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Argent BioPharma Ltd.

(**Argent BioPharma** or the **Company**)

CimetrA®

CimetrA® is a compounded multi-targeted anti-inflammatory and immunomodulatory formulation. It is designed to address severe inflammatory responses by specifically targeting multiple key cytokines and multiple inflammatory pathways involved in immune system regulation.

CimetrA® has undergone several formulation adaptations based on the data from stability and preclinical studies. Its precursor, ArtemiC, was initially developed and tested in preclinical and clinical studies, providing valuable insights that guide the ongoing development of CimetrA®. In this overview, we will focus solely on CimetrA®, without further reference to ArtemiC, as the relevant findings have been integrated into the ongoing development of CimetrA®.

Development and Reformulation

- **Initial Discovery (April 2020):**
  - CimetrA® was first developed in April 2020 with a complex initial formula aimed at treating anti-infective, anti-viral, and anti-inflammatory conditions. Through various clinical and preclinical trials, researchers were able to determine the safety profile and efficacy of the drug while also establishing an understanding of its mechanism of action.

- **Reformulation (2021, 2022):**
  - **In 2021 Artemisinin** was initially included in the CimetrA® formulation for its well-known anti-viral properties. However, over the course of its development, it was discovered that Artemisinin did not significantly contribute to the overall efficacy of CimetrA® in treating inflammatory conditions, leading to its removal from the formulation that same year. These changes reflect ongoing efforts to optimize CimetrA®'s effectiveness and stability as the product continues to evolve.
  - The updated CimetrA® now primarily relies on two active ingredients. These components have demonstrated substantial effects in reducing inflammation and modulating the immune response. This reformulation was likely driven by clinical trial results indicating that the combination of Curcumin and Boswellia serrata alone was sufficient to achieve the desired therapeutic outcomes.

Why CimetrA® is Multi-Targeted

CimetrA® is considered multi-targeted because it interacts with and modulates several critical immune response elements rather than focusing on a single pathway. This approach allows CimetrA® to exert a broader and more comprehensive effect on inflammation, making it effective in treating complex inflammatory conditions.

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1. **IL-32 Pathway Inhibition:**
    - CimetrA® inhibits the expression of **IL-32 mRNA**, a cytokine that plays a central role in triggering inflammatory pathways such as **NF-κB** and **p38 MAP kinase**. These pathways are responsible for the production of other pro-inflammatory cytokines like **TNF-α** and **IL-6**. By affecting the expression of IL-32, CimetrA® could aid in reduced B activation of these downstream pathways, effectively lowering inflammation across multiple fronts.

2. **HO-1 Pathway Activation:**

    - CimetrA® upregulates **Heme Oxygenase-1 (HO-1)**, an enzyme known for its antioxidant and anti-inflammatory properties. HO-1 breaks down heme into biliverdin, carbon monoxide, and free iron, substances that help protect cells from oxidative stress and reduce inflammation. This pathway adds another layer of protection by mitigating the effects of oxidative damage and chronic inflammation.

3. **Modulation of Cytokine Production:**

    - CimetrA® effectively reduces the production of several key cytokines, including IL-1α, **IL-1β** , **IL-6**, TNF-α, and IFN-γ which are central to the inflammatory response. This modulation helps to prevent excessive immune responses, such as cytokine storms, which can lead to significant tissue damage and severe complications.

Mechanism of Action

Multi-Targeted Approach: CimetrA®'s ability to simultaneously target multiple inflammatory pathways makes it a versatile and effective treatment for managing complex immune responses.

Therapeutic Application

CimetrA® is used in the treatment of inflammatory conditions where traditional therapies may be inadequate. Its multi-targeted action allows it to address complex immune responses, making it a valuable tool in managing diseases characterized by severe inflammation and immune dysregulation.

Clinical Pathway

- **Early Development and Preclinical Studies (Early 2020):**

    - Extensive preclinical studies were conducted to assess the safety, efficacy, and pharmacokinetics of CimetrA®, focusing on its ability to modulate immune responses and manage cytokine storms. These studies included experiments conducted in vitro on isolated human mononuclear cells and in vivo on mice and rats. The findings were crucial in demonstrating the potential of CimetrA® to reduce inflammation and prevent severe immune reactions, such as cytokine storms.

- **Clinical Trials and Development:**

    - **Phase II Clinical Trial (2020):**

      A pivotal Phase II clinical trial was conducted in 2020 to evaluate CimetrA®'s efficacy in patients hospitalized due to moderate pulmonary inflammatory conditions. This double-blind, placebo-controlled trial showed that patients treated with CimetrA® had significantly better clinical outcomes, with none requiring additional oxygen or intensive care.

- **Phase IIb Dose-Finding Study:**

  Following the success of the Phase II trial, a Phase IIb study was conducted to identify the optimal dosing regimen for CimetrA®. This study was essential in refining the treatment protocol to maximize efficacy and minimize side effects.

- **Open-Label Studies:**

  Additional open-label studies, including those on patients with long-lasting inflammatory conditions, provided valuable real-world data supporting CimetrA®'s therapeutic benefits in managing the severity of clinical symptoms associated with excessive immune stimulation. These studies contributed to the ongoing assessment of the product's safety and effectiveness.

- **Safety study in pigs:**

  A preclinical study involving healthy pigs was carried out to evaluate the safety of CimetrA® at doses intended for clinical use. Pigs were selected due to their physiological similarities to humans, making this study a critical step in evaluating the effects of CimetrA® on human systems.

- **Transition and Rebranding to CimetrA® (2021, 2022):**

  - **Reformulation and Rebranding:**

    In 2021/2022, the formulation was refined by removing Artemisinin due to its minimal contribution to overall efficacy and stability. The product was rebranded as CimetrA® and optimized with two primary active components. This change marked a significant shift towards improving the product's anti-inflammatory and immunomodulatory effects.

  - **Preclinical and Clinical Studies (2021-2022):**

    CimetrA® continued to undergo various preclinical and clinical studies. These included the evaluation of its efficacy in reducing cytokine production in severe inflammatory responses. The studies reinforced the safety and effectiveness of the rebranded formulation, confirming its potential in broader therapeutic applications beyond its initial use.

- **Phase III Clinical Trial (2021):**

  A Phase III clinical trial was initiated but later stopped. The trial was halted due to the company's ongoing communication with the FDA to identify the fastest and most effective pathway to marketing authorization. This process includes potential changes to the Phase III trial, and as such, the trial was paused until the FDA dialogue is completed.

- **Planned Preclinical Studies (2024-):**

  A series of preclinical studies to further evaluate CimetrA®'s efficacy for new indications is set to begin before the end of the year. These studies, conducted in collaboration with a renowned German institute, will include ex vivo testing across various indications and in vivo testing on a complex animal model.

—Ends—

Authorised for release by the board of directors, for further information please contact:

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About Argent BioPharma

Argent BioPharma Limited (the "**Company**") (ASX: RGT; LSE: RGT; OTCQB: RGTLF) an innovative multidisciplinary drug development Company within the biopharmaceutical sector. The Company focuses on multidisciplinary methods with Nanotechnology, developing multi-target therapies for comprehensive disease management, especially concerning the central nervous system ("**CNS**") and Immunology treatments.

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