VERICIGUAT: A MIRACULOUS THERAPEUTIC AGENT FOR HEART FAILURE

Abstract

The NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway regulates cardiovascular function and is disturbed in heart failure (HF), resulting in diminished protection against myocardial damage. In HF, impaired NO-sGC-cGMP signalling is caused by decreased NO bioavailability and an altered redox state of sGC, which makes it less sensitive to NO. Cinaciguat, a sGC activator, raises cGMP levels by direct NO-independent sGC activation and may be especially beneficial under settings of increased oxidative stress and endothelial dysfunction, and therefore lower NO levels, at the price of an increased risk of hypotension. sGC stimulators, on the other hand (riociguat and vericiguat), increase sGC sensitivity to endogenous NO, resulting in a more physiological effect. The review focuses on the complete drug profile of Vericiguat.

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I. DISCOVERY

Riociguat and Vericiguat are examples of sGC stimulators that function both in a NO-dependent and NO-independent way. They have the capacity to both directly stimulate heme-containing sGC and sensitize sGC to low NO concentrations.

The VICTORIA trial involved people with HFrEF who were receiving optimal neuro-hormonal blockade/modulation and had recently experienced an intensifying heart failure episode. Vericiguat, an oral soluble guanylate cyclase receptor activator, was compared to a placebo to determine its effectiveness and safety. In the vericiguat arm compared to the placebo, there was a lower incidence of the primary endpoint of cardiovascular death/heart failure hospitalization, but there was no decrease in cardiovascular mortality. Consequently, the heart failure guidelines from the European Society for Cardiology (ESC) for 2021 recommend that "Vericiguat may be considered in patients in New York Heart Association (NYHA) class II to IV who have had worsening heart failure despite treatment with an ACE inhibitor, angiotensin receptor-neprilysin inhibitor, a -blocker, and a mineralocorticoid antagonist to reduce the risk of cardiovascular mortality or heart failure hospitalization.

Bayer began exploring options for medications that could target sGC in 1994. In primary endothelial cell cultures, over 20,000 substances were examined for their ability to induce sGC. It was discovered that 5-substituted-2-furaldehyde-hydrazone derivatives can trigger sGC and accelerate the production of cGMP. A benzyl indazole molecule created in 1978 for treatment of thrombosis was shown to activate cGMP the same year by researchers from National Taiwan University and Yongshan Pharmaceuticals. They called this drug YC-1[1-2].The results of molecular docking between YC-1 and NO-activated sGC done by Lei Chen et al. revealed that the chemical primarily impacts subunits sandwiched between H-NOX and CC domains. This served as additional data supporting vericiguat's impact on sGC at the molecular level. In particular, vericiguat creates hydrophobic interactions with the side chains of TYR2, PHE4, and haem, as well as stacking the side chain of TYR112 with the terminal benzene ring of YC-1. In the H-NOX domain, the core indazole component of YC-1 interacts with TYR83 and PHE77. ARG40 and the furan group of YC-1 interact with one another [3]. The arylacrylamides were among the first sGC stimulators, along with the aminopyrimidine compounds [4]. Furthermore, Bayer's investigation on sGC stimulators persisted. Bayer developed BAY 41-2272 through the modification of the (hydroxymethyl) furan moiety of YC-1 to 5-substituted 4-aminopyrimidine and the benzyl indazole moiety to (2-fluorobenzyl) pyrazolopyridine within the context of the development of next-generation stimulators [5]. BAY 41-2272 demonstrated greater sGC selectivity and stimulating potency when compared to YC-1. Due to its potent inhibitory and inducing activities on cytochrome P450 (CYP) enzymes, BAY 41-2272 has a confined usage in medicine [6].

In order to have a more potent sGC-stimulating action and the specific 4,6-diamino-5-morpholine derivative BAY 41-8543, the pyrimidine ring of BAY 41-2272 was further transformed. However, the high blood clearance (CL_b) and the impact of dose nonlinearity also made BAY 41-8543's continued clinical use challenging [7]. Researchers discovered that the previously mentioned two issues were primarily focused in the C5 position on the pyrimidine ring after executing structure-activity relationship (SAR) analysis. Bayer started further screening and optimizing pyrimidine derivatives to further create sGC medicines, and after screening over 1000 compounds, they discovered BAY 63-2521 (riociguat). There were

no CYP adverse effects from rociguat, which had acceptable metabolic stability and oral bioavailability [8-9].

