NO–sGC–cGMP Pathway

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Verquvo▼(Vericiguat) Prescribing Information is available at the end of this slide deck.

Reporting adverse events and quality complaints

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc.

If you want to report an adverse event or quality complaint, reports can be directed to: Tel: 01182063500 or email: pvuk@bayer.com

Further information is available on the “contact” tab at www.bayer.co.uk.

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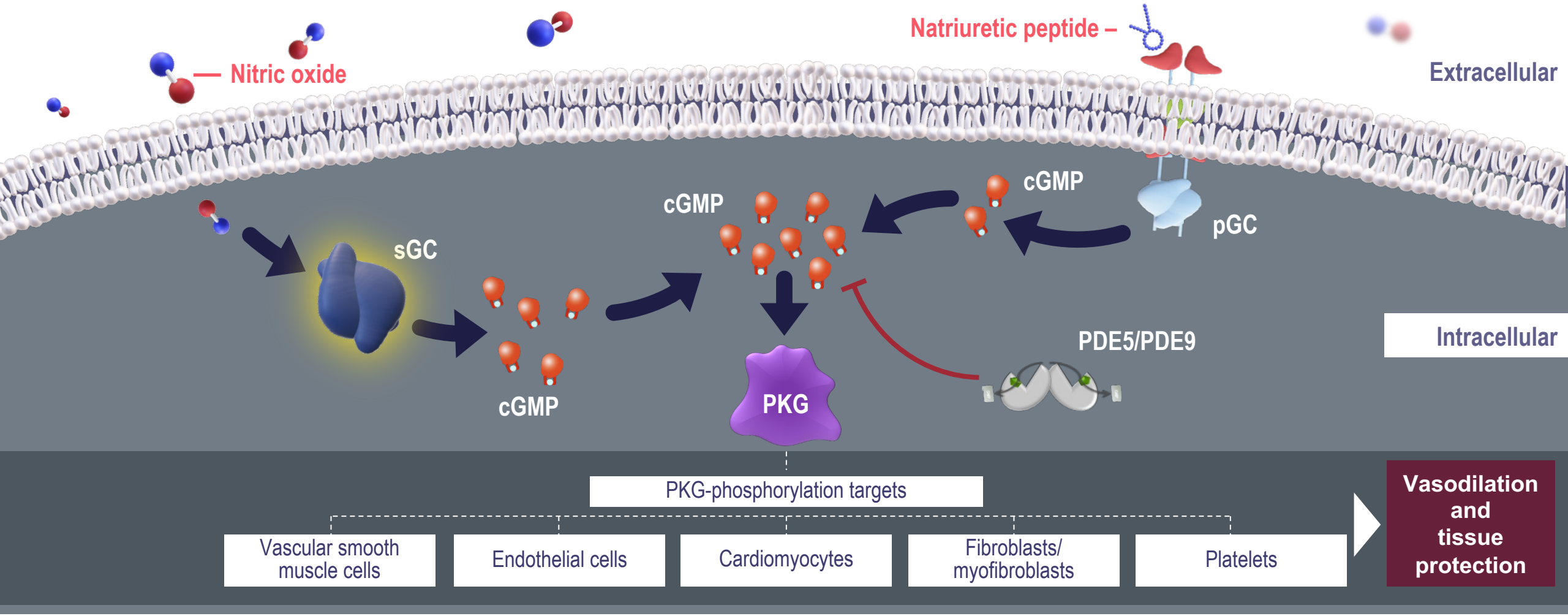
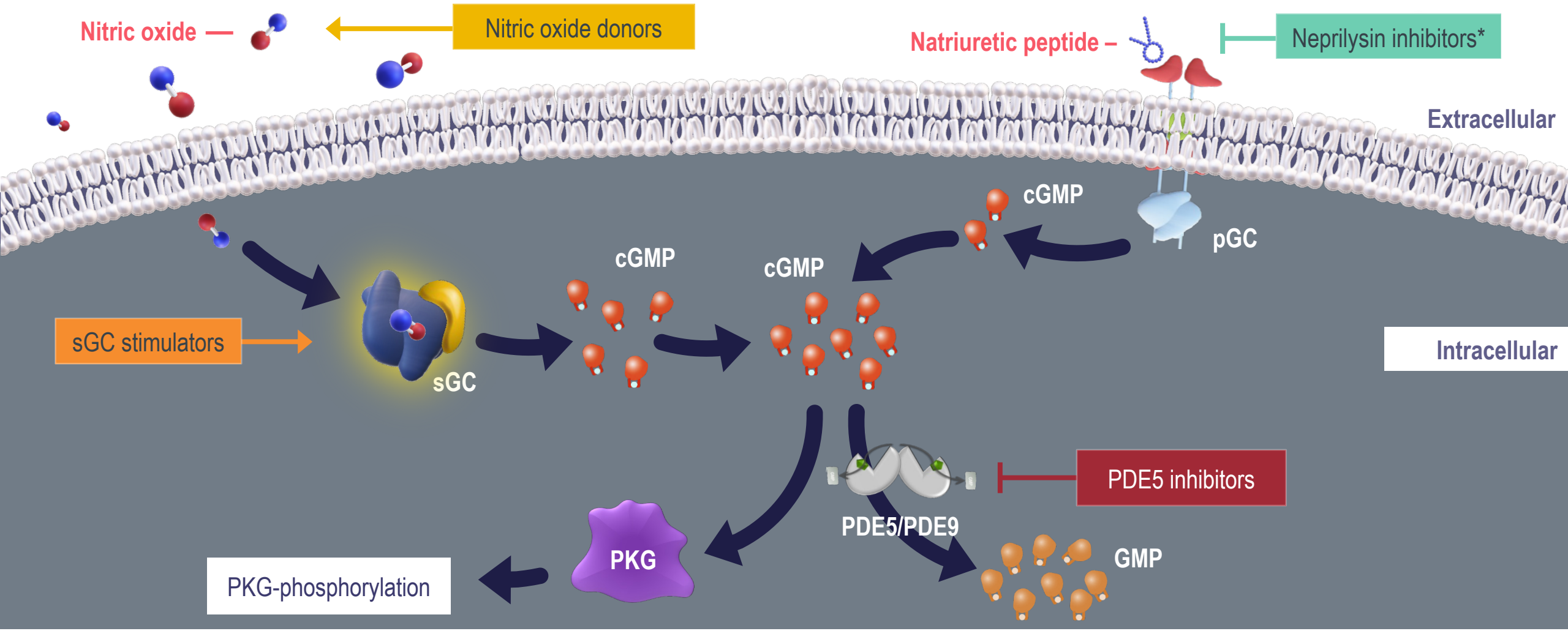
NO–sGC–cGMP Pathway & Role in Regulation of Tissue Function[1–8]



