ANTICOAGULANTS

**Xarelto (rivaroxaban) will be used to TREAT venous thromboembolism.**

It’s the first of the new oral anticoagulants approved to treat deep venous thrombosis or pulmonary embolism...and reduce the risk of a subsequent venous thromboembolism.

Xarelto has advantages over warfarin for treating venous clots...no anticoag monitoring, fewer interactions, and no bridging with low-molecular-weight heparin because of its fast onset.

It also seems similar to warfarin for preventing recurrent venous thromboembolism...and it might cause less major bleeding.

But be aware of Xarelto’s disadvantages too...no antidote and possibly higher cost.

Explain that warfarin plus INR monitoring is about $80/month...compared to $300 for Xarelto...and over $1000 for generic enoxaparin.

To switch from warfarin, recommend stopping the warfarin and waiting until the INR is below 3.0...then starting Xarelto.

Watch for appropriate Xarelto dosing...depending on the indication.

**Atrial fibrillation.** Expect to see 20 mg once daily...or 15 mg once daily for patients with impaired renal function.

**PREVENTION of venous thromboembolism.** Expect 10 mg once daily.

**TREATMENT of venous thromboembolism.** Expect patients to get 15 mg TWICE daily for the first 3 weeks...then 20 mg ONCE daily for a total of AT LEAST 3 months, depending on the cause of the clot.

Advise patients to take the 15 or 20 mg tabs with food...due to better absorption. The 10 mg tabs can be taken with or without food.

To hear our **PL experts discuss the pros and cons of using Xarelto or warfarin, go to our PL Detail-Document and click on PL VOICES.**

See our **PL Chart, Comparison of Oral Antithrombotics**, for indications, dosing, interactions, etc. It also has info about the Xarelto savings card, which can lower co-pays for some patients.

Go to the Using Xarelto (rivaroxaban) to Treat Venous Thromboembolism Detail-Document.
The recent proliferation of oral anticoagulants and antiplatelet agents has health care professionals questioning how to choose among them. The newest anticoagulants are dabigatran (*Pradaxa*) and rivaroxaban (*Xarelto*). Also look for the direct factor Xa inhibitor apixaban (in the U.S.) possibly in 2013, and edoxaban and betrixaban in the next few years. The following chart compares the indications, clinical benefit, antidotes, washout, and other therapeutic considerations for these agents.

**Abbreviations**: ACS = acute coronary syndrome; ADP = adenosine diphosphate; A fib = atrial fibrillation; AV = arteriovenous; BID = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; DVT = deep vein thrombosis; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; STEMI = ST segment elevation myocardial infarction; TIA = transient ischemic attack; VTE = venous thromboembolism.

### Comparison of Oral Antithrombotics

<table>
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<th>Drug: Mechanism</th>
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<th>Clinical Benefit In…</th>
<th>Antidote/ pre-op, pre-procedure washout (if indicated)</th>
<th>Therapeutic Considerations</th>
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<td><strong>ANTICOAGULANTS</strong></td>
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</table>
| Apixaban (*Eliquis*): direct factor Xa inhibitor | Canada: $134.78 | A fib (off-label): at least as effective as warfarin for stroke prevention, systemic embolism, death; less major bleeding | No specific antidote | • Requires BID dosing. ¹⁹  
• For every 1000 A fib patients treated for 1.8 years, apixaban prevents six more strokes, 15 major bleeds, and eight deaths compared to warfarin.¹¹  
• Caution if CrCl 15 to 29 mL/min, but no dosage adjustment necessary. Not recommended if CrCl <15 mL/min.¹⁹  
• Contraindicated in severe |
| (2.5 mg BID) | U.S.:  
  • Investigational  
  Canada: ⁶⁹  
  • VTE prevention post-hip or knee replacement (2.5 mg twice daily for 32 to 38 days [hip] or 10 to 14 days [knee], starting 12 to 24 hrs post-op) | Post-hip/knee replacement: at least as effective as enoxaparin for preventing VTE; comparable bleeding ²³ | See our PL Detail-Document, Preventing/Managing Bleeding with the New Anticoagu- lants |                            |
| Continued… | | | | |
Anticoagulants

You'll start hearing lots more about the comparisons between warfarin, dabigatran (Pradaxa), and rivaroxaban (Xarelto).

