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**VERICIGUAT : A MIRACULOUS THERAPEUTIC AGENT FOR HEART FAILURE**

Bijal Achelal Yadav, Akshat Jain, Somya Singh, Abhiram Patil.

**ABSTRACT**

Heart failure (HF) is a condition characterized by impaired pumping function of the heart and it remains a leading cause of illness and death worldwide. There is a need, for medications that can improve outcomes in patients with HF. Cyclase (sGC) stimulators are a new class of drugs that work by enhancing a signaling molecule called cGMP in the heart and blood vessels. In this review we provide an overview of the benefits of vericiguat, which is the first approved drug in its class for patients with worsening chronic HF and reduced ejection fraction. We discuss how sGC stimulators work and summarize studies that have looked at the effects of vericiguat on function and tissue remodeling both in animal models and human trials. Vericiguat has been shown to enhance contractility reduce fibrosis (scarring) inflammation and hypertrophy (enlargement) in animal models. Clinical trials have demonstrated that when used alongside HF therapies vericiguat leads to changes in biomarkers indicating HF severity improved quality of life scores as well as reduced risks of cardiovascular death and hospitalization due to HF compared to placebo. Ongoing studies are further exploring the effectiveness of vericiguat for acute decompensated HF situations. For patients with preserved ejection fraction. To summarize stimulating sGC, with vericiguat offers an approach to regulate nitric oxide signaling in heart failure patients showing potential based on early phase studies. Extensive randomized controlled trials will be conducted to determine the role of vericiguat, in the treatment approach, for heart failure.

**DISCOVERY**

The two drugs, riociguat and vericiguat, are able to influence the activity of soluble guanylate cyclase (sGC) through various mechanisms, both dependent on and independent of nitric oxide (NO). They work by directly activating the heme-containing sGC enzymes and enhancing the sensitivity of sGC to remaining NO.

In the VICTORIA trial, patients with heart failure with reduced ejection fraction (HFrEF) who were already receiving recommended medical treatment and had recently suffered from acute decompensation were enrolled. The aim of this study was to compare the effects of the oral sGC stimulator vericiguat to a placebo in terms of safety and effectiveness. The results showed that vericiguat was able to decrease hospitalizations due to heart failure, but did not have a significant impact on cardiovascular mortality when compared to the placebo. As a result, the 2021 ESC guidelines for heart failure recommend considering vericiguat for patients in NYHA classes II-IV who have experienced worsening heart failure despite being on standard neurohormonal blockade, in order to reduce the risk of hospitalization.

In 1994, Bayer, a pharmaceutical company, began their search for potential compounds that could activate soluble guanylate cyclase (sGC) and increase cGMP production. They screened over 20,000 compounds using primary endothelial cell cultures and discovered that derivatives of 5-substituted-2-furaldehyde-hydrazone were effective in activating sGC. This discovery was further supported by the findings of researchers at National Taiwan University and Yongshan Pharmaceuticals, who showed that the older antithrombotic agent benzyl indazole YC-1 also had the ability to stimulate cGMP production through sGC activation. According to molecular modeling studies, YC-1 interacts with the heme-nitric oxide/oxygen (H-NOX) and catalytic domains of sGC. Building upon these initial findings, Bayer made chemical modifications to YC-1's furan and indazole components, resulting in the development of BAY 41-2272. This new compound showed improved sGC selectivity and potency, but it also had some issues with inhibiting potent cytochrome P450 (CYP) enzymes.

In their pursuit of more potent sGC stimulation, the researchers at Bayer sought to enhance the effectiveness of BAY 41-2272 by altering its pyrimidine core to include a specialized 4,6-diamino-5-morpholine substituent. However, despite their efforts, BAY 41-8543 proved to have high clearance and nonlinear pharmacokinetics, rendering it less useful for clinical purposes [7]. After conducting extensive structure-activity studies, it was determined that the issues stemmed from the pyrimidine C5 position. This prompted Bayer to conduct a thorough screening of over 1000 optimized pyrimidine derivatives, ultimately leading to the discovery of riociguat (BAY 63-2521). Unlike its predecessors, riociguat did not have any CYP liabilities and displayed favorable metabolic stability and bioavailability [8-9]. While it showed promising sGC stimulation, its short half-life posed a limitation on its efficacy. To address this, further structural modifications were made to riociguat, resulting in the development of vericiguat (BAY 102-1189, MK-1242) [10].