cGMP, cyclic guanosine monophosphate; NO, nitric oxide; PDE5, phosphodiesterase type 5; PDE9, phosphodiesterase type 9; pGC, particulate guanylate cyclase; PKG, protein kinase G; sGC, soluble guanylate cyclase.

1. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123. 2. Boerrigter G et al. *Handb Exp Pharmacol*. 2009:485. 3. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 4. Armstrong PW et al. *JACC Heart Fail*. 2018;6:96. 5. Tsai E et al. *Pharmacol Ther*. 2009;122:216. 6. Sandner P. *Biol Chem*. 2018;399:679. 7. Kim JY et al. *Sci Rep*. 2016;6:36979; 8. Cerra M, Pellegrino D. *Curr Med Chem*. 2007;14:585.

Modulators of cGMP Pathways[1–9]



*Sacubitril/valsartan is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction[10]

1. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 2. Stasch JP and Hobbs AJ. *Handb Exp Pharmacol.* 2009;191:277. 3. Follmann M et al. *Angew Chem Int Ed Engl*. 2013;52:9442. 4. Sandner P. *Biol Chem*. 2018;399:679. 5. Greene S et al. *J Am Heart Assoc*. 2013;2:e000536. 6. Buys ES et al. *Nitric Oxide*. 2018;78:72; 7. Friebe A et al. *Naunyn Schmiedebergs Arch Pharmacol*. 2020;393:287; 8. Yandrapalli S et al. *Ther Adv Cardiovasc Dis.* 2018;12:217; 9. Cerra M, Pellegrino D. *Curr Med Chem.* 2007;14:585 10. Sacubitril/valsartan UK Summary of product characteristics (SmPC) https://www.medicines.org.uk/emc/product/5074/smpc Last accessed May 2022

Verquvo - Pharmacology & Mode of Action

Verquvo Pharmacokinetics & Pharmacodynamics (1)