Now that Xarelto is approved for atrial fib, people are asking if they should switch to it or Pradaxa as an alternative to warfarin.

Help keep their pros and cons in perspective.

Efficacy is where Pradaxa may have a slight edge. Pradaxa 150 mg BID prevents about 5 more strokes per 1000 patients/year than warfarin.

Xarelto 20 mg once a day doesn't seem to work better than warfarin.

Side effects such as overall bleeding are similar between Pradaxa and Xarelto compared to warfarin. Both seem to cause FEWER intracranial bleeds...and MORE GI bleeds than warfarin.

But dyspepsia is a problem with Pradaxa.

Cost is less with warfarin...totaling about $80/month with INR monitoring once/month. Pradaxa and Xarelto both cost about $260/month.

Continue to suggest warfarin for many atrial fib patients.

Suggest another oral anticoag if INR control is poor...warfarin interactions are a concern...or monitoring isn't feasible.

If a newer anticoagulant is needed, suggest Pradaxa first...it's more effective than warfarin in some patients. Tell patients that Pradaxa is now good for 4 MONTHS after opening...instead of just 60 days.

For now, suggest Xarelto for patients who can't tolerate Pradaxa due to dyspepsia...or have trouble with its BID dosing. Advise taking Xarelto with dinner to improve absorption.

Recommend monitoring renal function with the new anticoagulants...and lowering the dose if needed.

Discourage using aspirin for atrial fib. New evidence suggests that it's not much better than placebo...and it still increases bleeding.

Suggest saving aspirin for younger patients without additional stroke risk factors...or those who won't take an anticoagulant.

If you want to be the smartest person in your area about the new anticoags for atrial fib, go to our PL Detail-Document...and listen to our experts talking on PL Voices. Also see our PL Chart, Comparison of Oral Antithrombotics, for their indications, dosing, interactions, etc.

More . . .
**VACCINES**

*Prevnar 13 vaccine will be used in certain ADULTS...not just kids.*

We usually think of *Prevnar 13* as the pediatric version of the pneumococcal vaccine...and *Pneumovax 23* as the adult version. But now *Prevnar 13* will be used in adults who are immunocompromised. Both vaccines cover the same twelve serotypes. *Pneumovax 23* covers eleven other serotypes...and *Prevnar 13* just one more. But *Prevnar 13* is a conjugate vaccine so it might produce longer-lasting immunity than *Pneumovax 23*.

Continue to give *Pneumovax 23* to all adults at age 65.

Also give *Pneumovax 23* to younger adults who smoke...or have asthma, diabetes, or certain other chronic conditions.

Save *Prevnar 13* for adults who are immunocompromised due to HIV, cancer, asplenia, etc...and give it in ADDITION to *Pneumovax 23*.

Explain that giving both vaccines is an attempt to increase immunity in these high-risk patients.

If patients have NOT had *Pneumovax 23*, give *Prevnar 13* first...then *Pneumovax 23* after 8 weeks.

If patients HAVE had *Pneumovax 23*, give *Prevnar 13* at least one year after *Pneumovax 23*.

Keep in mind that immunocompromised patients still need a second dose of *Pneumovax 23* five years after the first dose...but they only need one dose of *Prevnar 13*.

Go to the Use of Pneumococcal Vaccines for Immunocompromised Adults Detail-Document.

