

# **PDLAC PPI and ACE Inhibitor Review**

**October 30, 2003**

**Plains Hotel**

**Drug Class Review – PPI's:** (A list of medications included in this class can be found in Attachment A)

**Presented by: Marian McDonagh**

In about two to three months the PPI's will be up for their six month review. The information presented is current up through April, 2003.

Data Collection came from such sources as Cochrane, Medline and Embase, as well as, Manufacturer submissions and reference lists.

The EPC's looked at adults with PUD, NSAID Induced Ulcers and esophageal reflux verified by diagnostic testing.

Key Questions were answered by reviewing Head to Head trials which showed comparative efficacy, safety, effects on specific sub-populations and comparisons to non-drug therapies.

For Duodenal Ulcers, there was no significant difference in healing between the PPI's. For the symptomatic relief of Duodenal Ulcers, the seven studies reviewed showed no overall difference among the PPI's.

For both Gastric Ulcer and NSAID Induced Ulcer Healing, no important or significant differences were seen amongst the PPI's studied.

No Head to Head studies were performed to study the prevention of NSAID Induced Ulcer with PPI's.

Out of 12 Head to Head studies and one Systematic Review, no difference was seen amongst the PPI's studied in regard to H. Pylori eradication.

In regard to adverse events, there were no long term Head to Head studies, but in short term Head to Head studies no significant differences were seen between PPI's, and the drop out rate due to adverse rates were low.

**Discussion:**

1. Unpublished studies? No Head to Head studies performed, so this would not have changed the outcomes.

2. Esomeprazole's comparison to Omeprazole 20mg was not significant. A comparison to Omeprazole 40mg would have been a more equivalent study.

3. Patients seem to prefer one drug to another for no clear reasons.

4. Are the comparisons truly comparing apples to apples? It seems that no clear studies have been done, but it appears that there still wouldn't be a difference among them.

5. What is the price to the physician's office? The increased stress and work load involved with changing drugs to the preferred one would increase the costs to each individual practitioner. However, after one year, these costs should be negated.

6. If a patient prefers one drug, they shouldn't be forced to be placed on a H2 Blocker or another PPI. To keep the patient on their current drug requires EGD's to be performed that are costly and unnecessary to prove the use of the current drug as being effective.

7. Consumer's need to be educated about equal efficacy, and in this case, price is the only difference. If a patient is paying out of their own pocket vs. a patient who has an insurance program covering the costs, the patient who is not responsible for paying their own costs doesn't care about the costs to their insurance program. Education to equivalency is important for all patients, especially when cost is factored in.

8. The PA Process: A PDL would be preferred by physicians rather than going through the PA process. The initial problems with PA were due to it being new, and now things have been smoothed out with very few problems occurring. Physician to physician contact has been helpful, and now that we have learned from our mistakes, it should go easier with PDL.

9. Communication: Always an issue, but all we can do is our best and go from there. Letters will be sent and a website will be in effect. Educational classes and the ability to download the PDL list on ePocrates can be looked into. Starting with straight forward classes of drugs will be a good way to get physicians use to the process.

10. A comparative list of all insurers? A yearly or bi-yearly list could be useful in a "book" form. Can this be kept up to date due to constant formulary changes? No, not really. It would be best just to write the prescription and deal with the problems later.

11. Would accessing PDL information from a website at the time a prescription is written be useful? It's not feasible in most cases. All methods of communication should be used for the convenience of each provider (e.g. website, letters, e-mail, faxes, etc.) It's best just to deal with the problems as they come.

### **Public Comment:**

#### **1. Paul Pereira with Tap Pharmaceuticals:**

On the topic of Esophagitis Healing, the conclusion was that all PPI's were effective. Paul felt the conclusion was misleading:

1. "What is effective?" (*Not addressed at any point.*)
2. Paul felt that the ranges of healing, which were listed from 61-91%, seemed significant. *The range comes from different studies performed in different populations. These were not head to head studies of different drugs where one was 61% effective and the other 91% effective.*
3. Paul felt pH control was not looked at. *The outcome*

*desired is healing and symptomatic relief, pH that is lowered but with no symptom relief is not significant to treatment.*

4. Administration options (how the PPI was taken) were not looked at.
5. Five PPI's were reviewed, but seven will be considered for the PDL. *The studies did not include generics or OTC versions, thus they could not be reviewed, but it can be concluded that the outcome would not have changed.*

**2. Dyan McGrath with Astra-Zeneca – A Company Representative Presentation by Fran Treadway:**

1. Astra-Zeneca feels that the even though the studies were small, they were significant in regard to the differences between Nexium vs. Prilosec and Prevacid vs. Nexium.
2. The point needs to be made that the severity of the symptoms is not always related to the severity of the disease.
3. Also pointed out were the large differences in healing rates that were seen in more severe cases of esophagitis.
4. Referred to maintenance studies that showed at six months significant differences in doses being given for each PPI, which is not an accurate comparison.
5. Commented that treatment was initiated based on symptoms not diagnostic testing, and that once a test is performed, a PPI has already been given, thus an accurate initial grade of disease was not established or healing rate shown.
6. Commented that an OTC trial was performed and that the OTC product failed. Esomeprazole should be given because it's the only one shown to be more efficacious. The EPC commented that a 40 mg vs. 40 mg study between omeprazole and esomeprazole has not been done, and if it were, it probably would not show a difference between the two. The 20 mg vs. 40 mg study was not statistically

significant.