ADME Profile	
Absorption	• Rapidly absorbed[1] – T_{max} 1hr (fasted) to 4 hr (fed)* 10mg o.d.[2] – Increased bioavailability & reduced variability observed in the fed state relative to the fasted state support administration of Verquvo with food[1] – Absolute bioavailability of Verquvo is 93% when taken with food. Results were comparable when Verquvo was administered orally as a whole tablet or as a crushed tablet in water[2] • Displays dose proportional pharmacokinetics (PK)[3]
Distribution	• Primarily plasma with mean steady-state volume of distribution approximately 44 L in healthy subjects[2] • Highly protein bound (98%, primarily serum albumin)[2] • Plasma protein binding of vericiguat is not altered by renal or hepatic impairment[2]
Biotransformation	• Primarily via glucuronidation by UGT1A9 & to a lesser extent, by UGT1A1 to form an inactive N-glucuronide metabolite[2] • CYP-mediated metabolism is a minor clearance pathway (<5%)[2] • Verquvo is a substrate of P-glycoprotein (P-gp) & breast cancer resistance protein (BCRP) but is not a substrate of organic cation transporter (OCT1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3)[2] • Verquvo is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1/1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K[2]
Elimination	• Mean half-life approx. 22 hrs (range 17.9 – 27 for single & multiple doses)[1] • Following oral administration of radiolabelled Verquvo to healthy subjects, approximately 53% of the dose was excreted in urine (primarily as inactive metabolite) and 45% in faeces (primarily as unchanged drug)[2]

* *Effect of Food :* Administration of Verquvo 10 mg with a high-fat, high-calorie meal increases Tmax from about 1 hour (fasted) to about 4 hours (fed), reduces PK variability, and increases Verquvo AUC by 44% and Cmax by 41% compared with administration in the fasted state. Similar results were obtained when Verquvo was administered with a low-fat, low-calorie meal when compared to administration with a high-fat, high-calorie meal.[2]

ADME, absorption, distribution, metabolism, elimination; Tmax, time to maximum concentration; o.d., once daily; UGT1A9/1A1, uridine 5'-diphospho gluconoronsyltransferase 1A9 & 1A1 respectively; N, nitrogen; CYP, cytochrome P; BSEP, bile salt export pump, MATE1/2K, multi drug & toxin extrusion protein 1 & 2K respectively

1. Boettcher M *et al*. Eur J Clin Pharmacol. 2021; 77(4): 527-537 2. Verquvo UK Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/12775/smpc Last accessed May 2022 3. Boettcher M *et al.* Clin Pharmacokinet. 2021; 60(3): 337-351

Verquvo Pharmacokinetics & Pharmacodynamics (2)