### DISCUSSION POINTS

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<td>November 2010 Article – More adults are now candidates for pneumococcal vaccination</td>
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<td>May 2007 Article – when to give pneumococcal vaccine <em>(Pneumovax 23)</em></td>
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<th>Common questions about vaccines</th>
<th>October 2007 Article – when to avoid live vaccines</th>
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<td>October 2012 Article – New virus strains in the 2012-2013 influenza vaccine</td>
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PL CE LIVE December 2012
Long Guide

Vaccines

More adults are now candidates for pneumococcal vaccination...plus there's a new version of the vaccine for children.

Pneumovax 23. We usually think of this as a one-shot vaccine for seniors...but it's now being given more to younger patients, too.

Recommend it for adults UNDER age 65 who smoke or have asthma...in addition to those who have chronic diseases or are immunocompromised.

Recommend a REPEAT dose at age 65...as long as it has been 5 years since the last dose.

Give immunocompromised patients their repeat dose 5 years after their first dose.

Continue to vaccinate low-risk patients at age 65. If older patients can't remember if they were vaccinated, go ahead and give it.

Prevnar 13. The original 7-serotype conjugated vaccine (Prevnar) is being replaced by Prevnar 13...to cover 6 more serotypes.

Recommend Prevnar 13 to start OR finish the vaccine series in kids. Also recommend one additional dose for kids 15 months to 5 years who already completed their series with the old Prevnar.

You can get our Immunization Update 2010 for the latest vaccine schedules...plus a Pneumococcal Shot reminder for patients. To get all your required immunization CE, see our PL CE & Training Organizer™.
Vaccines

There's disagreement on when to give pneumococcal vaccine (Pneumovax 23).

CDC says to give it ONCE to adults 65 and older...or earlier for anyone who is immunocompromised or has certain chronic diseases.

They say to revaccinate after 5 years IF a patient is immunocompromised...has renal failure...or got a first dose before age 65.

But some experts question whether revaccination is beneficial.

They say that revaccinating can increase antibody TITERS...but isn't proven to prevent more pneumococcal INFECTIONS.

Err on the side of caution and follow the CDC recommendations.

Pneumonia complications can be severe in high-risk patients...and a second dose appears safe and well-tolerated.

But don't recommend MORE than one booster...even if the second dose was given many years ago. The safety and tolerability of more than two doses of Pneumovax is not known.
GOUT

Reps will **rev up promotion of Uloric (febuxostat) for managing gout**. They’ll mention that guidelines now recommend Uloric or allopurinol as first-line meds for lowering uric acid.

Reps will also say that Uloric lowers uric acid more than allopurinol...but this is compared to only 300 mg/day of allopurinol.

Keep all this in perspective...there’s no difference in the frequency of gout flares with Uloric or allopurinol.

Allopurinol is still the first choice for most patients. Allopurinol costs only about $10/month...compared to $180 for Uloric.

For patients with normal renal function, recommend starting with allopurinol 100 mg/day...and titrating up to 800 mg/day if needed.

For those with renal insufficiency, recommend starting with allopurinol 50 mg/day. Suggest monitoring for hypersensitivity, etc...side effects are more common in patients with renal dysfunction.

Advise patients to stop allopurinol if they develop itching or a rash. In these patients, suggest Uloric or probenecid instead.

Recommend probenecid if patients can’t tolerate allopurinol or Uloric...IF renal function and urine uric acid levels are normal.

Suggest adding probenecid to allopurinol or Uloric if patients can’t reach their uric acid goal with max tolerated doses of one med.

For patients starting uric acid lowering therapy, recommend using daily colchicine or an NSAID for at least 6 months to prevent gout flares.

See our PL Chart, Colchicine Dosing and Drug Interactions, for the new, safer dosing regimens. Also see our new PL Chart, Comparison of Gout Therapies, for indications, place in therapy, side effects, and more.

To hear our team discuss how to manage gout with a gout expert, go to our PL Detail-Document and click on PL VOICES.

Go to the Strategies for Managing Gout Detail-Document.