Despite having a good sGC-stimulating effect, riociguat's half-life was short, according to clinical research on the treatment of HF. Vericiguat (BAY 102-1189, MK-1242) was created as a result of several improvements in structure made to riociguat to decrease the CL_b and extend the half-life [10].

II. 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 a^0
	Solubility	Soluble in Dimethyl sulfoxide Slightly soluble in acetone, Very slightly soluble in ethanol, methanol, Acetonitrile and ethyl acetate
	pKa	Strongest acidic 11.84 Strongest basic 3.53
	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

III. 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.	C_{max}		350 mcg/L
2.	AUC		6680 mcg.h/L
3.	T_{max}		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 an oral medication with an approximate absolute bioavailability of 93% when taken with food. Co-administration with meals has been demonstrated to decrease pharmacokinetic variability, extend Tmax to almost 4 hours, and enhance Cmax and AUC by 41% and 44%, respectively. It is extensively (~98%) protein-bound in plasma, primarily to serum albumin. Phase II conjugation processes (glucuronidation) with oxidative metabolism mediated by CYP are the main metabolic pathways involved. UGT1A9 and, UGT1A1 are responsible for producing vericiguat N-glucuronide (M1), a primary inactive metabolite. A debenzylated molecule and an M15 metabolite, both of which are believed to be the end products of oxidative metabolism, are other discovered metabolites, although they have not yet been given adequate scientific scrutiny. Vericiguat is a medication that has minimal clearance but when administered in healthy volunteers shows 1.6L/h clearance value.[11-12]

IV. MECHANISM OF ACTION

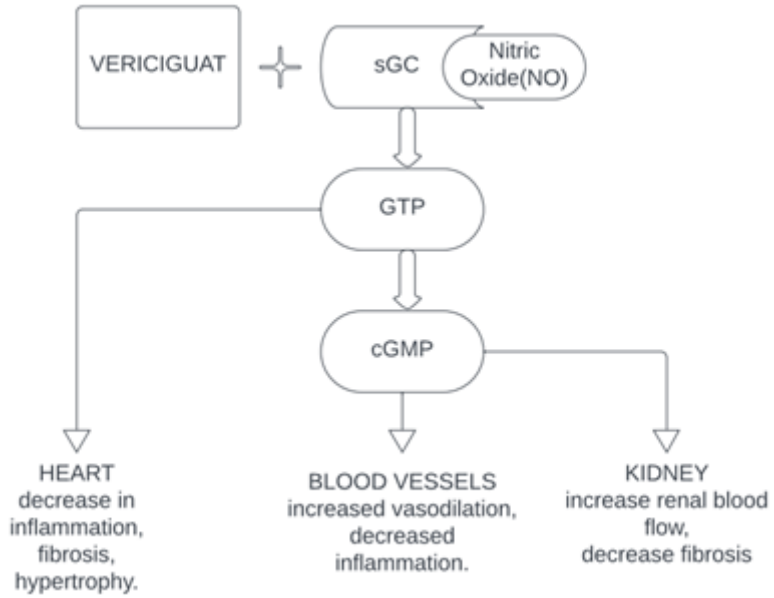

Figure 1.1: Mechanism of action of Vericiguat

Heart failure could be a clinical disorder characterized by dyspnoea or exertional restriction due to disability of ventricular filling or ejection of blood or both.

