TROMBOPROFILASSI NEI PAZIENTI AMBULATORIALI SOTTOPOSTI A CHEMIOTERAPIA

- La tromboprofilassi nei pazienti ambulatoriali sottoposti a chemioterapia non è raccomandata di routine, ma deve essere considerata in pazienti selezionati ad alto rischio (Korana > 3) vedi score.
- I pazienti con mieloma multiplo che ricevono antiangiogenetici con chemioterapia e desametasone devono essere profilassati.
- I pazienti con neoplasia devono essere periodicamente rivalutati per il rischio di malattia tromboembolica.
- Gli oncologi/ematologi devono educare I pazienti ariconoiscere segni o sintomi di TVP.

- Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014 J Clin Oncol. 2015 Feb
- Linee guida AIOM 2016, tromboembolismo venoso nei pazienti con tumori solidi

Scheda Profilassi Trombo-Embolia Venosa (TEV)
"Score Korana"

Nome, Cognome e data di nascita ……..

Unità Operativa …….. Cartella Clinica ……

Data di ricovero ……

Valutazione del rischio			Score
Sede Tumore	stomaco, pancreas	altissimo	**2**
	polmone, tumori ginecologici, vescica, testicolo, linfoma	alto	**1**
Piastrine pre-terapia	> 350.000		**1**
Emoglobina (Hgb)	< 10 g/dl		**1**
Leucociti pre-terapia	> 11.000		**1**
BMI	> 35 Kg / m^2		**1**

O uso di EPO

Rischio trombo embolico: basso - intermedio score 1 - 2
Rischio trombo embolico: elevato score ≥ 3

Paziente a rischio: BASSO ☐ INTERMEDIO ☐

ALTO ☐ ALTISSIMO ☐

Firma del Sanitario

……

✓ Regimi di chemioterapia contenenti:

- platino /cisplaltino/carboplatino
- gemcitabina
- associazione dei 2 farmaci

→ aumentano rischio trombotico (vedi **PROTECHT** score)

✓ In pz con masse Bulky che comprimono i vasi e rallentano il flusso deve essere eseguita profilassi.

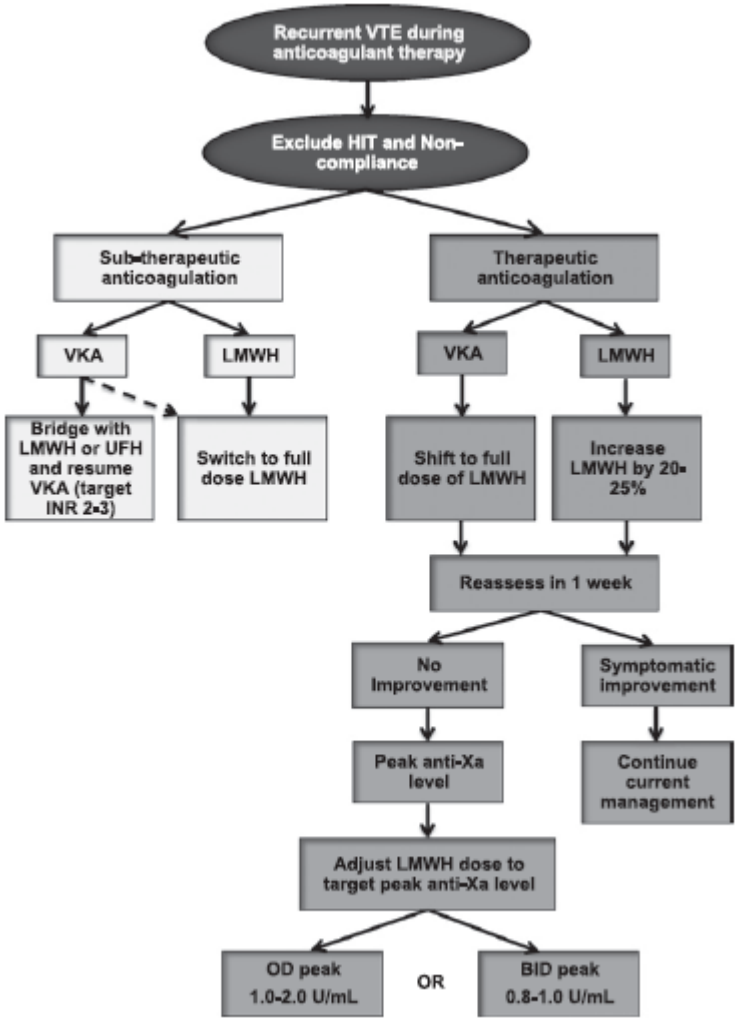
Legge 648/96
Prescrivibilità di EBPM come farmaci «off-label»

