



STATE MEDICAID P&T COMMITTEE MEETING
 FRIDAY, December 21, 2007
 7:00 a.m. to 8:30 a.m.
 Cannon Health Building
 Room 125



MINUTES

Committee Members Present:

Lowry Bushnell, M.D.
Karen Gunning, Pharm. D.
Raymond Ward, M.D.
Koby Taylor, Pharm D.

Kort DeLost, R.Ph.
Thomas Miller, M.D.
Duane Parke, R.Ph.
David Harris, M.D.

Board Members Excused:

Jerome Wohleb, Pharm D.

Dept. of Health/Div. of Health Care Financing Staff Present:

RaeDell Ashley
Jennifer Zeleny

Lisa Hulbert
Tim Morley

University of Utah Drug Information Center Staff Present:

Chris Beckwith, Pharm. D.

Linda Tyler, Pharm. D.

Other Individuals Present:

Reed Murdoch, Wyeth	Joseph Truong, Pharm. D., Boehringer Ingelheim	Crystal McCoy, U of U
Jay Jennings, Sanofi-Aventis	Trish McDaid-O'Neill, AstraZeneca	Doug Vogeler, MD, Forest
Sabrina Aery, BMS	Sean McGarr, Forest	Dr. Joann Ginal, BMS
Tom Sanders, U of U	Ben Focht, Amylin	Mark German, Novartis
Craig Boody, Lilly	Amberlie Storddard, Pharm. D. Student	Jan Lawrence, Merck
Linda Craig, AstraZeneca	Robert Jaramillo, Novartis	Barbara Boner, Novartis
Kate Ryan, AstraZeneca	Catherine Summers, Daichi Sankyo	Roy Lindfield, Schering

Meeting conducted by: Karen Gunning, Pharm. D., Chairperson.

1. Minutes for December 2007 were reviewed. Duane Parke made a motion to approve the minutes. The motion was seconded by Dr. Miller. The motion passed with a unanimous vote by Dr. Harris, Dr. Miller, Dr. Bushnell, Dr. Ward, Dr. Gunning, and Duane Parke.
2. DUR Board Update: Tim Morley addressed the Committee. The DUR Board did not meet in January 2008.

3. P&T Committee Update: Duane Parke addressed the Committee. For the long-acting narcotics, Medicaid will cover all of the generics, as well as Kadian and Avinza. Other long-acting narcotics will be non-preferred.
4. Antihypertensives - ARBs: Dr. Christina Beckwith addressed the Committee. The main document for the ARB class review is the document prepared by the Oregon Health Sciences University Evidence-Based Practice Center. In their review, they included the seven ARB's that are available in the U.S. The main questions that were evaluated had to do with the safety and efficacy of the ARB versus each other. They set key questions to evaluate in adults efficacy, and safety. For efficacy, they selected outcomes that would reflect clinical importance, such as survival, quality of life, organ damage, and hospitalizations due to the disease state. The indications that they reviewed were essential hypertension, patient with high cardiovascular risk factors, recent myocardial infarction, heart failure, and diabetic and non-diabetic nephropathy. For safety, they evaluated the same disease states, they reviewed overall adverse effects, withdrawals due to adverse effects, serious adverse events, and specific withdrawals due to specific adverse effects such as renal impairment, cough, or angioedema. The third thing that they looked at was whether there are specific subgroups of patients based on demographics, other disease states, or medications for which one agent would be safer or more effective than another. They included English-language reports of controlled clinical trials for evaluating the efficacy question. Their goal was to evaluate head-to-head trials comparing one agent to another so they could have direct evidence. For the safety question, they also included observational studies, when available. Overall, they identified 1,700 articles. Of this, they selected 64 randomized controlled clinical trials and 4 systematic reviews for the efficacy question. For safety, they evaluated 8 randomized controlled trials and 3 observational studies. For the subgroup question they evaluated 18 randomized trials.