Heart failure with preserved ejection fraction (HFpEF) represents a heterogeneous collection of conditions that are unified by the presence of a left ventricular ejection fraction ≥50%, evidence of impaired diastolic function and elevated natriuretic peptide levels, all within the context of typical heart failure signs and symptoms.[13]

A vital enzyme in the nitric oxide (NO) signaling pathway is soluble guanylate cyclase (sGC). When NO links to its prosthetic haem group, sGC catalyzes the production of the second messenger cyclic guanosine monophosphate (cGMP), which permits vasodilation.[14] Two homologous α and β subunits make up the structure of the sGC. Four domains make up each sGC subunit: a coiled-coil (CC) domain, a catalytic (CAT) cyclase domain, an N-terminal haem nitric oxide (H-NOX) domain, and a central Per-ARNT-Sim (PAS) domain.[15]The development of a pentacoordinated Fe-NO complex, stimulation of cyclase activity, and synthesis of cGMP from GTP are all instances of NO binding to the haem in the β1-subunit.[16]

cGMP is a chemical messenger that mediates a number of physiological and tissue-protective impacts, such as peripheral, coronary, and pulmonary vasorelaxation, regulation of smooth muscle proliferation, leukocyte recruitment, and platelet function.[17] It is considered that the oxidative stress brought on by cardiovascular disease alters sGC and decreases its ability to react to NO. In the absence of NO, vericiguat increases the synthesis of cGMP via binding to the sGC. Additionally, it strengthens the effect of endogenous NO on the synthesis of cGMP and stabilizes the NO-sGC interaction.[18] (Fig 1.1)

V. MEDICINAL SYNTHESIS

Vericiguat (also known as MK-1242) is an orally bioavailable drug. It is chemically known as methyl(4,6-diamino-2-(5-fluoro-1-(2-fluorobenzyl)-*1H*-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl) carbamate Tosylate and morpholine undergoes substitution reaction in an autoclave at a high temperature to start the synthesis. Methyl methanesulfonate was used to activate the end product in order to produce ammonium salt. A molecule of hydrogen fluoride was removed under basic circumstances to produce an intermediate, alkene ammonium salt. The geminal difluoride was hydrolyzed to produce unsaturated aldehyde in this active state. Aldehyde and amino pyrazole form a pyridine ring to create pyrazolopyrimidine.

Dehydrating the amide produced a nitrile group, which was then changed into amidine. The pyrimidine ring system was constructed via the second ring-closing process. To get to diazene, amidine interacted with a claimed intermediate created by combining aniline and malononitrile. The third amino group on the pyrimidine ring was then afforded by reducing the diazene. To provide the API carbamate in hydrogen chloride salt form, methyl chloroformate performs a chemoselective acylation on the electron-rich amino group. Tributylamine was used to neutralise the salt in DMSO so that the DMSO solvate form could be used as the end product.[19-23]

1. Reagents

Step 1. **Nucleophilic Substitution**: 130 °C, 85%.
Step 2. **Alkylation**: $MeSO_2Me$, 87%.
Step 3. **Elimination**: NaOH, H2O
Step 4. **Geminal Halide Hydrolysis**: Morpholine, Et_3N, H2O, 78% (2steps).
Step 5. **Pyridine Ring Formation**: LiCl, EtOH; Me3SiCl; NH_4CHO, NaOMe, MeOH, 83%.
Step 6. **Dehydration**: $POCl_3$, MeCN/sulfolane, 96%.
Step 7. **Amidine Synthesis**: NaOMe, MeOH; NH_4Cl, MeOH, 89%.
Step 8. **Triaminopyrimidine Formation**: HC, $NaNO_2$; NaOAc; Et_2N, 78%.
Step 9. **Diazene Reduction**: H_2, 5% Pd/C, NMP, 96%.
Step 10. **Carbamate Formation**: THF, 96%.
Step 11. **Neutralization:** Bu_3N, DMSO/EtOAc, 78%.