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<tr>
<th>DISCUSSION POINTS</th>
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<tr>
<td>Management of gout</td>
<td>November 2010 Article – lots of ads for new gout drugs...Uloric, Colcrys, and now Krystexxa</td>
</tr>
<tr>
<td></td>
<td>Detail-Doc 281210 – Comparison of Gout Therapies</td>
</tr>
<tr>
<td>Questions about gout therapies</td>
<td>April 2009 Article – Uloric (YOU-lor-ik, febuxostat) is the first new chronic treatment for gout in over 40 years</td>
</tr>
<tr>
<td></td>
<td>Detail-Doc 281210 – Colchicine Dosing and Drug Interactions</td>
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</table>
Comparison of Gout Therapies

Gout is one of the most commonly reported rheumatic diseases in adults.\textsuperscript{1,2} Approximately 2\% to 4\% of adults in the U.S. and Canada are affected and the prevalence is increasing.\textsuperscript{5} Increasing rates of hypertension, obesity, metabolic syndrome, type 2 diabetes, and chronic kidney disease are thought to contribute to this rise. The minimum goal of therapy is a serum uric acid level of less than 6 mg/dL (360 umol/L), but levels lower than 5 mg/dL (300 umol/L) may be necessary to prevent symptoms in some patients.\textsuperscript{1} The table below summarizes the recently released guidelines for the treatment and prevention of gout by the American College of Rheumatology.\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Role in Therapy</th>
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<tr>
<td>PREVENTION:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Consider in patients with tophi, those with two or more attacks of gout a year, those with stages 2 to 5 chronic kidney disease (creatinine clearance &lt;90 mL/min), and in those with a history of uric acid kidney stones.\textsuperscript{1}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Initiate anti-inflammatory prophylaxis when starting or just prior to starting uric acid lowering therapy to help prevent an acute gout flare. First-line options include low-dose colchicine 0.5 to 0.6 mg once or twice daily or a low-dose nonsteroidal anti-inflammatory drug (NSAID) (e.g., naproxen 250 mg twice daily). The second-line option (if colchicine and NSAIDs are contraindicated, ineffective, or not tolerated), consider low-dose prednisone or prednisolone (≤10 mg/day). Anti-inflammatory prophylaxis should be continued for at least six months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpharmacologic</td>
<td>Mainstay in all patients. To be used in conjunction with pharmacotherapy.</td>
<td>• In patients who are obese, encourage weight loss.\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exercise, hydration, and smoking cessation should be encouraged.\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Organ meats high in purine (e.g., sweetbreads, liver, kidney) should be avoided and serving sizes of beef, pork, lamb, and certain seafood (e.g., sardines, shellfish) should be limited.\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High fructose corn syrup sweetened beverages and foods should be avoided. Naturally sweetened fruit juices, desserts and table sugar, and table salt should be limited.\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alcohol, particularly beer, but also wine and spirits, should be used in moderation (avoid more than two servings per day in men and one serving daily in women). During an acute attack of gout, or in patients who have frequent attacks of gout, alcohol should be avoided.\textsuperscript{1}</td>
</tr>
</tbody>
</table>
Colchicine Dosing and Drug Interactions

Colchicine is a very old drug that has a history of serious safety issues. It has a narrow therapeutic index, is metabolized by the liver, and excreted by the kidneys.\(^1\),\(^2\) Acute ingestion of less than ten times the daily dose has resulted in death.\(^2\) About nine out of ten patients who take colchicine for gout flares will have gastrointestinal symptoms such as diarrhea and nausea before they have pain relief.\(^2\) Signs and symptoms of colchicine toxicity include gastrointestinal symptoms as well as organ failure (e.g., arrhythmias, myopathy, seizures, etc.).\(^2\) With the approval process for Colcrys, the first FDA-approved single-ingredient colchicine product available in the U.S., more information on safe doses and drug interactions of colchicine has become available. However, dosing for Colcrys can be tricky, since there are differences depending on the indication, concomitant drug therapy, and liver and kidney function. The following chart lists doses and dose adjustments from the Colcrys product labeling. A listing of some drugs that interact with colchicine is also included.