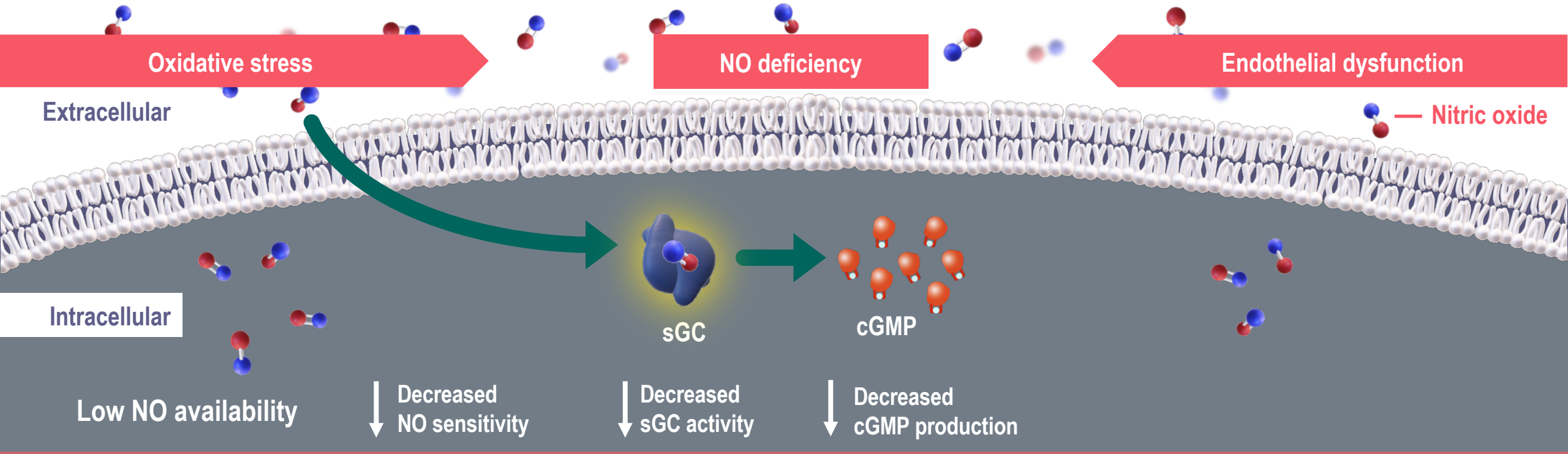
Drug to drug interactions

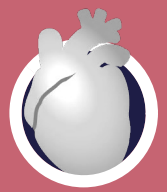
Co-medication	Effect on PK/PD
Sacubitril/valsartan[1]	• No clinically relevant PK/PD interaction
Warfarin[1] & aspirin[1]	• No clinically relevant PK/PD interaction • No dose adjustment of warfarin • No dose adjustment of aspirin
Nitrates[2,3,4]	• No significant effect on BP or HR with SL nitrates (VENICE study) • No significant effect on BP or HR with concomitant long acting nitrates (VISOR study) • Limited experience with concomitant use of vericiguat & long acting nitrates in patients with HF • In patients with HF, concomitant use of short-acting nitrates was well tolerated
Effect of Verquvo on PK (digoxin; midazolam)[5]	• No clinically relevant PK interaction • No dose adjustment of digoxin • No dose adjustment of co-medications metabolized by CYP3A4
Effect of PK on Verquvo (ketoconazole, rifampicin, mefenamic acid)[5]	• No clinically relevant PK interaction • No dose adjustment of Verquvo
PDE5 inhibitors[4]	• Co-administration with sildenafil associated with additional reductions in BP • No dose-dependent trend was observed with the different sildenafil doses • Not recommended in patients with HF due to the potential increased risk for symptomatic hypotension
Proton pump inhibitors (omeprazole), H2-receptor antagonists or antacids (aluminium hydroxide/magnesium hydroxide)[4]	• Co-treatment did not affect Verquvo exposure when Verquvo was taken as directed with food in heart failure patients

1. Boettcher M *et al.* Clin Pharmacokinet. 2021; 60(3): 337-351 2. https://www.ahajournals.org/doi/10.1161/circ.136.suppl_1.19938 Last accessed May 2022
3. Boettcher ESC-HF 2019. Abstract #1184. 4. Verquvo UK Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/12775/smpc Last accessed May 2022
5. Boettcher M *et al.* Clin Pharmacokinet. 2020; 59(11): 1407-1418

PK, pharmacokinetic; PD, pharmacodynamic; BP, blood pressure; HR, heart rate; SL, sublingual

Current therapies do not directly address reduced sGC activity[1-6]





Heart

↑ Progressive myocardial stiffening
↑ Myocardial thickening
↑ Ventricular remodeling
↑ Fibrosis

Vasculature

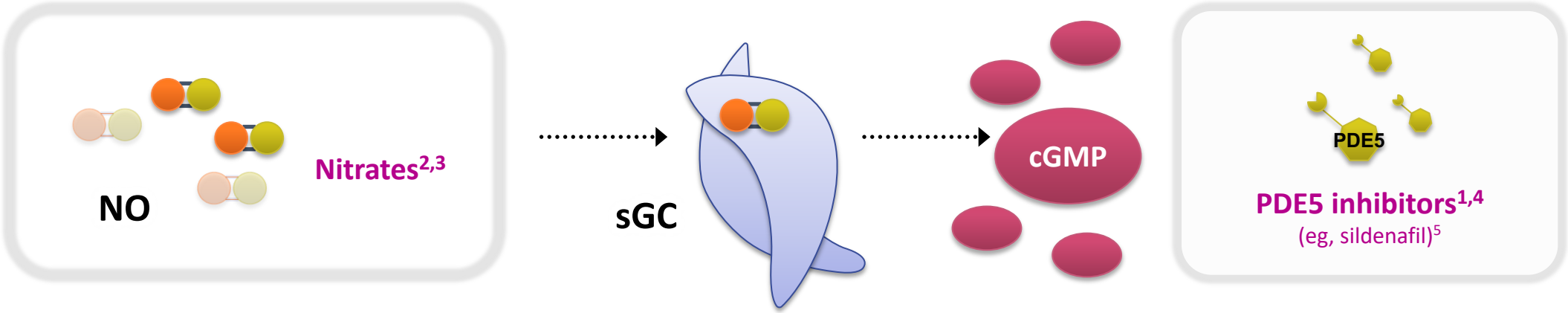
↑ Arterial constriction
↑ Vascular stiffness

Renal system

↑ Na+ and fluid retention
↓ Renal blood flow

1. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123. 2. Boerrigter G et al. *Handb Exp Pharmacol*. 2009;191:485. 3. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247.4. Armstrong PW et al. *JACC Heart Fail*. 2018;6:96-104; 5. Follmann M et al. *J Med Chem* 2017;60:5146; 6. Mathar I et al. *Circulation*. 2018;138:A15553.