2. Synthesis Scheme:- (Fig 1.2)

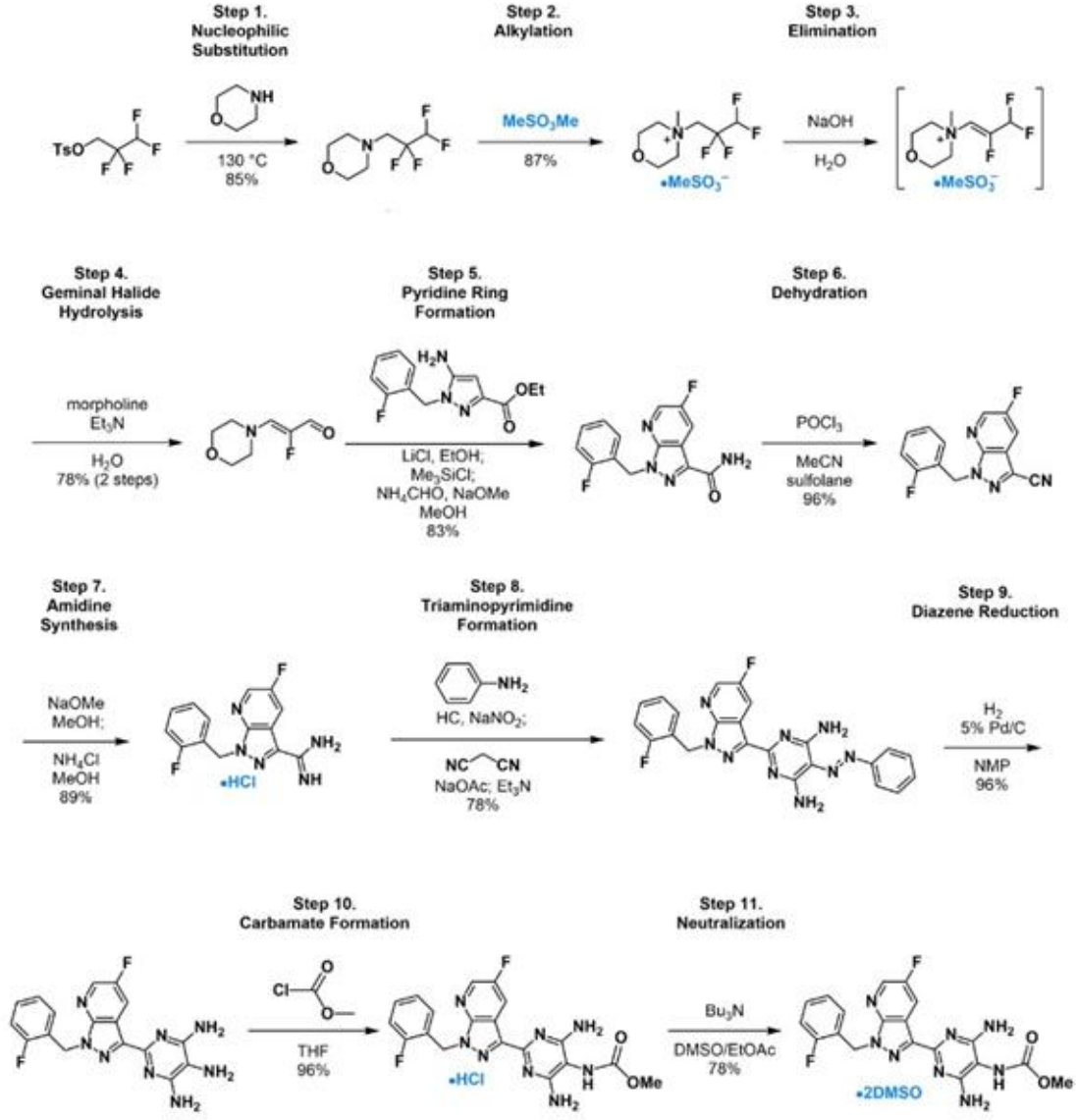

Figure 1.2: Synthesis of Vericiguat

VI. MEDICINAL USES

Verquvo comes in tablet form, and a starting dose of 2.5 mg once daily is suggested. Once the maintenance dose of 10 mg once a day is attained, the amount should be increased every two weeks if tolerated. Lowering the dose or stopping the medication should be done if the patient is experiencing problems tolerating Verquvo. The drug Verquvo is used together with other drugs for treating heart failure. The only thing needed to get the drug is a prescription. If a dose is forgotten, the patient should take it as soon as they recall the next day. Vericiguat shouldn't be taken in two doses on the same day by the patient. Vericiguat needs to be consumed with meals. For patients who can't take whole tablets, Verquvo can be split and mixed with water shortly before administration.