Le EBPM sono prescrivibili come farmaci «off-label» per l'utilizzo nella profilassi delle trombosi venose profonde in pazienti oncologici ambulatoriali a rischio (KORANA > 3)[con condizione che l'indicazione sia posta dallo specialista ematologo o oncologo]

- prescrizione mediante piano terapeutico redatto dello specialista ematologo o oncologo

- dispensazione presso i Servizi Farmaceutici dello specialista prescrittore o di afferenza dell'assistito, sulla base del distretto di sua appartenenza

Recurrent VTE in cancer



Blood. 2013;122(14):2310-2317

VTE in pazienti trombocitopenici

Blood. 2013;122(14):2310-2317

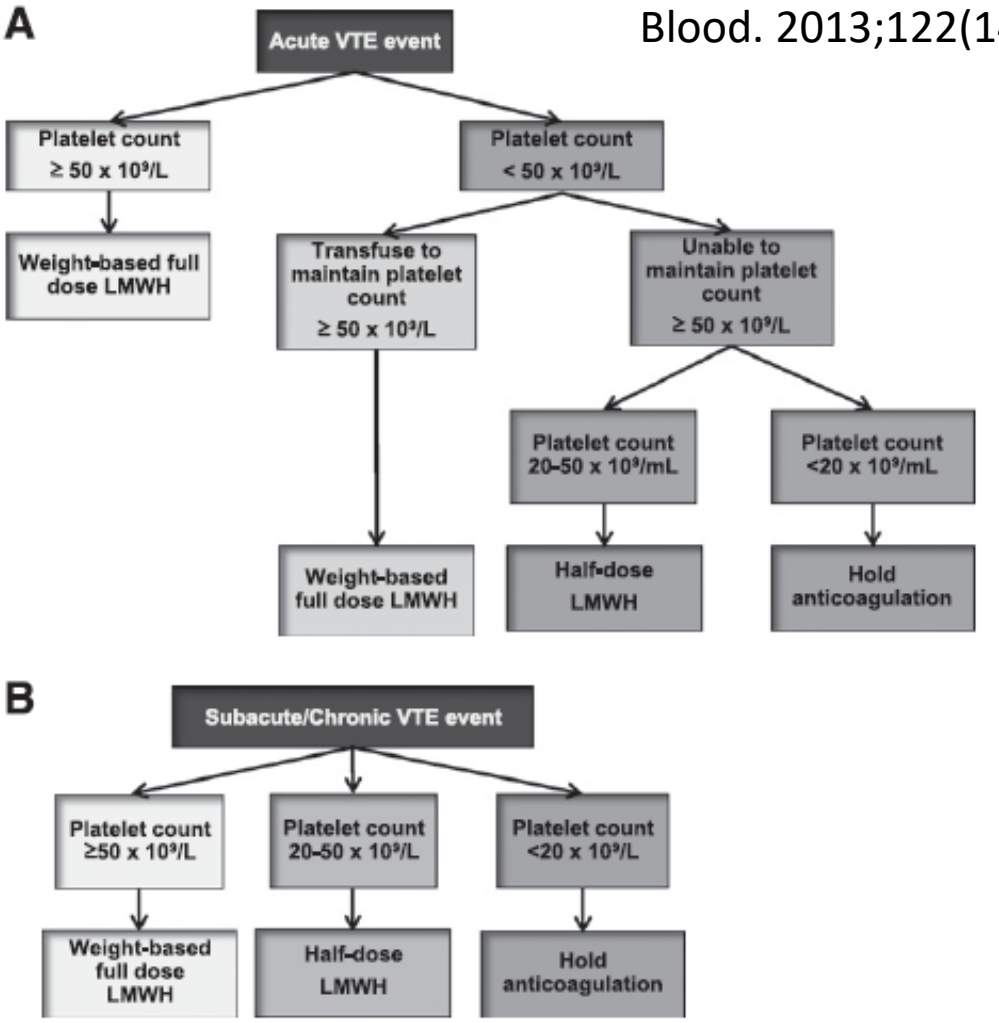


Figure 3. Management algorithm of VTE in patients with cancer and thrombocytopenia. Management of acute VTE (<1 month) and subacute or chronic VTE (≥1 month) are outlined in panels A and B, respectively.