**NOTE:** Information in Canadian colchicine labeling may differ. The following chart reflects the most current safety information for colchicine.

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<tr>
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<th>Prophylaxis of gout flare (&gt;16 years old)</th>
<th>Treatment of gout flare (&gt;16 years old)</th>
<th>Familial Mediterranean fever (&gt;12 years old)</th>
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<td><strong>Normal Dose</strong></td>
<td>0.6 mg once daily or BID Max is 1.2 mg per day</td>
<td>1.2 mg x1 dose then 0.6 mg one hour later Max is 1.8 mg in a one-hour period Wait 12 hours to resume prophylactic dose Wait at least three days to repeat</td>
<td>1.2 to 2.4 mg per day given once daily or BID Increase in increments of 0.3 mg per day to max of 2.4 mg per day Decrease in increments of 0.3 mg per day if side effects are intolerable</td>
</tr>
<tr>
<td><strong>Strong CYP3A4 Inhibitors</strong></td>
<td>0.3 mg once daily if original dose was 0.6 mg BID 0.3 mg once every other day if original dose was 0.6 mg once a day Avoid colchicine in patients with kidney or liver impairment</td>
<td>0.6 mg x1 dose then 0.3 mg one hour later Wait at least three days to repeat Avoid colchicine for treatment if patient also taking colchicine for gout prophylaxis</td>
<td>0.6 mg once daily or 0.3 mg BID Max is 0.6 mg per day Avoid colchicine in patients with kidney or liver impairment</td>
</tr>
</tbody>
</table>

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More...
**DRUG INTERACTIONS**

You’ll see warnings that using **PPIs with methotrexate can lead to methotrexate toxicity**.

- PPIs seem to decrease the renal clearance of methotrexate and its active metabolites...and increase their serum levels.
- The greatest risk is with high-dose methotrexate infusions for cancer...but problems might also occur with lower doses.
- Recommend holding PPIs a couple of days before and after high-dose methotrexate infusions.
- Patients taking methotrexate for rheumatoid arthritis often need a PPI due to its adverse GI effects...but be careful.
- Even low weekly methotrexate doses may be affected by PPIs...especially if they’re given with other meds that may reduce methotrexate clearance such as NSAIDs or aspirin.
- Advise prescribers to lower the methotrexate dose if signs of MILD toxicity occur, such as mildly elevated liver enzymes, mouth ulcers, and minor GI side effects. But recommend stopping it for more SERIOUS side effects...bone marrow suppression, lung damage, etc.

Go to the Proton Pump Inhibitor-Methotrexate Interaction Detail-Document.

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<td>Continuing Education Course – Drug Interaction Overload: Problems and Solutions for Drug Interaction Alerts</td>
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<td>Unique considerations with methotrexate</td>
<td>July 2012 Article – Aggressive management of rheumatoid arthritis often means monitoring multiple meds</td>
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<td>Detail-Doc 260704 – Liver Function Test Scheduling</td>
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Liver Function Test Scheduling

Monitoring LFTs, particularly aminotransferase (ALT, AST) levels, is often recommended for medications that are known hepatotoxins. Patients can experience hepatotoxicity despite undergoing recommended monitoring because such reactions usually develop quickly. Death may be prevented if hepatotoxic drugs are discontinued at the first sign/symptom of hepatotoxicity. Educate patients to immediately report symptoms of liver injury (e.g., abdominal pain, fatigue, loss of appetite, dark urine, jaundice). In general, patients with preexisting liver disease are not at increased risk of drug-induced hepatotoxicity; however, patients with HIV and/or viral hepatitis are exceptions. Cirrhotic patients may decompensate when administered a hepatotoxic drug. Also, some hepatotoxic drugs require cautious use or specific dosage adjustment in patients with liver disease. For these reasons, checking LFTs at baseline is prudent before starting a potentially hepatotoxic drug. The following list includes some of the more common drugs for which routine (as opposed to symptom-triggered) liver function monitoring is recommended. These are suggested monitoring guidelines for adults. Canadian products with recommendations that are more conservative than those in the U.S. are identified. There may be situations where more frequent monitoring is required.