**PHYSICOCHEMICAL PROPERTIES** [49]

**Table 1.1 Physicochemical Properties**

|  |  |  |
| --- | --- | --- |
| Sr  no. | PARAMETER | INFERENCE |
|  | Molecular weight | 426.4g/ml |
|  | Partition coefficient | 0.2 |
|  | Hydrogen bond donor count | 3 |
|  | Hydrogen bond acceptor count | 10 |
|  | Rotatable bond count | 5 |
|  | Topological polar surface area | 147 a0 |
|  | Solubility | In simpler terms, Vericiguat dissolves well in dimethyl sulfoxide, but only has a moderate ability to dissolve in acetone and a very low ability to dissolve in ethanol, methanol, acetonitrile, and ethyl acetate. |
|  | pKa | Strongest acidic 11.83-11.85  Strongest basic 3.52-3.54 |
|  | Boiling point | 535.9 ± 0.5°C |

**Table 1.2 UV Spectrophotometer & RP-HPLC**

|  |  |  |
| --- | --- | --- |
| Sr  no. | PARAMETER | INFERENCE |
|  | Zero Order Method |  |
|  | Concentration range | 5-25µg/ml |
|  | Wavelength | 323nm |
|  | Co-relation coefficient | 0.9999 |
|  | LOD | 0.0812µg/ml |
|  | LOQ | 0.2462µg/ml |
|  | First order Method |  |
| 1. | Concentration range | 5-25µg/ml |
| 2. | Wavelength | 340nm |
| 3. | Co-relation coefficient | 0.9993 |
| 4. | LOD | 0.2894µg/ml |
| 5. | LOQ | 0.8770µg/ml |
|  | Area Under Curve Method |  |
| 1. | Concentration range | 5-25µg/ml |
| 2. | Wavelength | 318-328nm |
| 3. | Co-relation coefficient | 0.9999 |
| 4. | LOD | 0.0227µg/ml |
| 5. | LOQ | 0.0688µg/ml |
| D. | RP-HPLC |  |
| 1. | Concentration range | 5-25µg/ml |
| 2. | Co-relation coefficient | 0.994 |
| 3. | LOD | 0.0822µg/ml |
| 4. | LOQ | 0.2492µg/ml |

**PHARMACOKINETICS**

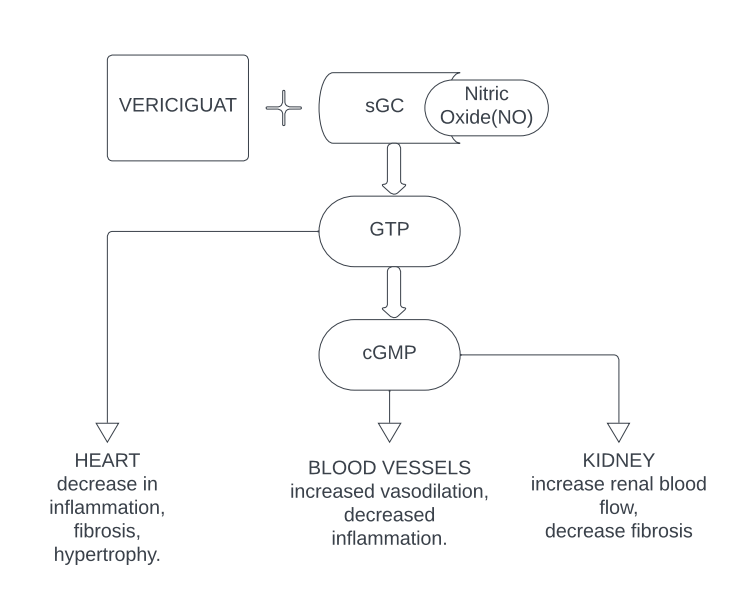
Vericiguat comes under Class II as per Biopharmaceutical Classification System. It has high permeability to cross biological membranes but less solubility. It is taken orally 10 mg daily. **(Table 1.3)**