Criteria for NOAC use in cancer patients requiring anticoagulation

TheOncologist 2014;19:82–93

1. **SANGUINAMENTO**
2. **PIASTRINE**
3. **COAGULAZIONE**
4. **FUNZIONE EPATICA**
5. **FUNZIONE RENALE**
6. **FARMACI**

Patient assessment
Risk factors for bleeding No major bleeding events in the past 2 months Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets Platelet count >50,000 per μL No anticipated decrease due to disease or chemotherapy
Coagulation studies Normal PT, PTT, and fibrinogen
Liver function tests No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function CrCl >30 mL/min (rivaroxaban) CrCl >15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein Fig. 1 lists strong CYP3A4 and/or P-glycoprotein inhibitors and inducers Table 4 lists chemotherapy drugs that modulate CYP3A4 and/or P-glycoprotein Good medication compliance

Table 3 Summary of pharmacological properties of novel oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mode of action	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Approved for VTE treatment in Europe and the US?	Yes	Yes	Yes	Yes
VTE treatment regimen	Parenteral anticoagulant for 5–10 days, then 150 mg bid	15 mg bid for 21 days, then 20 mg od	10 mg bid for 7 days, then 5 mg bid	Parenteral anticoagulant, then 60 mg od
Dose adjustments for VTE treatment	None tested	None mandated[a]	None tested	30 mg od tested in patients who were expected to have an increased bleeding risk[b]
Food	Take with or without food	VTE treatment doses to be taken with food	Take with or without food	Take with or without food
Time to maximum concentration/anticoagulant effect (hours)	0.5–2	2–4	3–4	1–2
Half-life in healthy individuals (hours)	12–14	5–13	~12	8–10
Proportion of drug subject to renal clearance[c] (%)	85	33[d]	27	35
Co-medications contraindicated/ not recommended	Strong P-gp inhibitors and inducers	Strong CYP3A4 and P-gp inhibitors	Strong CYP3A4 and P-gp inhibitors	Strong P-gp inhibitors

Notes: [a]A reduced dose of rivaroxaban 15 mg od after the initial period of 15 mg bid dosing (ie, after 21 days) may be considered based on individual patient benefit–risk analysis (Europe only, not tested in Phase III treatment studies); [b]creatinine clearance 30 mL/min –50 mL/min, body weight ≤60 kg, taking co-medications that are potent P-gp inhibitors; [c]unchanged drug; [d]33% of the dose also undergoes renal excretion as inactive metabolites. Data from previous studies.[4,14,22–24]
Abbreviations: bid, twice daily; CYP3A4, cytochrome P450 3A4; od, once daily; P-gp, P-glycoprotein; VTE, venous thromboembolism.

Vascular Health and Risk Management 2016:12 23–34

DOACS
Trasporto, metabolismo ed eliminazione

	P-gp substrate	CYP3A4 substrate (% of drug metabolized via CYP3A4)	% renal elimination
Dabigatran	Yes	No	≈80
Rivaroxaban	Yes	Yes (≈33)[a]	≈33
Apixaban	Yes	Yes (≈25)[b]	≈25
Edoxaban	Yes	No	≈50

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Table 13 Permeability glycoprotein (p-gp) drug–drug interactions with dabigatran and edoxaban [16, 48, 59, 130–135] (list is not exhaustive)

P-gp inducers	Interacting drug's effect on dabigatran and edoxaban concentrations	Suggested management
Barbiturates	↓, no specific studies	Avoid use of dabigatran or edoxaban with p-gp *inducers*
Carbamazepine	↓, no specific studies	
Dexamethasone	↓, no specific studies	
Phenytoin	↓, no specific studies	
Rifampin	↓ dabigatran exposure by 66 %	
	↓ edoxaban exposure	
St John's Wort	↓, no specific studies	

P-gp inhibitors	Interacting drug's effect on dabigatran and edoxaban concentrations	Suggested management
Amiodarone	↑, dabigatran exposure by 12-58 %	Avoid use of dabigatran with any p-gp *inhibitor* if the patient's CrCl is < 50 mL/min Reduce edoxaban dose from 60 mg once daily to 30 mg once daily if patient is also taking a p-gp *inhibitor*
	↑, edoxaban exposure by 40 %	
Carvedilol	↑, no specific studies	
Clarithromycin	↑, dabigatran exposure by 49 %	
	↑, no specific studies with edoxaban	
Conivaptan	↑, no specific studies	
Cyclosporine	↑, dabigatran exposure in in vitro studies	
	↑, edoxaban exposure	
Diltiazem	↑, no specific studies	
Dronedarone	↑, dabigatran exposure by 70–140 %	
	↑, edoxaban exposure by 85 %	
Erythromycin	↑, no specific studies with dabigatran	
	↑, edoxaban exposure	
Grapefruit	↑, no specific studies	
Indinavir	↑, no specific studies	

