Ranexa® (ranolazine) – new agent for chronic angina

- Ranexa® is specifically indicated for “add-on” treatment of chronic angina in patients who have failed to respond to prior angina therapy; it is not approved as first-line treatment.

- The drug has been shown to exert its anti-anginal and anti-ischemic effects without reducing heart rate or blood pressure.

- Clinical trials have demonstrated a very modest benefit. Patients receiving Ranexa® experienced about one less angina episode per week as compared to the placebo group. The drug may also show greater efficacy in male patients.

- **Ranolazine dose-dependently prolongs the QTc interval and thus increases the risk of arrhythmias.**

- This drug is **contraindicated** for use with other drugs that increase the QTc interval, such as:
  - Amiodarone
  - Quinidine
  - Sotalol
  - Ziprasidone

- Ranolazine is primarily metabolized by CYP3A.

- Ranexa® **should not be used in combination** with drugs that inhibit CYP3A4 metabolism as this can also increase the QT interval:
  -azole antifungals, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit juice or grapefruit-containing products

- Co-administration of ranolazine and **digoxin** increases the plasma concentrations of digoxin by approximately 1.5-fold and the dose of digoxin may have to be reduced accordingly.

- Co-administration of ranolazine and **simvastatin** results in about a 2-fold increase in plasma concentrations of simvastatin, and its active metabolite; alternative statins should be considered.

- Ranexa’s QTc-prolonging effects are increased in patients with hepatic dysfunction.

- Ranexa should be reserved for chronic stable angina patients who have inadequate response to conventional therapy due to the risk of prolonged QT interval and its extensive drug interaction profile. Patients should be advised to contact their physician if they experience palpitations or fainting spells while taking ranolazine.

- Ranexa dosing should be initiated at 500 mg b.i.d. and increased to 1000 mg b.i.d., as needed, based on clinical symptoms. The maximum recommended daily dose of Ranexa is 1000 mg b.i.d. Doses greater than 1000 mg BID increase the risk of QTc-prolongation.

- Baseline and follow-up ECGs should be obtained to evaluate effects on QT interval.

- **Cost data for 30-day supply**

<table>
<thead>
<tr>
<th>Ranexa® (ranolazine)</th>
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<tbody>
<tr>
<td>500 mg</td>
<td>#60</td>
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<td>1000 mg (2 x 500 mg)</td>
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HVPA Pharmacy and Therapeutics Committee “Bottom Line” on Ranexa®:

- Ranexa® is an expensive agent with limited clinical benefit.

- Significant safety concerns with QTc-prolongation and drug interactions.
Amitiza® (lubiprostone) – new agent for chronic constipation

- Lubiprostone is a newly approved agent for the treatment of chronic idiopathic constipation in the adult population. It has not been evaluated by the FDA for the treatment of irritable bowel syndrome.

- Lubiprostone is a locally acting chloride channel activator that increases chloride-rich intestinal fluid secretions without altering the concentrations of sodium and potassium in the serum. The proposed mechanism of action involves increased intestinal fluid secretion and consequently the motility in the intestine, therefore, increasing the passage of stool and alleviating the symptoms associated with chronic idiopathic constipation.

- In clinical trials, almost one third of patients receiving Amitiza® 24 mcg twice daily reported nausea, with 8.7% discontinuing treatment. Nausea appears to be dose-dependent and decreases with dose reduction to 24 mcg once daily and with food.

- Diarrhea, which did not seem dose-dependent, occurred in 13.2% of Amitiza® patients in clinical trials, with 2.2% discontinuing treatment. Gastrointestinal side effects also included abdominal distension (7.1%), abdominal pain (6.7%), gas (6.1%), vomiting (4.6%) and loose stools (3.4%).

- Lubiprostone is considered Pregnancy Category C. The safety of lubiprostone in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to increase the risk of fetal loss. Women who may become pregnant should have a negative pregnancy test prior to initiation of lubiprostone and be capable of complying with effective contraceptive measures.

- The usual dose of Amitiza® is 24 mcg BID.

Cost Information:

- Amitiza® 24 mcg BID $151.95 for 30-day supply

Comparison:

- Zelnorm® 6 mg BID $168.51 for 30-day supply
- Miralax® $41.67 for 30-dose 527-gm bottle

HVPA Pharmacy and Therapeutics Committee “Bottom Line” on Amitiza®

- There is limited clinical data on the use of Amitiza® and no comparative studies have been published.
- Patients should be trialed on increased fiber or laxatives such as Miralax® before moving to an agent such as Amitiza®.
- Nausea occurs in up to 30% of patients who take the drug.

A publication of the HVPA Pharmacy Department
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