end of the semester.

b. **Target Product Cost**

i. The product was aimed to cost similarly with an Epipen, which the average cost is around 126.35 per unit [ ].

3. **Miscellaneous**

a. **Standards and Specifications**

The proposed device would deliver milrinone through a new method of administration, so regulatory approval would be required before it could be marketed for clinical use. The following standards and regulatory requirements must be considered depending on the final design pursued:

1. ISO 10993 ~ Biological Evaluation of Medical Devices
2. USP <711> ~ Dissolution
3. USP <905> ~ Uniformity of Dosage Units
4. FDA Nasal Spray Drug Product Guidance
5. USP <601> Inhalation and Nasal Drug Products

The above specifications and regulatory requirements ensure consistent and accurate dosage, dosing frequency, absorption rate, and maintenance of required therapeutic plasma concentration.

b. **Customer**

The current method of continuous IV delivery of milrinone is uncomfortable, restrictive, and has negative health effects. So the alternative method of delivery must be more comfortable and have fewer health risks for the customer while effectively delivering the drug.

The final design should eliminate long-term vascular access, be suitable for outpatient use, require minimal maintenance, improve customer ability to perform daily activities, be portable, minimize dosage frequency, and consistently administer the correct drug dosage.

c. **Patient-related concerns**

The device is intended for patients with stage D congestive heart failure who currently require continuous IV milrinone. Therefore, patient safety, dosing accuracy, and ease of use. The delivery device must minimize risk of infection and reliably deliver the therapeutically appropriate dose. The final design should consider the following patient-related concerns:

1. Cleaning and sterilization: reusable parts of the device that come into contact with the patient must be replaceable or be easily sterilized
2. Dose accuracy: the device must prove the accurate dose of the drug consistently
3. Ease of use: patients must be able to administer the drug themselves with minimal physical effort
4. Mucosal safety: repeated administration of intranasal delivery of the drug must not irritate the nasal mucosa
5. Patient variability: Patient differences such as nasal anatomy, technique, gastrointestinal absorption, and others must be considered

d. **Competition**

The current method of delivery is continuous IV milrinone, which is the method that the final design should be compared against. The benefits of this method include: delivering a constant dosage of the drug. Limitations associated with the continuous IV include: patient mobility, infection, infusion equipment, and long-term vascular access. Other similar methods already exist and are present in literature and patents, including:

- WO2016131051A1 Patient Milrinone composition and method for administering same
  - Nebulized/inhaled milrinone formulations for treating heart failure
  - Formulations containing 10-20mg/mL milrinone and single doses of 6-24mg

    - Administration includes nasal administration
- US20190091156A1 Milrinone Controlled-release Formulation
    - An oral controlled-release formulation for treating heart failure
    - Drug containing core and sustained release coating designed for extended release
- WO2023/133460A1 Improved Nasal Administration of Pharmaceutical Formulations
    - Nasal drug delivery patent
    - Identifies milrinone as a drug that can be used in the system