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Switching to Rezolsta®/Prezcobix® (darunavir+cobicistat) or Evotaz® (atazanavir+cobicistat)

- Rezolsta/Prezcobix and Evotaz are once daily fixed dose combinations (FDCs) of darunavir (DRV) 800 mg with cobicistat 150 mg, and atazanavir (ATV) 300 mg with cobicistat 150 mg respectively, and are indicated in combination with other antiretroviral medicinal products for the treatment HIV-1 infection in adults aged 18 years or older*.
- There are clinical differences between ritonavir (r) and cobicistat boosted protease inhibitors (PIs) which need to be considered prior to switch:
  - Cobicistat's drug interactions differ in that, unlike ritonavir, cobicistat does not induce glucuronidation (UGT1A1) or some CYP enzymes. Consequently, switching from PI/r to PI/cobicistat may increase levels of some drugs metabolised via these routes and require monitoring and/or dose modification (see table). Alternatively, consider remaining on ritonavir-boosted PI.
  - Cobicistat decreases estimated creatinine clearance by average 10 ml/min due to inhibition of tubular secretion of creatinine. This does not affect the actual glomerular filtration rate (GFR).
- Although bioequivalent to DRV+r 800+100 mg, DRV Cmin reduces by ~25-30% with cobicistat, but remains above the IC50 for DRV wild type virus. This may be relevant for some cohorts.
- The guidance below addresses key differences when switching from DRV+r or ATV+r to the FDCs and should be used in addition to the Product Labels and www.hiv-druginteractions.org.

Darunavir+ritonavir to Rezolsta/Prezcobix

Rezolsta/Prezcobix is NOT RECOMMENDED* if:

- Patient requires DRV 600 mg twice daily.
- Taking any of the following, which are not recommend with Rezolsta/Prezcobix but may be used with DRV+r (with dose adjustment to twice daily for some drugs):

ARVs:	Anti-convulsants:	Other:
Efavirenz	Carbamazepine	Bosentan
Etravirine	Phenobarbital	Dabigatran
Nevirapine	Phenytoin	OBV/PTV/r ± DSV (AbbVie "2D/3D")*†

- There are any DRV resistance associated mutations.
- eGFR <70 ml/min when co-administered with medicines that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
- Patients aged <18 years where the safety and efficacy of Rezolsta/Prezcobix has not been established.

Rezolsta should be used with CAUTION* when:

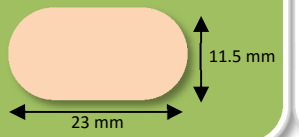
- There are concerns about lower DRV exposure (compared to DRV+r) such as:
  - Protease inhibitor monotherapy.
  - Pregnancy, including if actively planning to conceive.
  - Where DRV is part of a regimen for patients with HIV encephalopathy or in patients with CSF HIV RNA escape.
- Taking any other medicines, particularly those listed in the table. Conduct full medicines review.
- Any combinations other than 2 NRTIs + Rezolsta/Prezcobix as these have not been studied.

Specific counselling points for Rezolsta/Prezcobix:

- The recommended dosing regimen is one tablet of Rezolsta/Prezcobix taken once daily with food.
- Use up all Prezista (DRV) and ritonavir prior to switch to Rezolsta.
- There may be a requirement to switch away from the fixed dose combination when a generic darunavir become available.

Patient factors for Rezolsta/Prezcobix:

- The Rezolsta/Prezcobix tablet is larger than other ARVs and may not be acceptable to some. Ensure the patient has seen the tablet prior to leaving clinic.



Atazanavir+ritonavir to Evotaz

Evotaz is NOT RECOMMENDED* if:

- Patient requires ATV 400 mg daily, with or without pharmacokinetic booster.
- Taking combined hormonal contraceptives, including those containing 30 µg of ethinylestradiol due to potential increase in estrogen exposure. Alternative forms of contraception should be considered.
- Taking any of the following, which are not recommend with Evotaz but may be used with ATV+r:

ARVs:	Anti-convulsants:	Other:
Efavirenz	Carbamazepine	Bosentan
Etravirine	Phenobarbital	Dabigatran
	Phenytoin	OBV/PTV/r ± DSV (AbbVie "2D/3D")*†

- There are any ATV resistance associated mutations.
- eGFR <70 ml/min when co-administered with medicines that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
- Patients aged <18 years of age where the safety and efficacy of Evotaz has not been established.

Evotaz should be used with CAUTION* when:

- Pregnant, including if actively planning to conceive due to a lack of data.
- Taking any other medicines, particularly those listed in the table. Conduct full medicines review.
- Any combinations other than 2 NRTIs + Evotaz as these have not been studied.

Specific counselling points for Evotaz:

- The recommended dosing regimen is one tablet of Evotaz taken once daily with food.
- Use up all Reyataz (ATV) and ritonavir prior to switch to Evotaz.
- There may be a requirement to switch away from the fixed dose combination when a generic atazanavir becomes available.

*Consult Product Label for country-specific full indications, cautions, and contraindications.

† 2D = OBV/PTV/r (Viekirax®, Technivie®); 3D = OBV/PTV/r + DSV (Viekirax® + Exviera®, Holkira®, Viekira Pak®, Viekira XR®). Note, OBV/PTV/r ± DSV can be administered with DRV or ATV alone (i.e. without cobicistat or additional ritonavir).

Monitoring considerations for both Rezolsta/Prezcobix and Evotaz:

- Consider additional monitoring post switch for those with identified "cautions" or other clinical indications.
- Serum creatinine is expected to increase with a resulting reduction in eGFR of ~10 ml/min. Typically this plateaus after 4 weeks of cobicistat-based ART. If a further change in eGFR is observed, or other renal markers change, this should prompt review.
- Advise GP/primary care physician and other health care professionals of the change including interpretation of eGFR and impact on non-ARVs.

This document is intended as a guide for healthcare professionals switching patients from Prezista® tablets or Reyataz® capsules with ritonavir to Rezolsta®/Prezcobix® or Evotaz® respectively. Full prescribing accountability is the responsibility of the prescriber.

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Effect on key drug-drug interactions of switching from ritonavir- to cobicistat-boosted DRV or ATV

(Refer to Product Labels and/or www.hiv-druginteractions.org for full list of DDIs)

Drug class	Non-ARV Drug	Potential impact of switch on non-ARV	Recommendations *In all cases review risks versus benefit of switch, and liaise closely with other prescribers*
Analgesics	Methadone	Exposure ↑	Consider counselling patient on potential need for reduction in methadone dose. Advise methadone prescriber of potential for dose modification.
	Diamorphine, morphine, hydromorphone, pethidine	Exposure ↑	Consider dose reduction and re-titration and/or monitor for signs of opiate toxicity.
	Dihydrocodeine	Unclear, may ↑ or remain unchanged	Counsel patient that may need to re-titrate dose.
Anti-microbials	Atovaquone, proguanil, sulfadiazine	Exposure ↑	Monitor for side effects.
	Rifabutin	Unclear	Caution or avoid; Consult HIV/TB co-infection guidelines.
Anticoagulants	Warfarin, acenocoumarol, eltrombopag	Exposure ↑	Liaise with anti-coagulant prescriber prior to switch. For warfarin & acenocoumarol check INR within one week of switch. For eltrombopag monitor impact on platelets.
Anti-convulsants	Lamotrigine, valproate	Exposure ↑	Consider dose reduction if currently exceeding maximum recommended dose; liaise with prescriber.
	Carbamazepine, phenytoin	(↓PI & ↓Cobicistat)	Not recommended with Rezolsta/Prezcobix or Evotaz due to reduced PI and cobicistat exposure.
Anti-diabetics	Metformin	Exposure ↑	Careful patient monitoring and dose adjustment of metformin is recommended.
	Gliclazide, glimepiride, glipizide, rosiglitazone, tolbutamide	Exposure ↑	Advise patient to check BMs frequently 1-2 weeks post switch and monitor for hypoglycaemia.
	Nateglinide	Unclear, may ↑ or remain unchanged	Advise patient to check BMs frequently 1-2 weeks post switch and monitor for hypoglycaemia.
Anti-hypertensives	Losartan, labetalol, irbesartan, torasemide	Exposure ↑	Counsel patient to monitor for hypotensive episodes and consider dose titration.
Anti-fungals	Voriconazole	Exposure ↑	Voriconazole levels may increase. PI and cobicistat exposure may also increase.
Anti-Parkinson's agents	Apomorphine, rasagiline, ropinirole	Exposure ↑	Monitor for side effects and consider dose adjustment.
Beta-Blockers	Carvedilol	Unclear, may ↑ or remain unchanged	Counsel patient to monitor for hypotensive episodes and bradycardia and consider dose titration.
Bronchodilators	Theophylline	Exposure ↑	Consider theophylline baseline (pre-switch) drug level and repeat levels. Monitor for signs of toxicity such as vomiting, agitation, restlessness, dilated pupils and sinus tachycardia.
Contraceptive & HRT	Estrogen-based contraceptives: estradiol, ethinylestradiol, norethisterone	Exposure ↑	Avoid coadministration as no dosing recommendations can be made on the use of Rezolsta/Prezcobix or Evotaz (unlike ATV/r) with contraceptives or HRT. Consider alternative forms of (non-hormonal) contraception.
Cytotoxics	Anastrozole	Unclear, may ↑ or remain unchanged	Review risk versus benefit of change.
	Dacarbazine, droloxifene, epirubicin, formestane, procarbazine	Exposure ↑	Careful monitoring for signs of toxicity
Hepatitis C DAAs	Ombitasvir/Paritaprevir/r ± DSV (AbbVie "2D/3D")†	Exposure ↑	Rezolsta/Prezcobix and Evotaz are contraindicated with ombitasvir/paritaprevir/r ± dasabuvir.
Immuno-suppressants	Mycophenolate	Exposure ↑	Review risk versus benefit of change.
	Tacrolimus, ciclosporin, sirolimus	Unknown	An effect is unlikely, however, close monitoring of the immunosuppressant is recommended.
Mental health	Olanzapine	Exposure ↑	Consider dose reduction if currently exceeding maximum recommended dose. Write to mental health provider as may require monitoring and dose modification.
	Bupropion, paroxetine, sertraline	Exposure ↑	Counsel patient about potential for side effects.
	Duloxetine	Exposure ↑	Levels may significantly increase compared to PI/r. Write to prescriber and advise of need to monitor and dose reduction of duloxetine, especially if currently exceeding maximal dosing.

† 2D = OBV/PTV/r (Viekirax®, Technivie®); 3D = OBV/PTV/r + DSV (Viekirax® + Exviera®, Holkira®, Viekira Pak®, Viekira XR®)

There is a lack of data about the magnitude or clinical significance of any changes.

Table adapted from Marzolini et al (J Antimicrob Chemother 2016; 71: 1755–1758), Rezolsta®/Prezcobix® and Evotaz® Product Labels, and www.hiv-druginteractions.org.

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