The first question was efficacy in hypertension. For the endpoint selected, there were no clinical trials. However, there were some active-controlled trials and placebo-controlled trials that evaluated the endpoints of interest. Overall, in hypertension, all of the drugs have been evaluated for these endpoints, except for olmesartan and telmisartan. In the active-controlled trials, individually just ibresartan showed all-cause mortality, cardiovascular mortality, and cerebrovascular events. Ibresartan was 13% and nitridipine was 17% for the trial that was available for those 2 agents. That difference was statistically significant. The endpoints are different for each of the different drugs, so it is difficult to make a direct comparison. One trial evaluated end-stage renal disease and deterioration of renal function with losartan compared to enalapril. GFR increased a similar amount with both drugs; there was no difference. Quality of life was very difficult to compare, in general. The ARBs were better than placebo for effects on quality of life. They were about equal to other medications. There were some individual differences, but this is the overall conclusion. In placebo-controlled trials, for all cause mortality, candesartan was equivalent to other antihypertensive medications in elderly patients. For cardiovascular mortality, first cardiovascular event was similar with candesartan and other antihypertensives. It was 10-11% for both drugs. The only difference that was seen was for non-fatal stroke, which was 3% for candesartan and 4% for other antihypertensives. That was statistically significant. Looking at subgroups, there was benefit seen to patients who had a previous stroke. With irbesartan, that one was evaluated for progression to end-stage renal disease or deterioration of renal function. Patients progressed to diabetic nephropathy: 5% given irbesartan 300mg, 10% given irbesartan 150mg, and 15% of patients given placebo. Valsartan was also evaluated for effects on renal function. It was similar to placebo in the one available trial. For patients

with high cardiovascular risk factors there was no head-to-head trials. There were 2 controlled trials of losartan and valsartan that compared it to other active comparators. In the LIFE study for losartan, there were over 9,000 patients with hypertension and left ventricular hypertrophy. For valsartan, there is the VALUE trial comparing valsartan to amlodipine in over 15,000 patients. The LIFE study found that all-cause mortality was similar in losartan and atenolol with 8-9% in both groups of patients. The VALUE study found that all-cause mortality was about 11% with either valsartan or amlodipine. For cardiovascular mortality, there were some differences. It was about 11% with losartan and 13% with atenolol, which was statistically significant. Cardiovascular mortality with valsartan and amlodipine were similar with 4% in both groups. Looking at individual cardiovascular events, with stroke the rate was about 5% with losartan and 7% with atenolol, which was statistically significant. There were no other significant differences. What was notable in the LIFE study was that there was no benefit seen in African-American patients, and they had overall worse outcomes than the other patients in the trial with losartan. The VALUE trial also evaluated fatal and non-fatal MI. The rates were 5% with valsartan and 4% with amlodipine, which was statistically significant. In patients with recent MI, there were, again, no head-to-head trials. In active control trials, there were some for valsartan and losartan. With valsartan, the VALUE trial compared it with captopril in over 14,000 patients and with losartan, the OPTIMAL trial compared losartan with captopril in over 5,000 patients. Overall, valsartan was as effective as captopril for all-cause mortality and cardiovascular mortality - about 17-20% for those. The other endpoints were similar between these two agents. With losartan versus captopril, losartan looked like it may be a little less effective for CV mortality - 15% for losartan and 13% for captopril. There was a similar trend for all-cause mortality with 16% for captopril and 18% for losartan. Again, this was a trend and there may have been some power issues with it. Other endpoints were similar for both groups.

In patients with heart failure, all the agents have been evaluated except for olmesartan. There are no head-to-head trials, again. Active control trials are available for candesartan, losartan, telmisartan, and valsartan. All-cause mortality, cardiovascular mortality, and hospitalizations have been evaluated in 3 trials. The ELITE trial found a downward trend for the risk of death and hospitalization with losartan at 9% and captopril at 13%. All cause mortality was, however, significantly lower with losartan than with captopril. In the ELITE 2 trial, which was another losartan versus captopril, there was no significant difference in all-cause mortality between the two groups. The other endpoints were similar as well. The RESOLVE trial compared candesartan, candesartan plus enalapril, and enalapril and found that hospitalizations were actually worse with candesartan or the combination therapy. Looking at the individual agents losartan, valsartan, and telmisartan, they may improve symptoms similar to enalapril or captopril in, but that may not actually translate to long-term effects.