**Table 1.3** represents Pharmacokinetic parameters and their Inference value.

|  |  |  |  |
| --- | --- | --- | --- |
| Sr no. | PARAMETER | | INFERENCE |
| 1. | Cmax | | 350 mcg/L |
| 2. | AUC | | 6680 mcg.h/L |
| 3. | Tmax | | 1 hour |
| 4. | Bioavailability | | 93% |
| 5. | Half life | | 30 hours |
| 6. | Volume of distribution | | 44 L |
| 7. | Protein binding | | 98% |
| 8. | Clearance | | 1.3 L/h in patients with systolic heart failure |
| 9. | Metabolism | | Phase II Conjugation reactions by UGT1A9 |
| 10. | Elimination | Urine | 53 |
| Faeces | 45% |

Vericiguat is a drug that can be taken orally and has a remarkable 93% bioavailability rate when consumed with food. Studies have shown that taking it with meals can reduce variations in its distribution within the body, resulting in a longer Tmax period of around four hours. Additionally, Cmax and AUC levels have been observed to increase by 41% and 44%, respectively [11]. The drug has a strong binding affinity (around 98%) to plasma proteins, mainly serum albumin [12]. It undergoes phase II metabolism through conjugative pathways, primarily glucuronidation, and also through oxidative cytochrome P450-mediated pathways. UGT1A9 and UGT1A1 are responsible for converting vericiguat into its inactive metabolite, vericiguat N-glucuronide (M1) [12]. Other metabolites, such as a debenzylated molecule and M15, have also been identified, but their properties are yet to be fully understood [12]. Despite its minimal clearance rate, vericiguat has a clearance value of 1.6 L/h when administered to healthy volunteers [12].

**MECHANISM OF ACTION**



**Fig 1.1 Mechanism of action of Vericiguat**

A clinical syndrome--heart failure--manifests as shortness of breath or exertional limitation: this results from impaired ventricular filling, ejection of blood, both factors; it presents a significant health concern [13]. Heart failure with preserved ejection fraction (HFpEF) denotes an amalgamation of diverse disorders marked by four key characteristics—a left ventricular ejection fraction ≥50%, evidence suggesting diastolic dysfunction elevated natriuretic peptide levels and typical signs/symptoms indicative heart failure [13]. The unifying factor among these conditions is their shared presentation under the umbrella term HFpEF.

The nitric oxide (NO) signaling pathway hinges on soluble guanylate cyclase (sGC), a pivotal enzyme. The catalytic production of the second messenger, cyclic guanosine monophosphate (cGMP), that enables vasodilation occurs when NO binds to sGC's heme prosthetic group [14]. Comprising this structure are homologous α and β subunits; each subunit contains four domains: a coiled-coil domain, the catalytic cyclase domain, an N-terminal heme nitric oxide/oxygen - H-NOX for short - domain associated with it centrally is Per-ARNT-Sim or simply referred as central Per-ARNT-Sim domain[15]. The β1 subunit forms a pentacoordinated Fe-NO complex when NO binds to the heme, stimulating cyclase activity and synthesizing cGMP from GTP [16].

Vericiguat may augment cGMP synthesis by forming an association with sGC, hypothesized to be impaired by oxidative stress consequent to cardiovascular disease, thereby compensating for the endogenous shortage of NO and promoting physiological and protective effects such as vasorelaxation in peripheral, coronary, and pulmonary circulations; smooth muscle proliferation regulation; leukocyte recruitment; and platelet function [17]. Endogenous NO's effect on cGMP production is intensified by it, and its interaction with sGC is stabilized [18].

**(Fig 1.1)**

**MEDICINAL SYNTHESIS**

The chemical name assigned to this orally bioavailable drug vericiguat, MK-1242 is methyl-(4,6-diamino-2-(5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate.

The synthesis begins with a substitution reaction of tosylate and morpholine that occurs in an autoclave where high temperature is sustained. Thirdly, the ammonium salt was produced by end product activation using methyl methanesulfonate. A molecule of hydrogen fluoride eliminated under the basic condition to form an intermediate alkene ammonium salt. In this active state, hydrolyze the geminal difluoride to produce unsaturated aldehyde. Unsaturated aldehyde and amino pyrazole form a pyridine ring and into pyrazolopyrimidine. Dehydrate the amide produced a nitrile group, then it was changed into amidine.