Therapies That May Target NO-sGC-cGMP Pathway in HF[1]



MOA	Upstream of NO-sGC-cGMP[2]
Benefit	Improved LV function & exercise capacity in combination with hydralazine[2]
Challenges	• Vascular tolerance to nitrates[3] • Required biotransformation into active NO donors[3] • Aggravation of endothelial dysfunction[3] • Confirmatory data lacking

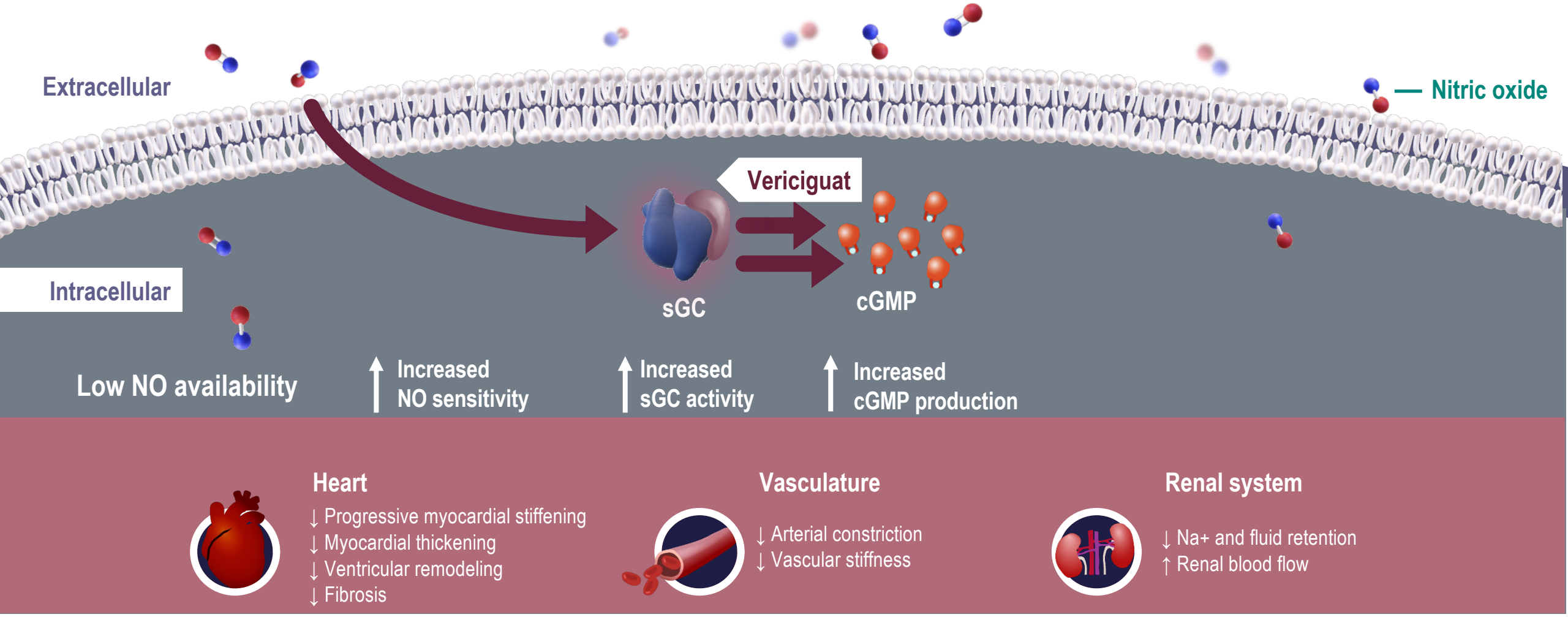
MOA	Downstream of NO-sGC-cGMP[4]
Benefit	Mitigates myocardial remodelling[4]
Challenges	• PDE5 is dependent on NO-sGC activity and cGMP production—often impaired in HF[1] • PDE5 expression is decreased in the myocardium

Impact of nitrates & PDE5 inhibitors is limited & they do not directly stimulate sGC[3,4]

LV, left ventricular; MOA, mode of action

1. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 2. Münzel T et al. *Circulation*. 2011;123(19):2132-2144. 3. Münzel T et al. *Vascul Pharmacol*. 2014;63(3):105-113.
4. Michalak M et al. *Circ Heart Fail*. 2018;11(3):e004813. 5. Franssen C et al. *Heart*. 2016;102:320-330.

sGC Stimulation Targets A Pathway That May Lead to Development & Progression of HF[1–6]



1. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123. 2. Boerrigter G et al. *Handb Exp Pharmacol.* 2009;191:485. 3. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 4. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96-104; 5. Follmann M et al. *J Med Chem* 2017;60:5146; 6. Mathar I et al. *Circulation.* 2018;138:A15553.