Looking at quality of life, the ARB's improve quality of life in heart failure similar to ACE inhibitors. They did not have direct comparisons to evaluate there. In placebo controlled trials, candesartan, irbesartan, losartan, and valsartan are better than placebo. One trial, the VAL-half trial showed mixed results when ACE-inhibitor and valsartan were used in combination therapy. Patients had a higher mortality rate on the combination of valsartan and ACE-inhibitor plus a beta-blocker, but that trial is somewhat of an outlier.

In patients with nephropathy, most of the ARBs have been studied, except for irbesartan and olmesartan. Again, no head-to-head trials. The agents that have been studied are better than

placebo for surrogate endpoints, such as proteinuria and creatinine clearance. It would appear in diabetic nephropathy that one can't draw conclusions because the endpoints are so varied and the patients studied are so varied. However, in diabetic nephropathy it looks like irbesartan and losartan have similar effects and are better than placebo. The trials that evaluated this, for irbesartan, patients progressed to doubling of serum creatinine, end-stage renal disease, or death in 33% of the patients on irbesartan compared to 39% on placebo - that was statistically significant. In the renal trial for losartan, 44% of the patients had this endpoint compared to 47% for placebo. The numbers looked different for the two trials, but overall the ARB did reduce this endpoint compared to placebo. There was one systematic review that looked at the ARBs as a class, and found that the ARBs did reduce the incidence of end-stage renal disease.

The second question that was evaluated was safety. Again, there is not enough information to determine whether or not they differ. Overall, they all cause cough, angioedema, and because of the way the studies were set up, they were not powered to compare adverse effects.

The last part, are there subgroups of patients for which one agent is safer or more effective than another? Again, inadequate data to compare. The one thing that stands out in the LIFE study is that the survival benefit was not seen in patients who are African-American who have an increased cardiovascular risk. That does not offer any comparative information between the agents; it is just notable. The one difference that does stand out with these agents is that there are differences in drug interaction risk. Although there are no studies that have evaluated this, there are 4 agents that are not metabolized by the cytochrome P450 - that would be candesartan, irbesartan, olmesartan, and valsartan. In some patients they may have a lower interaction risk.

Overall, it is difficult to determine how these agents compare. There are two for which there is not a lot of long-term efficacy data or long-term survival data. No studies are available for long-term outcomes on olmesartan, and irbesartan has only one trial.

Dr. Kate Ryan from AstraZeneca addressed the committee. With regards to candesartan, or Atacand, Atacand has two major indications in hypertension and heart failure. Specifically addressing heart failure, Atacand is indicated for the New York Heart Association Class 2 through Class 4 heart failure in patients with left ventricular systolic dysfunction and have an ejection fraction $\leq 40\%$. This is indicated to reduce cardiovascular death and hospitalization. Atacand also has an added effect on these outcomes, especially when added to an ACE inhibitor. This was reviewed in the CHARM studies. Also, Atacand is indicated for hypertension alone or in combination, as are the others. The existing therapies for heart failure have demonstrated to be life saving in patients with heart failure, but these patients still remain at very high risk for cardiovascular death and heart failure hospitalizations. In fact, it is estimated that 44% of Medicare enrollees who are discharged with heart failure diagnosis are readmitted once, and 16% are readmitted twice within 6 months. The CHARM program, the major heart failure trial with Atacand, was a multi-national program of 3 independent studies designed for 3 different types of heart failure patient populations; two with the ejection fraction of $\leq 40\%$ and one with a preserved systolic dysfunction with an ejection fraction $\geq 40\%$. The CHARM program took these independent double-blind randomized placebo-controlled clinical trials and also pooled some of the information. A total of 7,600 patients were in these trials. For all 3 trials, the primary endpoint was the same, which was time to cardiovascular death or hospitalization for heart failure. It should

be noted that heart failure symptoms improved in all 3 trials. All of these patients were already on optimal medication therapy. The first trial was the CHARM alternative, which was for patients who could not tolerate an ACE inhibitor. In this trial of over 2,000 patients with ejection fraction of $\leq 40\%$, there was a 23% reduction found in the rate of cardiovascular death or rate of hospitalization for heart failure. The second of the three CHARM added trials was also in a patient population of $\leq 40\%$, but Atacand was added to existing ACE inhibitor therapy. The primary endpoint was the same as in the CHARM alternative trial. There was 15% reduction in cardiovascular death and rate of hospitalization for heart failure. The third part of the CHARM trial was in the preserved population. While not significant, there was a trend toward a decrease in cardiovascular death and hospitalization due to heart failure. The addition of Atacand onto treatment for symptomatic heart failure or patients with left ventricular dysfunction does provide a significant net benefit as shown through the CHARM trial, whether added to an ACE inhibitor or other heart failure treatments.