**Abbreviations:** ALT - alanine aminotransferase; AST - aspartate aminotransferase; GGT - gamma-glutamate transferase; LFTs - liver function tests; ULN - upper limit of normal

*It is prudent to check baseline LFTs even if not specifically recommended in product labeling.

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<th>Drug</th>
<th>Monitoring Recommendations*</th>
<th>Comments</th>
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<td>Acarbose (Precose, Glucobay [Canada])</td>
<td>LFTs every 3 months during the first year and periodically thereafter.</td>
<td>If LFTs become elevated, reduce dose or discontinue, especially if elevations persist.</td>
</tr>
<tr>
<td>Acitretin (Soriatane)</td>
<td>LFTs at baseline, every one to two weeks until stable, and thereafter as clinically indicated.</td>
<td>Contraindicated in severe liver dysfunction. Discontinue if LFTs do not normalize or worsen. Discontinue if hepatotoxicity is suspected.</td>
</tr>
<tr>
<td>Alglucosidase alfa (Myozyme)</td>
<td>LFTs at baseline and periodically.</td>
<td>AST and ALT can also increase as a result of Pompe disease.</td>
</tr>
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</table>
**Rheumatology**

**Aggressive management of rheumatoid arthritis often means monitoring multiple meds.**

Rapidly reducing disease activity prevents joint damage...reduces disability...and improves long-term outcomes.

This can mean using combinations of disease-modifying antirheumatic drugs (DMARDs).

**Nonbiologic DMARDs** (methotrexate, etc). Methotrexate is used most often...with other DMARDs added if needed.

Recommend monitoring for infection, thrombocytopenia, leukopenia, and kidney or liver toxicity with most nonbiologic DMARDs.

Recommend even closer monitoring if methotrexate is used with leflunomide (Arava, etc)...due to additive GI and liver toxicity.

Recommend eye exams for patients on hydroxychloroquine.

**Steroids.** Some patients on methotrexate will get low-dose prednisone longer. Adding up to 2 years of prednisone can further reduce inflammation and slow joint damage.

Recommend monitoring for high blood pressure and diabetes...and adding vitamin D, calcium, a bisphosphonate, etc, to prevent bone loss.

**Biologic DMARDs** (Enbrel, etc). Patients end up on a biologic if their disease is more severe...or they don't respond to nonbiologics.

Recommend screening and treating for tuberculosis first.

Advise patients to report signs of an infection...and recommend holding therapy if the infection becomes severe.

**Vaccines.** Recommend giving any needed vaccines before DMARDs are started. Check for pneumococcal, influenza, hepatitis B, human papilloma virus, and herpes zoster vaccines.

Don't give LIVE vaccines such as FluMist or Zostavax to patients on biologic DMARDs...but it's okay to give others.
Reps will promote Tudorza Pressair (TU-door-za, aclidinium), a new inhaled anticholinergic for COPD.

It’s an alternative to tiotropium (Spiriva) for maintenance treatment of COPD bronchospasm.

Aclidinium is a bronchodilator comparable to tiotropium.

Tudorza comes in an easy-to-use inhalation device...but it must be used twice daily.

On the other hand, Spiriva is more complicated to use...but it can be used once daily.

Recommend picking a product based on cost and convenience.

Tudorza costs about $220 per monthly inhaler...compared to about $240 per month of Spiriva.

Continue to recommend Spiriva for once-daily dosing. Suggest Tudorza for patients who want an inhaler that’s easier to use.