The pyrimidine ring system was installed by the second ring-closing process. Amidine reacted with a claimed intermediate prepared through the condensation of aniline and malononitrile to reach diazene. Reducing the diazene then afforded the third amino group on the pyrimidine ring. Methyl chloroformate performs chemoselective acylation on an electron-rich amino group to provide API carbamate in a hydrogen chloride salt form. In this respect, tributylamine was used as neutralization to the salt in DMSO so that DMSO solvate form could be an end product.[19-23]

1. **Reagents:-**

Step 1. **Nucleophilic Substitution**: 130 °C, 85%.

Step 2. **Alkylation**: MeSO2Me, 87%.

Step 3. **Elimination**: NaOH, H2O

Step 4. **Geminal Halide Hydrolysis**: Morpholine, Et3N, H2O, 78% (2steps).

Step 5. **Pyridine Ring Formation**:  LiCl, EtOH; Me3SiCl; NH4CHO, NaOMe, MeOH, 83%.

Step 6. **Dehydration**: POCl3, MeCN/sulfolane, 96%.

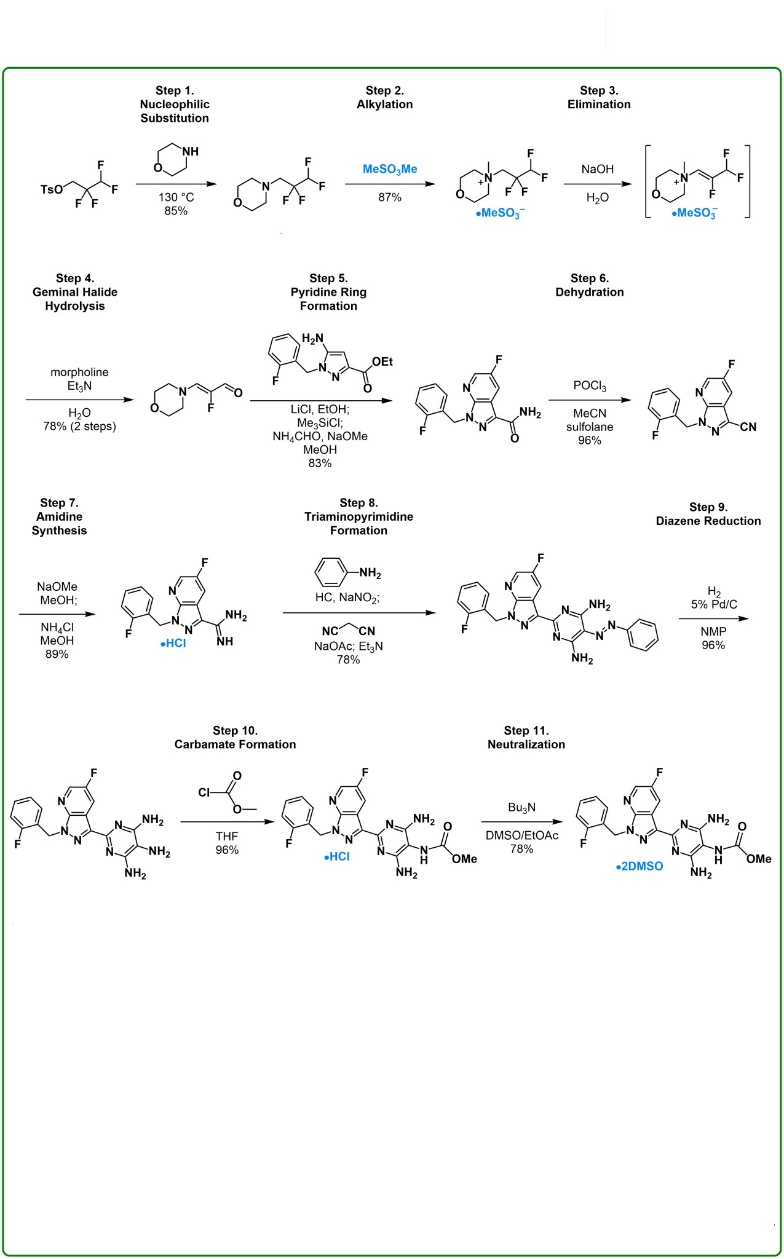
Step 7. **Amidine Synthesis**: NaOMe, MeOH; NH4Cl, MeOH, 89%.

Step 8. **Triaminopyrimidine Formation**:  HC, NaNO2; NaOAc; Et2N, 78%.