The Food and Drug Administration (FDA) authorised Vericiguat in January 2021. It can be used as an adjunct treatment for heart failure with a decreased ejection fraction that has worsened. Surprisingly, the fiscal effect of vericiguat per patient per month is less than ten cents, owing to the reduction in HF hospitalisations and CV fatalities.

The FDA authorised vericiguat for patients with HFrEF based on the findings of the phase III VICTORIA (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) study.VICTORIA was a multi-center, randomised, placebo-controlled, double-blind, pivotal phase III study assessing the oral soluble guanylate cyclase stimulator's effectiveness and safety.[24]

Clinical Application

- **Vericiguat in HFrEF:** In the most current VICTORIA study, patients with heart failure with decreased ejection fraction (HFrEF) showed encouraging outcomes when treated with vericiguat, a new activator of soluble guanylate cyclase (sGC). In heart failure, there is an imbalance in the nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) signalling pathway, which results in myocardial dysfunction, unfavourable left ventricular remodelling, and cardiorenal syndrome. Beyond neurohormonal blockade and afterload reduction, restoration of adequate NO-sGC-cGMP signalling has been suggested as an essential therapy target for heart failure. Vericiguat acts on this axis in two different ways; it can both directly activate sGC in the absence of endogenous NO and sensitise it to low levels of NO.

  Vericiguat added to standard of care (SOC) in the phase III VICTORIA trial was linked to a significantly lower risk of the primary composite endpoint of death from cardiovascular (CV) causes or first hospitalisation for heart failure (HHF) in adults with chronic HFrEF than placebo added to SOC. The risk of first HHF or all-cause death, as well as the overall number of HHF, was statistically significantly decreased by vericiguat medication. In a subset of individuals with noticeably high N-terminal pro-brain natriuretic peptide levels, vericiguat failed to demonstrate any effect with regard to the primary goal. [24-26]

- **Vericiguat in HFpEF:** Through cardiac, vascular, and peripheral processes, insufficient soluble guanylate cyclase (sGC) production of cyclic guanosine monophosphate (cGMP) may contribute to the pathogenesis of heart failure with preserved ejection fraction (HFpEF). In contrast to other medications that target the cGMP pathway, direct sGC stimulators have the potential to boost sGC activity without the need for nitric oxide (NO), making them interesting treatment options for HFpEF.There are no evidence-based treatments for individuals with HFpEF, and the rates of cardiovascular events after discharge are significant in the context of deteriorating chronic heart failure (HF) requiring hospitalisation.

  Vericiguat has been investigated in HF with preserved ejection fraction (HFpEF) due to its pharmacologic characteristics. The phase II study SOCRATES-PRESERVE and the phase III study VITALITY (Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Daily Living

Activities of Patients With Heart Failure and Preserved Ejection Fraction) are the two major clinical trials that have been published in this area.

Vericiguat was well tolerated, did not differ from placebo in terms of NT-proBNP and LAV after 12 weeks, but it was linked to improvements in patients with HFpEF's quality of life. Vericiguat's effects on patients with HFpEF merit further investigation, maybe with greater dosages, longer follow-up, and other endpoints, given the positive outcomes on quality of life.[27-30]

- **Vericiguat in CCS(Chronic Coronary Syndrome):** Based on the findings from this study, Vericiguat in combination with isosorbide mononitrate may exert therapeutic effects in patients with CCS without clinically relevant changes in BP and HR. However, whether these benefits may transfer to a broader, more severely ill population still needs to be established. There is currently limited experience with concomitant use of vericiguat and long-acting nitrates in patients with HF.[31-33]

VII. ADVERSE EFFECTS

The most frequent vericiguat adverse medication reactions include hypotension, syncope, and anaemia. Headache and postural dizziness may be caused by vericiguat-mediated vasodilation. Smooth muscle relaxation has been linked to diarrhoea, nausea, and stomach pain. Some of the recognised adverse effects of vericiguat include symptomatic hypotension, orthostatic hypotension, syncope, and anaemia. Researchers found a modest rise in heart rate, which they attributed to the compensatory baroreflex caused by vasodilation and blood pressure lowering.