Karen Gunning asked what doses were used in the CHARM trials. There was no target dose in any of the trials, but the maximum daily dose of Atacand is 32mg.

Dr. Joann Ginal from BMS addressed the Committee on behalf of irbesartan, or Avapro. Avapro is an ARB. The average absolute bioavailability of Avapro is 60-80%. Peak plasma concentrations occur at 1.5 to 2 hours post oral administration, elimination half-life is 11-15 hours, and food does not effect bioavailability. There are two indications for Avapro. One is for the treatment of hypertension either alone or in combination with other antihypertensive agents. The second is the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria greater than 300mg/day in patients with Type 2 diabetes and hypertension. There are long-term safety and efficacy hypertension studies. There was a pooled analysis of 1-2 years open-label multi-center double-blind studies of patients who had diastolic hypertension of 95-110 mm/Hg. Long-term, Avapro is considered safe and effective. Overall, the mean blood pressure change at months 12, 18, and 24 are noted. At 12 months it was -21/-16, at 18 months it was -19/-15, and at 24 months it was -17/-15 mm/Hg. For Type 2 diabetic nephropathy with hypertension, the IDNT trial is a multi-center randomized double-blind placebo and active controlled trial with a mean duration of 2.6 years. It included 1,700 patients with Type 2 diabetes, hypertension, and nephropathy and over 900mg of proteinuria. The patients were randomized into one of 2 arms: Avapro 300mg, amlodipine 10mg, or placebo. The primary endpoints were doubling of serum creatinine, end-stage renal disease, death, or a composite of all 3. The results of the IDNT trial were a 20% relative risk reduction for Avapro versus placebo, which significant; and a 23% relative risk reduction for Avapro versus amlodipine, which is significant. At one year, the mean reduction of proteinuria from baseline was 42% for Avapro, 15% with placebo, and 12% with amlodipine. IDNT study reported adverse events were comparable to those of other hypertension studies. As far as safety is concerned, as with all ARBs, there is a black box warning for use in pregnancy. Avapro has been evaluated for safety in more than 4,300 patients with hypertension and about 5,000 patients overall. The most commonly reported adverse events versus placebo were diarrhea, dyspepsia/heartburn, and fatigue. The initial recommended dose for hypertension is 150mg once per day titrated up to 300mg once per day for patients who require additional control of hypertension. In diabetic nephropathy, recommended target maintenance dose is 300mg per day.

Dr. Robert Jaramillo from Novartis addressed the Committee. The package insert was distributed to the Committee. It is common to lump ARBs and ACEs in a class effect. We

are finding that medications that have a similar primary outcome may have differences in a secondary outcome. Looking at Diovan, this is an agent where Novartis has devoted a significant amount of research beyond that which is required by the FDA to get the drug an approved indication. The first indication, of course, is treatment of hypertension, which all ARBs have. Looking at heart failure, candesartan is the only ARB to have this indication besides Diovan. This was supported by the VAL-HEALTH trial, which showed a 132% reduction in morbidity over 27 months, and a 27% reduction in hospitalization. There was no change in mortality. The other indication that is important to point out is cardiovascular mortality after myocardial infarction. Diovan is the only agent to have this indication. This was supported by the VALIANT trial, which was able to show that valsartan was not inferior to captopril in all-cause mortality. As most people know, captopril has been able to show a 26% reduction in the probability of MI. One of the most recent indications that Diovan has received is looking at pediatric hypertension. As we face the obesity crisis in this country, it will become more important to treat children for hypertension. Looking at the indication of diabetic nephropathy, Diovan does not have this indication, but has a 6 month study MARVEL, which shows a reduction in urinary albumin excretion rate of 44%. This has a direct correlation with proteinuria. Diastolic dysfunction has been studied in the VALID trial. Pro BMP was looked at in the VAL-HEALTH trial. The JIKEA study looked at Diovan on top of current therapy in 8,000 Japanese patients. This study, which was reported in Lancet, showed a 44% reduction in stroke, and was able to show a reduction in cardiovascular events. In 2009, other studies such as the NAVIGATOR trial will look at Diovan in addition to Starlix in patients who are glucose intolerant. This will look at time progression to diabetes, mortality, and morbidity. There are future studies looking at Diovan in African Americans. Diovan is supported by national organizations, JNC7, and American Heart Association. Diovan offers an important option in patients who cannot tolerate ACEs due to cough, or cannot get to their hypertension goal. It offers another agent in the armamentarium for physicians to get their patients to goal.