Step 9. **Diazene Reduction**: H2, 5% Pd/C, NMP, 96%.

Step 10.**Carbamate Formation**: THF, 96%.

Step 11.**Neutralization:**Bu3N, DMSO/EtOAc, 78%.

1. **Synthesis Scheme:-** **(Fig 1.2)**

**Fig 1.2** **Synthesis of Vericiguat**

**MEDICINAL USES :-**

Verquvo is a tablet medication used in combination with other drugs to treat heart failure. The initial recommended dose is 2.5 mg once daily, which can be increased every two weeks if tolerated until reaching a maintenance dose of 10 mg once daily.Patients should stop or lower the dose if they have trouble tolerating Verquvo. A prescription is required for this medication, and it should be taken as soon as remembered if a dose is missed.

Vericiguat was approved by the FDA in January 2021 and has been shown to reduce hospitalizations and cardiovascular fatalities in patients with heart failure with reduced ejection fraction (HFrEF). It costs less than ten cents per patient per month due to its positive impact on healthcare expenses.The approval of vericiguat was based on data from the VICTORIA study, which evaluated its effectiveness and safety in patients with HFrEF through a randomized, placebo-controlled, double-blind clinical trial.

**Clinical Application :-**

1. **Vericiguat in HFrEF :-**

The soluble guanylate cyclase (sGC) activator vericiguat demonstrated promising results in heart failure patients with reduced ejection fraction (HFrEF) during the phase III VICTORIA trial [24-26]. Imbalance in the nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) signaling axis in heart failure leads to myocardial dysfunction, adverse ventricular remodeling, and cardiorenal syndrome. In addition to current standard of care therapies such as neurohormonal blockade and afterload reduction, the restoration of adequate NO-sGC-cGMP signaling has been suggested as a vital supplementary therapeutic target. Vericiguat exerts its influence on this pathway by directly activating sGC regardless of NO bioavailability and enhancing sGC responsiveness to minimal levels of endogenous NO [24-26].

In the VICTORIA trial, the addition of vericiguat to the standard of care medication in adults with chronic HFrEF demonstrated a significant decrease in the risk of the primary composite endpoint of cardiovascular death or first hospitalization for heart failure, when compared to placebo plus standard of care [24-26]. Vericiguat also exhibited a significant reduction in the risks of first hospitalization for heart failure or all-cause death, as well as total heart failure hospitalizations [24-26]. However, in a subset of VICTORIA patients with markedly elevated levels of N-terminal pro-brain natriuretic peptide, vericiguat did not exhibit a statistically significant effect on the primary composite endpoint in comparison to placebo [24-26].

1. **Vericiguat in HFpEF**

Soluble guanylate cyclase (sGC) inadequately producing cyclic guanosine monophosphate (cGMP) may contribute to the pathogenesis of heart failure with preserved ejection fraction (HFpEF) by impacting cardiac, vascular, and peripheral processes [27-30]. In contrast to other medications that target the cGMP pathway, direct sGC stimulators possess the ability to enhance sGC activity autonomously from nitric oxide (NO), rendering them intriguing therapeutic alternatives for HFpEF. HFpEF patients lack therapies based on evidence, and the rates of cardiovascular occurrences following hospitalization for deteriorating chronic heart failure persist at elevated levels [27-30].

Researchers have studied Vericiguat in HFpEF due to its pharmacological profile as a direct sGC stimulator [27-30]. The major published clinical trials in this field are the phase II SOCRATES-PRESERVED trial and phase III VITALITY study [27-30]. After 12 weeks, Vericiguat was well-tolerated and showed no difference from placebo in terms of NT-proBNP or left atrial volume. However, it was associated with enhancements in quality of life for HFpEF patients [27-30]. Further investigation is warranted to study the impacts of vericiguat in HFpEF, potentially employing escalated dosing, extended follow-up periods, and supplementary endpoints, in light of the favorable indications for quality of life [27-30].

1. **Vericiguat in CCS(Chronic Coronary Syndrome)**

Vericiguat in combination with isosorbide mononitrate may potentially yield therapeutic benefits in patients with chronic coronary syndrome, as indicated by the findings of this study. These benefits, however, do not appear to result in significant alterations in blood pressure or heart rate [31-33]. Nevertheless, it remains uncertain whether these advantages can be extended to a more extensive and severely ill population. The current knowledge regarding the simultaneous usage of vericiguat and long-acting nitrates in heart failure patients is limited [31-33].