During the medication study, a few participants suffered proteinuria, influenza, and nasopharyngitis, but no serious adverse events or deaths were observed. There were increases in vasoactive hormones for cGMP, plasma renin activity, and noradrenaline, but no changes in aldosterone activity, urine, or serum electrolytes.There was a small but constant reduction in creatinine, urea, and uric acid. In contrast, one research found no significant difference in renal function deterioration between vericiguat and placebo usagess.[34-37]

VIII. TREATMENT OF OVERDOSE

Vericiguat is available only in one dosage form that is tablet and can be administered only through oral route.

To begin, take 2.5 mg orally once day with meals.

Maintenance dosage: Double the dose every two weeks until the goal dose of 10 mg daily is reached.

Primary Treatment for drug poisoning due to overdose:-

1. Stay calm.
2. Call triple zero (000) for an ambulance.

3. If the person is unconscious but breathing, place them gently on their side in the recovery position. Ensure their airway remains open by tilting the head back and lifting the chin. (This can help them to breathe and stop them from choking if they vomit.)
4. Check breathing and monitor their condition until help arrives.
5. Do not try to make the person vomit.
6. Do not give them anything to eat or drink.
7. Keep any pill containers to take to the hospital.
8. When there is a problem with breathing, clear the airway or insert a breathing tube.
9. Giving activated charcoal, which acts in the digestive tract to absorb the drug
10. Inducing vomiting to remove the substance from the stomach
11. pumping the stomach to remove the substance from the stomach
12. giving intravenous fluids along with diuretics to help speed up the body's removal of the substance. [38-39]

IX. CONTRAINDICATIONS

In order to prevent hypotension and syncope, vericiguat should not be used in patients who are also taking long-acting nitrates, soluble guanylate cyclase stimulators (such as riociguat), or PDE-5 inhibitors (such as tadalafil, sildenafil, vardenafil). Due to worries that vericiguat may cause a drop in hemoglobin level, doctors should also refrain from prescribing the medication to patients who have severe anemia. [40]

Blackbox Warning: Vericiguat may harm the developing baby if consumed by a pregnant woman, according to studies on animal reproduction. Mention the potential risk to a fetus to woman who are of childbearing age. Before starting vericiguat therapy, doctors should do pregnancy tests. During treatment and for at least a month following the last dosage of vericiguat, advise females to use contraception. [42]

X. INTERACTIONS

Drug interactions can affect the efficacy of your therapies or put you at risk for serious side effects.[42]

There are 121 drugs known to interact with vericiguat, along with 2 disease interactions, and 1 alcohol/food interaction. Of the total drug interactions, 5 are major, and 116 are moderate.[43]

Aminophylline, dipyridamole, pulmonary hypertension medications (sildenafil, tadalafil, vardenafil), riociguat, and theophylline are a few products that may interact with this medication.[42]

The combination of omeprazole and vericiguat inhibited vericiguat absorption. Vericiguat absorption was similarly reduced by magnesium hydroxide and aluminium hydroxide. According to a medication-drug interaction research, vericiguat is an appropriate treatment for treating patients with heart failure who have many comorbidities that necessitate polypharmacy.

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]

2. **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.

XI. 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.

XII. PATENT

Merck Sharp Dohme owns Verquvo.
Vericiguat is present in Verquvo.
Verquvo is the owner of a total of 6 drug patents, none of which have expired.
The market was given permission to employ Verquvo on January 19, 2021.
Oral dose versions of Verquvo are also offered in tablet form.
There are 213 patent family members for this medication spread throughout 48 nations.[47]

Verquvo may be administered in individuals with symptomatic chronic heart failure and an ejection fraction less than 45% to lower the risk of cardiovascular death and hospitalization for heart failure (hf) after an inpatient stay for hf or the requirement for outpatient iv diuretics. [48] Verquvo is open to drug patent challenges starting on 2025-01-19. Verquvo generics could be made available after November 26, 2032. [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. [50]

2. 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.[51]

3. 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.[52]

XIII. CONCLUSION

Recent clinical studies have revealed that vericiguat has a benefit and is safe in individuals with high-risk HF, with a decreased incidence of mortality from cardiovascular causes or HF hospitalisation. The future placement of vericiguat therapy must be more precisely defined, particularly in view of recent developments in acute and chronic heart failure therapy.

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