Karen Gunning asked if the trials had a target dose. The goal was to titrate patients upward at 4 week intervals until they got to the maximum dose.

Dr. Jaramillo asked if Tekturna would be under consideration for the PDL, since it is on the agenda. Karen Gunning explained that it was only on the agenda as an informational piece. It is not the purview of the P&T Committee to make recommendations for a preferred agent if there is only one agent in the class.

Dr. Katherine Summers from Daiichi Sankyo addressed the Committee. Benicar, also known as olmesartan medoxomil, is a once-daily selective AT1-subtype angiotensin 2 receptor agonist indicated for the treatment of hypertension. It can be used as either first line therapy either alone or in combination with other antihypertensive agents. The available doses of Benicar are the 20mg starting dose and the 40mg maximum dose. There is a 5mg dose that is available for dosing flexibility and as a consideration for patients who require a lower starting dose. An integrated analysis of the 7 clinical trials in approximately 2,600 patients with stage 2 hypertension showed that Benicar 20mg and 40mg once a day induced significant reductions in mean blood pressure - approximately 15/12 mmHg and 17/13 mmHg compared to the 5/6 mmHg in the placebo group. The effect of once daily dosing versus twice daily dosing of Benicar over a 24 hour period in ambulatory patients in both regimens of 20mg once a day or 10mg twice a day showed no benefit in the twice daily versus once daily dosing. This is truly a once-daily medication. In clinical trials, withdrawal rates for adverse events were 2.4% versus 2.7%. Incidence of adverse effects with Benicar

was comparable to placebo. The only difference occurred in a rare event, only 1% of the patients treated, and that was dizziness. The rates were 3% versus 1%. Benicar is not metabolized by the cytochrome P450 system, therefore interactions with drugs that inhibit, induce, or are metabolized by the cytochrome P450 system are expected. In addition, no dosage is recommended in the elderly or in patients with moderate or marked renal impairment that have a creatinine clearance of less than 40mg/minute or hepatic dysfunction.

Dr. Jan Lawrence from Merck addressed the Committee. The Oregon Health Sciences Summary by key clinical question does a great job in reviewing and citing studies available to help the Committee in making a decision. There are a few points to consider in favor of including losartan on the PDL. For every key clinical question on the summary of evidence, there is fair to good evidence cited for losartan. This means that losartan has been widely studied for safety and efficacy in various trials that have addressed important clinical issues. In all of the outcome studies, losartan has been dosed once daily. Most medical providers have clinical experience with losartan; it is the second most widely prescribed ARB in Utah as well as the United States. Although ARBs are generally used when patients are intolerant of ACEs these days, the American Diabetes Association recommends that ARBs may be considered as first line therapy in the slowing of the progression of nephropathy in patients with Type 2 diabetes. The ADA also recommends that it should be considered in patients who have hypertension and macroalbuminuria. Losartan is the only ARB that has statistically shown an impact on end-stage renal disease. Since the introduction of losartan in May 1995, it has been shown to be safe and well tolerated. The labeling does contain a black box warning about use in pregnancy, but that warning is similar among all of the ARBs. A current package circular is available now, or through Merck.com. Although the Committee is not discussing cost considerations, losartan was the first ARB on the market and it will be the first one available as a generic sometimes in the second quarter of 2010. Most insurance companies have losartan available on their formularies, including federal entities such as the Veteran's Administration and Tricare. No claims of efficacy of one ARB over another have been permitted by the FDA. Some companies have been sanctioned for implying or stating superiority in terms of efficacy for the treatment of hypertension.