**ADVERSE EFFECTS**

Vericiguat is associated with hypotension, syncope, and anemia [34-37], as well as headaches and postural dizziness arising from its vasodilatory properties. Additionally, smooth muscle relaxation may result in diarrhea, nausea, and abdominal discomfort [34-37]. Vericiguat has been associated with symptomatic hypotension, orthostatic hypotension, syncope and anemia [34-37], accompanied by a slight augmentation in heart rate likely due to homeostatic baroreflex from reduction in vasodilation and blood pressure [34-37].

Patients encountered proteinuria, influenza, and nasopharyngitis in trials; nevertheless, no serious adverse events or fatalities transpired [34-37]. Furthermore, vasoactive hormones for cGMP, plasma renin activity, and norepinephrine saw heightened levels with no changes to aldosterone, urine or serum electrolytes [34-37]. There was also diminutive yet incessant diminutions in creatinine, urea and uric acid [34-37]. No noteworthy divergences in deteriorating renal function were observed between vericiguat and placebo in one study [34-37].

**TREATMENT OF OVERDOSE**

The dosage, administration, and overdose treatment of vericiguat is hereby elucidated.

Vericiguat must be administered orally and is exclusively formulated in tablet form (38-39).

Begin treatment with a dosage of 2.5 mg ingested orally daily, concurrently with sustenance [38-39]. Subsequently augment the dosage by twofold increments every fourteen days until paralleling the designed prescription of 10 mg contracted for day-to-day consumption [38-39].

Suspicion of overdose necessitates the implementation of key steps [38-39].

Maintaining serenity and summoning emergency assistance.

Gently place them in the recovery position to preserve airway patency should they succumb to unconsciousness.

Observing respiration and state of health until assistance arrives.

Discourage administering food or drink, or any other endeavors to induce vomiting.

The hospital requires the presentation of medication containers.

Medical interventions for overdose may include [38-39].

If obstruction of the airway occurs, I shall administer measures to clear it or insert a breathing tube if necessary.

Administrating activated charcoal to absorb the medication.

Eliciting emesis or performing gastric lavage to expel the substance from the stomach.

Administering IV fluids and diuretics to augment medication elimination**.**

**CONTRAINDICATIONS**

Vericiguat must not be prescribed in conjunction with long-acting nitrates, soluble guanylate cyclase stimulators (e.g. riociguat) or PDE-5 inhibitors (e.g. tadalafil, sildenafil, vardenafil), lest hypotension and syncope should occur. In addition, given the potential risk of a decline of hemoglobin level, it is strongly recommended that those afflicted with severe anemia do not take vericiguat either.[40]

**Blackbox warning:**

Vericiguat is potentially hazardous to fetal development if ingested by a pregnant woman, as evidenced in animal reproduction studies. Consequently, physicians ought to apprise women of childbearing age of this hazard prior to initiating vericiguat therapy and to conduct pregnancy tests. For at least a month after the final dosage of vericiguat has been administered, it is recommended that females utilize contraceptive measures.[41-42]

**INTERACTIONS**

Vericiguat's efficacy and safety may besubject to significant alteration, contingent upon interactions with an abundance of medications. In fact, registry reveals 121 drug interactions associated with vericiguat, as well as two disease state interactions and one interaction pertaining to alcohol or certain foods [43]. Of these, five are considered major interferences that necessitate abstaining from concurrent use; the rest (116) are deemed moderate and mandate dosage corrections, supplementary surveillance or other precautions [43].

Aminophylline, dipyridamole, sildenafil and tadalafil for pulmonary hypertension, riociguat, and theophylline are some of the drugs that may interact potentially. The rationale behind these interactions varies; for instance, concurrent use of vericiguat along with phosphodiesterase inhibitors such as dipyridamole could potentiate hypotension [42]. Riociguat and other soluble guanylate cyclase stimulators may provoke hypotension or an array of averse outcomes from overactivation of the nitric oxide-cGMP pathway [42].

Proton pump inhibitors such as omeprazole, and antacids containing aluminum hydroxide or magnesium hydroxide may impede the absorption of vericiguat [42-43], yet studies on pharmacological interactions demonstrate that vericiguat remains a satisfactory therapy for heart failure patients with multiple medical conditions requiring simultaneous use of multiple drugs [42-43]. To abate the risk of drug associations, vigilance and dose adjustments should be considered.

