Riociguat + Claritromycine MFB 1301A

M1 = actieve metaboliet, heeft ongeveer 10-30% van de potentie van riociguat

Onderbouwend	Stof	Effect	Code
SPC + EPAR Adempas	riociguat + claritromycine	riociguat: toename AUC 41% door claritromycine, geen verandering Cmax en renale klaring. M1: toename AUC 19% geen verandering Cmax, afname renale klaring 18%. The data indicate a moderate PK interaction with clarithromycin, a strong inhibitor of CYP3A4 and weak-to-moderate inhibitor of P-gp. The unexpected increase in M1 exposure following CYP3A4 inhibition is probably a result of the multi-pathway biotransformation. These results were not considered to have any clinically relevant consequences.	1A

Overig	Stof	Effect
SPC Adempas	riociguat	rubriek Overdosering: onbedoelde overdosering is gemeld met totale dagdoses van 9 tot 25 mg riociguat gedurende 2 tot 32 dagen. De bijwerkingen waren vergelijkbaar met de bijwerkingen die bij lagere doses worden gezien.
Prescribing Information USA Adempas http://labeling.bayerhealthcare.com/html/products/pi/Adempas_PI.pdf, geraadpleegd 23-06-2015	riociguat + claritromycine	advies CYP3A4 inhibitors (claritromycine): no dose adjustment.
SPC + Prescribing Information USA Adempas	riociguat	riociguat pharmacokinetics are dose proportional from 0.5 to 2.5 mg. Inter-individual variability of riociguat AUC across all doses is approximately 60%, and within-subject variability is approximately 30%.
EPAR Adempas	riociguat	the dose range between 1.0 mg and 2.5 mg covers the range from minimum effective dose to maximum tolerated dose in healthy volunteers. Dose titration is necessary in order to improve tolerability (e.g. hypotension) and also takes into consideration the large inter-individual variability in PK. The reported adverse event profile is in line with the mechanism of action as a vasodilator; the most common drug related AE are headache, dyspepsia, dizziness and nausea and hypotension. Results are comparable to those reported with PDE5 inhibitors. The rate of reported AE declines in the long term extensions, which probably indicates some adaptation to the haemodynamic changes induced by riociguat.

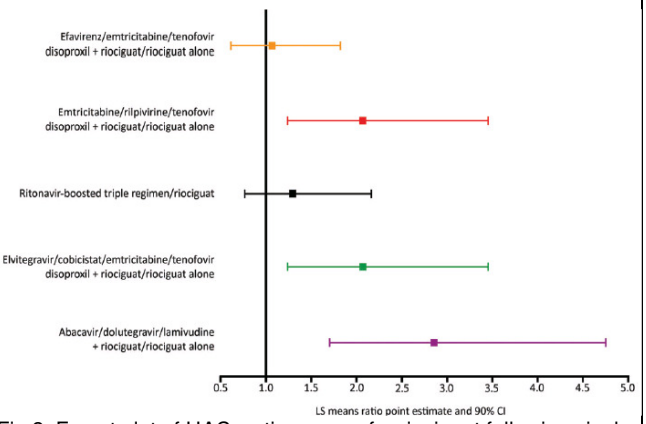
Opmerkingen
Stockley, Hansten, Pubmed, www.clinicaltrials.gov: geen aanvullende informatie.