Dr. Joseph Truong of Boehringer-Ingelheim addressed the Committee. Micardis is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents at doses of 20mg, 40mg, or 80mg. The antihypertensive effect of Micardis is maintained for a full 24 hour dosing interval. With ABPM monitoring and conventional blood pressure measurement, the 24 hour trough to peak ratio for 40mg to 80mg Micardis was 70%-100% for systolic blood pressure and diastolic blood pressure. This meets the FDA trough to peak ratio requirement for once daily dosing. Regarding efficacy, antihypertensive efficacy was evaluated in prospective randomized double-blind double-dummy placebo-controlled for titration multi-center parallel group study in over 1,000 subjects comparing Micardis 80mg with valsartan 160mg given as monotherapy for the first two weeks of treatment, followed by 6 weeks of fixed-dose combination therapy with Micardis 80mg / HCTZ 25mg versus valsartan 160mg / HCTZ 25mg in patients with stage 1 or stage 2 hypertension. Mean reductions in baseline for seated trough measurements at the end of 8 weeks were greater for telmisartan combination than valsartan combination therapy: -24 versus -21 mmHg systolic reductions respectively. The mean difference was -2.8 mmHg. This is also statistically significant in diastolic blood pressure with a mean difference of 1.8. Regarding regular efficacy in a community based pilot program including 1600 patients with stage 1 or stage 2 essential hypertension either untreated or uncontrolled on current therapy were switched over to Micardis 40mg once daily. After 2 weeks, if the

blood pressure was still high, the dose was increased to Micardis 80mg, and HCTZ was added if needed. There was no comparator in this study. The mean 24 hour reduction for the entire cohort was -10/-6 mmHg. Based on the APBM criteria, hypertension was controlled in 69.7% of all subjects, and based on seated office blood pressure measurements, blood pressure was controlled according to the JNC7 guidelines in 78.9% of subjects. Other efficacy studies of telmisartan or telmisartan/HCTZ are available for specific patient populations, such as seniors, Type II diabetics, obese / overweight diabetics, or those with chronic kidney disease. Due to time constraints, these will only be addressed if the Committee has specific questions. Regarding safety, when used in the second or third trimesters of pregnancy, drugs that act directly on the renin-angiotensin system can cause harm or death to the developing fetus. If a patient becomes pregnant, Micardis or Micardis/HCTZ should be discontinued as soon as possible. They are contraindicated in patients who have a sensitivity to any of the components. Safety and efficacy has not been established in pediatric patients. Telmisartan is not metabolized by the cytochrome P450 system, and has no effects in vitro on cytochrome P450 enzymes.

Dr. Doug Vogeler addressed the Committee on behalf of Benicar. In personal experience, Benicar is important for treating people with hypertension who cannot tolerate an ACE. People who have diabetes, or renal disease are usually started on an ACE and have an ARB added, if needed, or are switched to an ARB if they cannot tolerate the ACE. When using the ARB class, Diovan and Cozaar have been around the longest, are extensively used, and are on most insurance formularies. Benicar is the “newest kid on the block” and therefore does not have outcomes studies and may not. In personal experience, 60%-80% patients who are switched to Diovan, Cozaar, or Benicar get to goal. In personal experience, Benicar is stronger. Before adding another blood pressure medicine to a different ARB, a patient is switched to Benicar. About 80% of those patients get to goal without needing another blood pressure medication. There are no head-to-head studies comparing one ARB to another, but in personal experience Benicar appears to be a better ARB, and seems to be more effective than the two most widely used agents in getting patients to goal.

A letter from Dr. John Muris was read by Karen Gunning. He wrote in regards to the medication Micardis. Micardis is one of the ARBs used to manage hypertension. In his practice, he has found that this is one of the better ARBs. Compared to Cozaar and Diovan, it appears to be more potent than these two drugs. With Cozaar or Diovan, he has had to use the maximum dose or twice-daily dosing to get the same results for lowering blood pressure. In addition, he has seen fewer side-effects from using Micardis. Please consider Micardis as a PDL selection.