**Committee Recommendation:**

**Dr. William Harrison moved to recommend that the evidence does not show any significant clinical differences between all of the PPI's. The motion was seconded. There being no discussion, the motion passed.**

**Drug Class Review – ACE Inhibitors:** (A list of medications included in this class can be found in Attachment A)

**Presented by: Marian McDonagh**

EPC's reviewed ACE Inhibitors for use in hypertension with and without compelling implications, as well as in patients with high cardiovascular risk, post or recent MI, heart failure, diabetic nephropathy and non-diabetic nephropathy.

All ACE's reduced hypertension, with no Head to Head trials to review. No safety differences were seen.

There were also no Head to Head trials for the use of ACE's in high cardiovascular risk patients. There were various studies, but with different outcomes.

For post MI, there was a small fair quality study of captopril vs. enalapril, and a fair quality study of perindopril vs. captopril.

For heart failure, there was one fair quality study and 13 short Head to Head studies, with no differences in adverse effects.

No Head to Head studies were conducted for diabetic neuropathy.

There was either no data available or no differences in ACE's in population sub-groups based on race, age or sex.

### **Discussion:**

1. "Events" can be broad, so the focus should be on mortality.
2. The dosing for captopril vs. enalapril vs. others is different, and not really addressed in the studies.
3. FDA approval is not relevant, the PDLAC can approach reviews by what is important in a practice setting.
4. Accupril's wide range of dosing is preferred by nephrologists in Casper.
5. Casper nephrologists use captopril on an out-patient basis and enalapril with a b.i.d dosing.

### **Public Comment:**

#### **Betty Iverson with Wyeth introduced Dr. Krantz, a cardiologist from Denver, CO:**

1. Offered his services to the PDLAC as a resource.
2. Passed information out on the HOPE Trial and other trials. Dr. Krantz discussed the benefits of ACE's and the importance of closely looking at differences amongst them for different diseases, races, sexes and ages.
3. In regard to Dr. Krantz's association with drug companies, he responded that he does receive grants from Merck, and he speaks for Wyeth for the American Heart Association. He did stress the importance of the use of evidence-based data.
4. Dr. Krantz spoke to why drug companies are not doing Head to Head studies to show that their product is better than the others. Some factors include the expense of such studies, with the risk that the drug manufacturer's drug may not be better, and the bottom line for the drug companies is making money. The EPC commented that each study has different patient populations, drugs (generics and brand), and other factors which makes it difficult to compare drugs. The EPC also commented that Head to Head studies are hard to find.

#### **Nancy Brown with Pfizer:**

Spoke to the issue that trials studied were not comparative, and asked the PDLAC to look at utility of drugs (What is most useful in practice), especially in hypertension.

#### **Betty Iverson with Wyeth:**

1. Pleaded for the use of Altace (ramipril) for a branded drug on the PDL.
2. Handed out a study on ACE's published by the Journal of the American College of Cardiology along with overviews of other studies.

### **Further Committee Discussion:**

Dr. Smith encouraged looking at q.d. dosing, and inquired as to what indications the committee would look at.

Roxanne spoke to the fact that the Pharmacy Unit and the DUR Board would look at dosing and indications when reviewing the PDL and PA criteria. She reminded the PDLAC that its recommendations need to be based on evidence.

The committee as a whole expressed concern with recommending one ACE Inhibitor over another, and that one drug would be picked over all the others based on price.

Dr. Broomfield moved that one factor in the recommendation should be that of q.d. dosing. The motion was seconded with discussion following about compliance issues and the equality of each drug for various uses. **The motion passed.**

Dr. Broomfield moved to not break recommendations down to disease classes. There was no second.

Dr. Broomfield moved that no drug be removed from the list. The motion was seconded with discussion about efficacy, safety and the fact that not all drugs were included in all the studies. The motion failed.

Dr. Broomfield moved that the data shows that the efficacy for all the ACE's are the same. Discussion followed that there were differences, but the data did not show this. No second.

Dr. Johnston moved that there are differences amongst the ACE's. No second.

Chad Panning, PharmD moved that moexipril and fosinopril *not* be considered due to no mortality data for either drug. The motion was seconded with discussion to clarify that the evidence showed that they are not equivalent to the others, based on their mortality data. **The motion passed.**

Dr. Johnston moved that for hypertension and heart failure, there be no recommendation that one is superior to another. No second.

Dr. Harrison moved that there be consideration to dosing, the removal of moexipril and fosinopril for consideration, and that all the others be considered equivalent. There was a second with a discussion on the significance of the evidence reflecting their differences. Dr. Harrison withdrew his motion.

Dr. Johnston moved that there is no evidence showing significant clinical differences in the ACE's, excluding moexipril and fosinopril. The motion was seconded with no discussion. **The motion passed.**

**Final Committee Recommendation:**

**There is no evidence showing significant clinical differences between the ACE inhibitors, with the exception of moexipril and fosinopril. The committee recommended a consideration for once daily dosing.**

## Attachment A

PPIs: (includes generic and OTC formulations when available)

esomeprazole (Nexium®)  
lansoprazole (Prevacid®)  
omeprazole (Prilosec®)  
pantoprazole (Protonix®)  
rabeprazole (Aciphex®)

ACE Inhibitors: (includes generic and OTC formulations when available)

benazepril (Lotensin®)  
captopril (Capoten®)  
enalapril (Vasotec®)  
fosinopril (Monopril®)  
lisinopril (Zestril®, Prinivil®)  
moexipril (Univasc®)  
perindopril (Aceon®)  
quinapril (Accupril®)  
ramipril (Altace®)  
trandolapril (Mavik®)