Risicogroep	

	Interactie	Actie	Datum
Beslissing WFG	Ja	Nee	22 september 2015

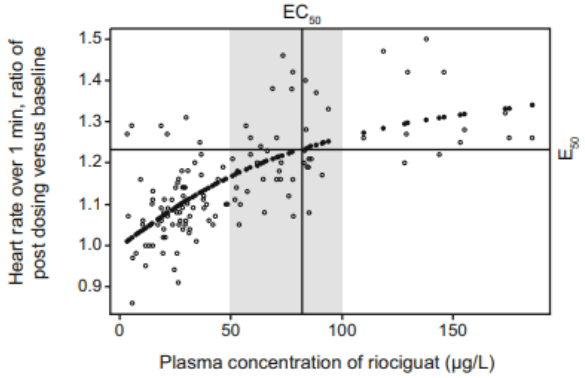
Riociguat + Ritonavir B

M1 = actieve metaboliet, heeft ongeveer 10-30% van de potentie van riociguat

Onderbouwend	Stof	Effect	Code
DeJesus E. Pulm Circ 2019;9:1-10. doi: 10.1177/2045894019848644 cART : abacavir/dolutegravir/lamivudine (Triumeq) elvitegravir/cobicistat/emtricitabine/TDF (Stribild) emtricitabine/rilpivirine/TDF (Complera (Eviplera)) ritonavir-geboost triple regimes efavirenz/emtricitabine/TDF (Atripla) TDF= tenofovir disoproxil	riociguat + cART abacavir cobicistat rilpivirine **ritonavir** controle abacavir	AUC riociguat was het hoogst bij gebruik van abacavir (/dolutegravir/lamivudine), dan elvitegravir/cobicistat (/emtricitabine/TDF), dan rilpivirine (/emtricitabine/TDF), dan ritonavir-geboost triple regime, dan efavirenz/emtricitabine/TDF ('geen effect') Cmax riociguat vergelijkbaar over 5 cART groepen. AUC riociguat ca. 3x hoger bij abacavir dan bij efavirenz/emtricitabine/TDF (→GIC: dat halen wij niet uit onderstaande getallen:) riociguat AUC (µg*h/l) ratio abacavir 255 2.7 cobicistat 185 1.9 rilpivirine 185 1.9 ritonavir-geboost regime 116 1.2 efavirenz/emtricitabine/TDF 95.5 1* (*geen effect= AUC zelfde als met historische data van riociguat alleen)  Fig.2: Forest plot of UAC vs time curve for riociguat following single dose riociguat in adults with HIV on cART compared with when given alone in healthy volunteers. Regime: riociguat 0.5 mg 1x bij 40 HIV-geïnfecteerden op cART (n = 8 in each arm); data vergeleken met historische data 40 gezonde vrijwilligers op dezelfde dosis riociguat alleen. Auteurs: the study did not include a riociguat alone control arm, as this would not be ethically acceptable in HIV-infected individuals. →GIC: riociguat is substraat voor CYP1A1 (hoofdroute); abacavir remt CYP1A1; cobicistat en RTV remmen CYP3A4; rilpivirine remt P-gp; de overige componenten van cART hebben geen relevante invloed op CYP; efavirenz induceert vooral, maar is in vitro ook een remmer van CYP3A4, CYP2C19 en CYP2C9.	3A

SPC Adempas Procedural steps after authorisathion 28/02/2019 https://www.ema.europa.eu/en/medicines/human/EPAR/adempas#assessment-history-section	riociguat + cART	↑AUC riociguat 2.6x en Cmax 1.2x door cART Regime: riociguat 0.5 mg 1-malig, verschillende cART bij hiv-patiënten → GIC: getallen uit DeJesus 2019 in vitro remden abacavir, rilpivirine, efavirenz, ritonavir, cobicistat en elvitegravir CYP1A1 en het metabolisme van riociguat in de vermelde volgorde met abacavir als de sterkste remmer; cobicistat, ritonavir, atazanavir en darunavir zijn ook CYP3A-remmers; bovendien remt ritonavir P-gp. Study 17957: → GIC: getallen uit DeJesus 2019 ↑AUC riociguat 2.6x door Triumeq (oa abacavir); ↑AUC 1.88x door Complera (oa rilpivirine) ↑AUC 1.88x door Stribild (oa cobicistat) ↑AUC 1.18x door ritonavir boosted protease inhibitors In vitro data showed that the increase is mainly due to inhibition of CYP1A1 and partial to CYP3A4.	1A