1. **Dietary interactions**:

Consume with food. There is evidence that pharmacokinetic variability can be reduced and absorption can be greatly increased by administration with food.[44]

1. **Disease interactions:**

Vericiguat has 2 disease interactions, including: liver disease, kidney impairment.[43]

In patients who are already taking other soluble guanylate cyclase (sGC) stimulants, VERQUVO is contraindicated.

Due to the risk of hypotension, it is not advised to use VERQUVO with PDE-5 inhibitors together.

**MARKETED FORMULATIONS**

Vericiguat is a biconvex film coated drug. The strip consists of 14 tablets. The drug is available in three different doses which is described below: **(Table 1.4)** [45-46]

**Table 1.4 Marketed Formulation of Vericiguat**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| TYPE | BRAND NAME | COMPANY NAME | DOSE | PRICE |
| Film-Coated Tablet | Verquvo | Bayer Zydus Pharma | 2.5mg | Rs.1784.00 /- |
| Verquvo | Bayer Zydus Pharma | 5mg | Rs.2039.00 /- |
| Verquvo | Bayer Zydus Pharma | 10mg | Rs.2294.00 /- |

**NOVEL FORMULATIONS**

No novel formulation of Vericiguat are still available in market.

**PATENT**

Verquvo is a medication used to manage symptomatic chronic heart failure in patients with an ejection fraction less than 45%. It works by reducing the risk of cardiovascular death and hospitalization for heart failure. Verquvo, which contains vericiguat as its active ingredient, is available in tablet form for oral administration.

Merck Sharp Dohme owns the drug Verquvo and holds six patents related to it. These patents are still valid and none have expired yet. Verquvo was approved by regulatory authorities on January 19, 2021, allowing its use in the market. Verquvo has been found to be generally well-tolerated with few adverse reactions reported during clinical trials. Some common side effects include hypotension (low blood pressure), syncope (fainting), dizziness, anemia (a decrease in red blood cells or hemoglobin levels), myalgia (muscle pain), chest pain, shortness of breath,and palpitations.In rare cases, more severe side effects such as diarrheoa, nausea and abdominal pain may occur but overall profile establishes benefits out weigh.[47-49]

**Merck Sharp Dohme , company who filed various patent for vericiguat synthesis and manufacturing procedure.**

1. Patent No.: US10736896

Grant date: 23-02-2016

Expiry date: May, 2031

This application relates to novel substituted 5-fluoro-1H-pyrazolopyridines, methods for their preparation, uses of these compounds alone or in combination for the treatment and/or prophylaxis of diseases, and uses of these compounds for the production of medications for the treatment and/or prophylaxis of diseases, specifically for the treatment and/or prophylaxis of cardiovascular disorders. [46]

1. Patent No.: US9604948

Grant date: 28-03-2017

Expiry date: November, 2032

This application relates to a brand-new, effective process for making novel substituted 5-fluoro-1H-pyrazolopyridines, which are used as an intermediary in the manufacturing of drugs and drugs for the treatment and/or prophylaxis of cardiovascular problems.[47]

1. Patent No.: WO2021156223A1

Grant date: 2-2-21

Expiry date: Under evaluation

This invention focuses on stable nanosuspensions of methyl {4,6-diamino-2-[5-fhioro-l-(2- fluorobenzyl)-lH-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate (Vericiguat), techniques for creating stable nanosuspensions, nanoparticles, and solid pharmaceutical compositions made from the nanosuspensions.[48]

**CONCLUSION**

Vericiguat has shown efficacy and safety in high-risk heart failure patients, resulting in a diminished risk of cardiovascular mortality or hospitalization for heart failure [42-43]. Nevertheless, the exact capacity of vericiguat therapy necessitates further investigation, especially regarding recent advancements in circumstances concerning both acute and chronic heart failure [42-43].

Further exploration should persist to ascertain which patient cohorts may garner the maximum advantage from vericiguat administration. Investigations should additionally be conducted of the efficiency of vericiguat incorporated with other modern pharmacotherapies for heart failure. As pragmatic expertise related to vericiguat increases, its position in the transforming heart failure treatment paradigm will become elucidated.

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