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P-gp inhibitors	Interacting drug's effect on dabigatran and edoxaban concentrations	Suggested management
Itraconazole	↑, dabigatran exposure in in vitro studies	
	↑, no specific studies with edoxaban	
Ketoconazole	↑, dabigatran exposure by 153 %	
	↑, edoxaban exposure	
Lapatinib	↑, no specific studies	
Mefloquine	↑, no specific studies	
Nelfinavir	↑, dabigatran exposure in in vitro studies	
	↑, no specific studies with edoxaban	
Nicardipine	↑, no specific studies	
Propafenone	↑, no specific studies	
Quinidine	↑, dabigatran exposure by 53 %	
	↑, edoxaban exposure by 77 %	
Ritonavir	↑, dabigatran exposure in in vitro studies	
	↑, no specific studies with edoxaban	
Saquinavir	↑, no specific studies	
Tacrolimus	↑, dabigatran exposure in in vitro studies	
	↑, no specific studies with edoxaban	
Tamoxifen	↑, no specific studies	
Verapamil	↑, dabigatran exposure by 23–54 %	
	↑, edoxaban exposure by 53 %	

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Table 14 Permeability glycoprotein (p-gp) and Cytochrome 3A4 drug–drug Interactions with rivaroxaban and apixaban) [134–139] (list is not exhaustive)

P-gp and *strong* CYP3A4 inducers	Interacting drug's effect on rivaroxaban/apixaban concentration	Suggested management
Barbiturate	↓, no specific studies	Avoid use of rivaroxaban or apixaban with p-gp and strong CYP3A4 *inducers*
Carbamazepine	↓, no specific studies	
Phenytoin	↓, no specific studies	
Rifampin	↓, rivaroxaban and apixaban exposure by 50 %	
St John's Wort	↓, no specific studies	

P-gp and *strong* CYP3A4 inhibitors	Interacting drug's effect on Factor Xa inhibitor concentration	Suggested management
Clarithromycin	↑, rivaroxaban exposure by 54 % ↑,no specific studies for apixaban	Rivaroxaban: Avoid use of rivaroxaban with p-gp and strong CYP3A4 *inhibitors* Apixaban: If taking 5 mg or 10 mg BID reduce dose by 50 % if combined with strong p-gp and CYP3A4 *inhibitors* If taking 2.5 mg BID avoid apixaban with strong p-gp and CYP3A4 *inhibitors*
Conivaptan	↑, no specific studies	
Grapefruit	↑, no specific studies	
Indinavir	↑, no specific studies	
Itraconazole	↑, no specific studies	
Ketoconazole	↑, rivaroxaban exposure by 160 % ↑, apixaban exposure by 200 %	
Nelfinavir	↑, no specific studies	
Posaconazole	↑, no specific studies	
Ritonavir	↑, rivaroxaban exposure by 160 % ↑, no specific studies for apixaban	
Saquinavir	↑, no specific studies	

P-gp and *moderate* CYP3A4 inhibitors	Interacting drug's effect on rivaroxaban/apixaban concentration	Suggested management
Cyclosporine	↑, no specific studies	Rivaroxaban: Avoid use of rivaroxaban with p-gp and moderate CYP3A4 inhibitors if CrCl is < 80 mL/min Apixaban: No dose adjustment is recommended with p-gp and *moderate* CYP3A4 inhibitors. Use with caution
Diltiazem	↑, apixaban exposure by 30–40 % ↑, no specific studies with rivaroxaban	
Dronedarone	↑, no specific studies	
Tamoxifen	↑, no specific studies	
Verapamil	↑, no specific studies	

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The Oncologist®

New Drug Development and Clinical Pharmacology

New Oral Anticoagulants and the Cancer Patient

NICHOLAS J. SHORT,[a] JEAN M. CONNORS[b,c]

[a]Department of Medicine and [b]Hematology Division, Brigham and Women's Hospital, Boston, Massachusetts, USA; [c]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

TheOncologist 2014;19:82–93

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		

Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimetabolites						
Antifolates						
Methotrexate				●		
Pemetrexed						
Purine analogs						
Mercaptopurine						
Thioguanine						
Pentostatin						
Cladribine						
Clofarabine						
Fludarabine						
Pyrimidine analogs						
Fluorouracil						
Capecitabine						
Cytarabine						
Gemcitabine						
Azacitadine						
Decitabine						
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						

Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Carmustine						
Lomustine			+			
Busulfan	+++					
Procarbazine						
Dacarbazine						
Temozolomide						

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Platinum-based agents						
Cisplatin						
Carboplatin						
Oxaliplatin						
Intercalating agents						
Bleomycin						
Mitomycin C				●		
Dactinomycin						
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Alemtuzumab						
Cetuximab						
Trastuzumab						
Bevacizumab						

Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	**+++**	**+++**				●
Abiraterone	**+++**		++			●
Mitotane						
Immune-modulating agents						
Cyclosporine	**+++**		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	**+++**	**+++**		●	●	●
Prednisone	**+**	**++**				

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

Interazioni farmacologiche e DOACS

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	No data yet	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[247]

Europace 2015
doi:10.1093/europace/euv309

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling