Use of Apixaban with Strong CYP3A4 and P-gp Inhibitors

Indications and dosing

- Apixaban is a direct oral anticoagulant (DOAC) which inhibits factor Xa thereby blocking the coagulation cascade.
- Apixaban is indicated for the prevention of stroke and blood clots in individuals with non-valvular atrial fibrillation. Apixaban is also used for the treatment and prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) as well as the prevention of venous thromboembolic events (VTE) after knee or hip replacement surgery.
- The dose of apixaban depends on the indication, age of the patient, serum creatinine and body weight [1, 2].

Indication	Dose
Prevention of stroke and blood clots in case of atrial fibrillation	5 mg twice daily *OR* 2.5 mg twice daily in the presence of 2 of the following factors: • age ≥80 years • body weight ≤60 kg • serum creatinine >1.5 mg/dL or 133 µmol/L
Treatment of DVT/PE	10 mg twice daily for the first 7 days then 5 mg twice daily
Prevention of DVT/PE	2.5 mg twice daily after at least 6 months of DVT/PE treatment
Prophylaxis of DVT following hip/knee surgery	2.5 mg twice daily for 35 days after hip surgery 2.5 mg twice daily for 12 days after knee surgery

Metabolism and elimination

- Apixaban is metabolized mainly by CYP3A4/5 (~25%) and to a lesser extent by CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2J2.
- Renal excretion accounts for approximately 27% of total clearance.
- Apixaban is a substrate of P-gp and BCRP.

Interactions with strong inhibitors of CYP3A4 and P-gp

- Medications that inhibit CYP3A4 and P-gp can increase the exposure of apixaban and the associated risk of bleeding.
- Coadministration of apixaban (10 mg single dose) with ketoconazole (400 mg once daily), a strong inhibitor of CYP3A4 and P-gp, increased apixaban AUC and Cmax by 99% and 62% (n=18) [3].
- The European product label for apixaban does not recommend the use of strong inhibitors of CYP3A4 and P-gp [1], whereas, the American product label gives the option to use apixaban at a dose reduced by 50% [2].
- There is growing evidence that dose-reduced apixaban can be safely administered concurrently with ritonavir- or cobicistat-containing regimens.

Use of Apixaban with Strong CYP3A4 and P-gp Inhibitors

Case reports of administration with ritonavir or cobicistat

- A 73-year-old man with a history of atrial fibrillation on darunavir/ritonavir (800/100 mg twice daily) did not suffer thrombus or bleeding on treatment with apixaban at 2.5 mg twice daily as recommended by the US Prescribing Information in the presence of ritonavir [4].
- No adverse outcomes were reported in six individuals on ritonavir- or cobicistat-containing regimens and receiving a reduced dose of apixaban as detailed in the table below [5].

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Medical History	HIV, HCV, T2DM, NSTEMI	HIV, HTN, COPD, CKD III	HIV, CAD, AF	HIV, HCV, T2DM, HTN	HIV, HTN, prior VTE, PVD	HIV
ARVs	**LPV/r** + 3TC + ABC	**DRV/r** + 3TC + ABC	**DRV/r** + ETV + RAL	**DRV/r** + ETV + RAL	**EVG/c**/F/TAF + **DRV**	**ATV/r** + 3TC + ABC
DOAC Indication	Acute VTE	Acute VTE	AF	Acute VTE	Acute VTE	Acute VTE
Apixaban Dose (twice daily)	10 mg ×4 doses, then 2.5 mg	5 mg x 7 days, then 2.5 mg	2.5 mg indefinitely	10 mg ×7 days, then 2.5 mg	5 mg ×7 days, then 2.5 mg	10 mg ×7 days, then 5 mg ×7 days, then 2.5 mg
Laboratory values	Hgb 8.7 g/dL CrCl 35 mL/min	Hgb 11.7 g/dL CrCl 60 mL/min	Hgb 13.3 g/dL CrCl 65 mL/min	Hgb 9.9 g/dL CrCl <15 mL/min	Hgb 16.1 g/dL CrCl 65 mL/min	Hgb 11.4 g/dL CrCl >100 mL/min
Adverse Events	Surgical site bleed while on 10 mg. No adverse events with 2.5 mg	No adverse events	No adverse events	No adverse events	No adverse events	No adverse events

T2DM: type 2 diabetes mellitus; NSTEMI: non-ST elevated myocardial infarction; HTN: hypertension; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; AF: atrial fibrillation; VTE: venous thromboembolism; PVD: peripheral vascular disease; Hgb: haemoglobin; CrCl: creatinine clearance per Cockcroft–Gault

Dose adjustments with strong inhibitors of CYP3A4 and P-gp

- Based on the case reports and in line with the American product label, the following dose adjustments could be applied when administering apixaban with strong inhibitors of CYP3A4 and P-gp:

Indication	Dose with strong CYP3A4 and P-gp inhibitors
Prevention of stroke and blood clots in case of atrial fibrillation	2.5 mg twice daily Avoid strong inhibitors if already on 2.5 mg twice daily
Treatment of DVT/PE	5 mg twice for the first 7 days then 2.5 mg twice daily
Prevention of DVT/PE	The reduced dose of apixaban in this indication prevents coadministration of strong inhibitors
Prophylaxis of DVT following hip/knee surgery	The reduced dose of apixaban in this indication prevents coadministration of strong inhibitors

Notes: Ritonavir and cobicistat cause a mechanism based inhibition of CYP3A4 which takes several days to resolve. The full dose of apixaban should be reinstated 3 days after the last administration of a boosted regimen.

Apixaban does not need to be adjusted in presence of moderate CYP3A4 and P-gp.

References

1. Eliquis (apixaban) *Summary of Product Characteristics*, Bristol-Myers Squibb / Pfizer, May 2023 (accessed March 2024).
2. Eliquis (apixaban) *US Prescribing Information*, Bristol-Myers Squibb /Pfizer, April 2021 (accessed March 2024).
3. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Frost CE, Byon W, Song Y, et al. *Br J Clin Pharmacol. 2015, 79(5):838-46*.
4. Use of apixaban in atrial fibrillation with ritonavir-boosted antiretroviral therapy: a case report. Lomakina V, Sozio SJ, Tekle J. *J Pharm Pract. 2023, 36(3):728-732*.
5. Ritonavir- or cobicistat-boosted antiretroviral therapy and direct oral anticoagulants: A case for apixaban. Nisly SA, Stevens BN. *Int J STD AIDS. 2019, 30(7):718-722*.