The next letter is from Dr. Peter Sundwall, also regarding Micardis. He has used Micardis since it has come on the market. He has used it frequently in his practice with few problems.

Another letter from Dr. Steven Foote in Syracuse. It does not necessarily pertain to this class of medications, but it concerns restricting access to certain types of medications. He understands that saving money is imperative, but asks that in treating certain life-threatening conditions such as asthma, hypertension, etc. be excluded from the list. If a list is necessary, he asks that it be broad in these categories.

Karen Gunning felt that she needed to make a statement that it is not the purview of the Committee to discuss step therapy for situations such as ACEs versus ARBs. This was

requested as more of an informational piece. The Committee is here to look at classes of medications, and not broad classes like antihypertensives, but very specific therapeutic classes like ACEs or ARBs. Similarly, the Committee would not look at immunosuppressants as one large class or take that action with similar broad classes. This is a little misunderstood, and hopefully the Committee process will allow for education of providers and legislators who are concerned about this.

Kort DeLost asked about the incidence of cough with the ARBs. The studies were not set up to evaluate whether one ARB has a higher incidence of cough than another. As far as cough with ACEs versus ARBs, this will be addressed later.

The Committee felt that there are no significant differences in safety differences in the ARBs, but asked Dr. Beckwith if they needed to consider which drugs are metabolized by the cytochrome P450 pathway as a safety issue when making a recommendation to the Division. Dr. Beckwith said that these are mostly interactions that can be managed if the prescriber considers what else the patient may be taking when prescribing the ARB.

Dr. Ward made a motion that the Committee finds that the ARBs are all equal in terms of safety, and that the Division should make a decision based on cost. Dr. Miller seconded the motion. The motion passed unanimously with votes by Dr. Harris, Dr. Miller, Dr. Bushnell, Dr. Ward, Dr. Gunning, Duane Parke, Kort DeLost, and Dr. Taylor.

The question of efficacy is more complex due to the different indications of the various agents. Dr. Ward asked Dr. Harris if this is a drug class that he uses frequently in pediatric practice. Dr. Harris stated that most pediatric hypertension is severe enough that it is managed by either renal or cardiovascular specialists. It is important that an agent with a pediatric indication is included on the list.

Dr. Gunning asked if Dr. Harris is seeing an increased use of these agents in children due to obesity. Dr. Harris stated that once weight comes down and insulin intolerance is resolved, blood pressure seems to come down with this management. However, counseling patients to do this is not always successful. Past management of these patients has been by endocrinologists, but they are so overloaded that generalists are likely to start seeing these patients in the future.

Based on Dr. Beckwith's report, Dr. Ward felt that there was no way to determine that any one agent is more efficacious than another. He made a motion to report back to the Division that all of the ARBs are medically equivalent, and that the Division make a decision based on cost, and include at least one agent with a pediatric indication. Dr. Miller seconded the motion. The motion passed unanimously with votes by Dr. Harris, Dr. Miller, Dr. Bushnell, Dr. Ward, Dr. Gunning, Duane Parke, Kort DeLost, and Dr. Taylor.

5. Antihypertensives - ACEIs: Dr. Tyler addressed the Committee. This class of drugs is the Angiotensin Converting Enzyme Inhibitor class, common known as the ACEs, block the activity of the renin-angiotensin system. In addition to their effects on blood pressure, ACEs are thought to have beneficial effects on cardiovascular remodeling following myocardial infarction, in patients with heart failure, and in preventing diabetic nephropathy. There are 11 ACE inhibitors that were included in the Oregon review. There is a supplemental table showing the ten ACEs available in the United States. All of them are available as generics, except for two. The Oregon review included cilalopril. This will not be discussed further.