Overig	**Stof**	**Effect**
SPC Adempas	riociguat + sterke CYP- en P-gp-/BCRP-remmers van meerdere routes	monitor op tekenen en symptomen van hypotensie; overweeg verlaagde aanvangsdosis riociguat van 0.5 mg 3dd bij gebruik van sterke CYP- (met name CYP1A1 en CYP3A4) en P-gp/BCRP-remmers van meerdere routes, bijvoorbeeld als onderdeel van cART; overweeg dosisverlaging bij gebruik van doses ≥ 1.0 mg bij tekenen of symptomen van hypotensie De klaring van riociguat verloopt voor het grootste deel via CYP450 gemedieerde (CYP1A1, CYP3A4, CYP3A5, CYP2J2) oxidatieve metabolisatie, directe uitscheiding van onveranderd riociguat via de gal of de feces en renale uitscheiding van onveranderd riociguat via glomerulaire filtratie.
Jungmann NA. Expert Opin Drug Metab Toxicol 2019;15:975-84. doi: 10.1080/17425255.2019.1681968. *Niet in bezit* cART: Triumeq (oa abacavir), Complera (oa rilpivirine), Atripla (efavirenz/emtricitabine/TDF), Stribild (oa cobicistat), and 2 ritonavir-boosted regimens	riociguat + cART	in vitro: the predicted increase in AUC riociguat was highest with Triumeq® followed by Complera®, Atripla®, Stribild®, and the ritonavir-boosted regimens → GIC: komt grotendeels overeen met DeJesus 2019, behalve de plek van Atripla. Methods: the inhibitory potential of the components of cART on riociguat metabolism were evaluated in recombinant human CYP1A1 and CYP3A4 as well as in human hepatocytes exhibiting both CYP1A1 and CYP3A4 activity. Conclusion: the potent CYP1A1 inhibitor abacavir had the greatest impact on riociguat metabolic clearance. The impact of comedications containing only strong CYP3A4 inhibitors e.g. ritonavir was less pronounced, suggesting a benefit of riociguat over PAH-targeting medications with contraindications for use with strong CYP3A4 inhibitors. Further experiments in human hepatocytes confirmed CYP1A1 to be the predominant enzyme in the metabolic clearance of riociguat.
SPC Norvir	riociguat + ritonavir	geen getallen; “spiegel riociguat kan verhoogd zijn door CYP3A en P-gp remming door ritonavir. Combinatie niet aanbevolen.”
EPAR Adempas	riociguat dynamiek	p.42+46: 1.0 - 2.5 mg covers the range from the minimum effective dose to the maximum tolerated dose in healthy volunteers based on the effects seen for heart rate, blood pressure and plasma renin activity. Therefore, 1.0 mg was selected as the starting dose and 2.5 mg as the maximum dose in the clinical phase II study 12166. 5 mg riociguat is not well tolerated due to the associated drop in blood pressure.

Frey R. Clin Pharmacokinet 201857:647–61. https://doi.org/10.1007/s40262-017-0604-7.	riociguat kinetiek en dynamiek	clinical pharmacokinetic and pharmacodynamic profile of riociguat. -rapid absorption, almost complete bioavailability, and dose-proportional exposure which correlates with its pharmacodynamic effects.  **Fig. 3** Relationship between riociguat plasma concentration and heart rate over 1 min, described using a sigmoid E_{max} model. Relative change in heart rate = 1 + [(0.47 × Cp)/(82.3 + Cp)]. The shaded area represents the effective concentrations as characterized using the sigmoid E_{max} model. *Cp* riociguat plasma concentration, EC_{50} half maximal effective concentration, E_{50} half of E_{max}, E_{max} estimated maximal effect. Reproduced from Frey R, et al. J Clin Pharmacol. 2008;48(8):926–34, with permission. Copyright © 2008 John Wiley & Sons, Inc. Riociguat exposure variability has been addressed by use of an individual dose-adjustment scheme at initiation. Single doses of 1 mg or 2.5 mg caused clinically relevant, concentration-dependent decreases from baseline in mean pulmonary arterial pressure, pulmonary vascular resistance (PVR), SBP, and systemic vascular resistance (SVR), as well as an increase in cardiac index. Heart rate was significantly increased from baseline by 2.5 mg but not 1 mg. Both doses of riociguat showed greater potency and duration of action than inhaled NO in reducing PVR, SBP, and SVR, and increasing cardiac index. The 2.5 mg dose of riociguat reduced mean pulmonary arterial pressure to a greater extent than NO. - single dose 1 and 2.5 mg: AUC 602 resp. 1411 mcg*h/L (in the proof-of-concept study); - multiple doses 0.5–2.5 mg 3dd (steady state): AUC 1174 mcg*h/L in patients with PAH and 1433 mcg*h/L in patients with CTEPH (pivotal phase III trials).

Opmerkingen
Werkgroep Interacties & MFB's 4-7-22: + ritonavir (actie Nee; abacavir, cobicistat, rilpivirine actie Ja).

Stockley: geen aanvullende informatie.

Risicogroep	

	Interactie	**Actie**	**Datum**
Beslissing WG IA	Ja	Nee	4 juli 2022