Verquvo® (vericiguat) 2.5, 5, 10 mg film-coated tablets
Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5 mg / 5 mg / 10 mg vericiguat tablet. **Indication:** Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy. **Posology & method of administration:** Vericiguat is administered in conjunction with other heart failure therapies. Before starting vericiguat, optimise volume status & diuretic therapy to stabilise patients after the decompensation event, particularly those with very high NT-proBNP levels. ***Adults:*** *Dose titration:* recommended starting dose is 2.5 mg once daily. Double the dose approx. every 2 weeks to reach target maintenance dose of 10 mg once daily, as tolerated by patient. If patient has tolerability issues, temporary down-titration or discontinuation is recommended. Do not initiate treatment in patients with SBP <100 mmHg. If dose is missed, it should be taken as soon as patient remembers on same day of missed dose. Patients should not take 2 doses on the same day. ***Elderly:*** no dose adjustment ***Renal impairment:*** no dose adjustment in patients with eGFR ≥15 mL/min/1.73 m^2 (without dialysis). Treatment not recommended in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis. ***Hepatic impairment:*** no dose adjustment for mild/moderate hepatic impairment; treatment not recommended in patients with severe hepatic impairment. ***Paediatrics:*** Safety & efficacy have not been established. No clinical data available. Undesirable effects were observed on growing bone in non-clinical studies. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients; concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat. **Warnings & precautions (W&P):** Vericiguat may cause symptomatic hypotension. Patients with SBP less than 100 mmHg or symptomatic hypotension at treatment initiation were not studied. The potential for symptomatic hypotension should be considered in patients with hypovolaemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, history of hypotension, or concomitant treatment with antihypertensives or organic nitrates. If patients experience tolerability issues (symptomatic hypotension or SBP less than 90 mmHg), temporary down-titration or discontinuation of vericiguat is recommended. Concomitant use of vericiguat & PDE5 inhibitors, such as sildenafil, has not been studied in patients with heart failure & is therefore not recommended due to the potential increased risk for symptomatic hypotension. This medicinal product contains lactose. **Interactions:** see Contraindications, W&P section and SmPC for full details. **Pregnancy & breast feeding:** No data on use of vericiguat in pregnant women. Animal studies have shown reproductive toxicity in presence of maternal toxicity. As a precautionary measure, vericiguat should not be used during pregnancy & in women of childbearing potential not using contraception. No information regarding presence of vericiguat in human milk, the effects on breasfed infant or milk production. Vericiguat is present in the milk of lactating rats. Risk to a breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from vericiguat therapy, taking into account the benefit of breast-feeding for the child & the benefit of therapy for the woman. **Effects on ability to drive & use machines:** Vericiguat has minor influence on the ability to drive or use machines. When driving vehicles or operating machines it should be taken into account that dizziness may occur occasionally. **Undesirable effects:** *Very common:* hypotension; *Common:* anaemia, dizziness, headache, nausea, dyspepsia, vomiting, gastro-oesophageal reflux disease. **Overdose:** Overdose of vericiguat may lead to hypotension. If necessary, treat symptoms. Vericiguat is unlikely to be removed by haemodialysis due to high protein binding. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *2.5mg* - 14 tablets: £45.78. *5mg* – 14 tablets: £45.78. *10mg* - 28 tablets: £91.56. **MA Number(s):** *Great Britain* – PLGB 00010/0748 (2.5 mg), 00010/0749 (5 mg), 00010/0750 (10 mg); *Northern Ireland* - EU/1/21/1561/001–011 (2.5 mg), EU/1/21/1561/012–022 (5 mg), EU/1/21/1561/023–033 (10 mg). **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD, U.K. Telephone: 0118 206 3000.
Date of preparation: July 2021

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Bayer plc. Tel.: 0118 206 3500, Fax.: 0118 206 3703, Email: pvuk@bayer.com