The agents available in the US market are benazepril, enalapril, captopril, lisinopril, fosinopril, moexepiril, perindopril, quinapril, ramipril, andtrandolapril. These drugs all have FDA indications for treating hypertension. Table 2 in the review shows that most of them have indications for the treatment of heart failure, and some of them have indications for the treatment of recent MI, one has labeling for diabetic nephropathy. The Oregon Evidence-Based Center review was the primary document used for this class review. They did a thorough search of the literature and identified seven categories that they looked at: hypertension without high cardiovascular risk, hypertension with high cardiovascular risk, high cardiovascular risk, recent MI, heart failure, diabetic nephropathy, and non-diabetic nephropathy. They selected those trials that evaluated the outcomes. In particular, they selected trials that looked at all-cause and cardiovascular mortality; trials that looked at cardiovascular events, often as composite endpoints; trials that looked at end-stage renal disease; and trials that looked at quality of life. In heart failure, they also looked at trials that included hospitalizations for heart failure. They were looking specifically for any systematic reviews that evaluated outcomes, both in terms of efficacy and adverse event rates, they were looking at randomized controlled clinical trials that compared one ACE inhibitor to another ACE inhibitor, or large studies with greater than 100 patients that looked at placebo-controlled trials. They also looked at any randomized controlled trials as well as good-quality observational studies that evaluated the adverse event rate of the ACE inhibitors. Based on the initial search of the literature, they identified over 7,000 articles that they looked at. They excluded all but 500 for not meeting the criteria they were looking for, and reviewed those 500 to see if they had the endpoints they were looking for. From there, they got down to 154 articles. In this group of articles, there were 24 head-to-head comparisons, 81 that were comparisons to placebo, 14 that were active control, and 10 that were systemic reviews of meta-analysis. There were also some additional studies that were observational.

The first key question related to differences in efficacy. The Oregon review did include the ACE inhibitors compared to active controls and the ACE inhibitors compared to placebo. The emphasis will be on the studies that looked at head-to-head comparisons. The first indication was hypertension without compelling indications. The studies that were evaluated do not provide any useful information to compare the effectiveness ACE inhibitors to other ACE inhibitors in no conditions. There was some post-hoc analysis for several large studies that suggested that ACE inhibitors delay or prevent diabetes, particularly in patients who have glucose intolerance. There were a couple of trials that looked at the quality of life. One good quality trial was a 24 week trial for blood pressure, and showed that captopril was equivalent to enalapril. However, as it was measured at the end of the follow-up period, the patients who were on captopril had a better quality of life than those assigned to the enalapril group. The strength of this particular trial is that investigators measured several aspects of quality of life. Because of the detailed measurement of quality of life, the investigators were able to determine among the patients who had good quality of life prior to taking ACE inhibitors, those taking captopril remained with a good quality of life, while those taking enalapril worsened. The major weakness of this study was that the results were reported as averages for the comparison groups rather than as percentages of those who maintained stable. The second group that was looked at was hypertension with compelling indications. Again, there are no head-to-head trials comparing the ACE inhibitors. In patients who have a history of coronary artery disease with or without hypertension or other patients with coronary artery disease, ramipril is the only ACE inhibitor to reduce all-cause mortality. Enalapril, perindopril, ramipril reduced major cardiovascular events in patients who had coronary artery disease. In patients who have had a recent MI, there is one head-to-head trial of captopril versus enalapril and found a significant difference in mortality with captopril at

12% and enalapril at 1%, but this was a relatively small trial. There was another fair-quality head-to-head trial that found no difference in mortality or revascularization rates in captopril versus perindopril. Captopril, lisinopril, ramipril andtrandilopril reduced mortality in heart failure in good-quality placebo-controlled trials. Enalapril had a slight trend towards increased mortality in large good-quality placebo-controlled trials, but significantly reduced the risk of heart failure requiring hospitalization. In smaller placebo-controlled trials, there was a trend of increased mortality and decreased heart failure with lisinopril. In heart failure, one fair-quality head-to-head trial showed no difference in mortality in fosinopril versus enalapril. In the one meta-analysis of 32 placebo-controlled trials, there seemed to be no difference in the drugs that were evaluated. The drugs that were evaluated included benazapril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril. There were 15 head-to-head trials that showed no differences in improvement in the NYHA Class or exercise duration in captopril, enalapril, lisinopril, fosinopril, quinapril, or ramipril. The next indication looking at diabetic and non-diabetic nephropathy, again, there are no head-to-head trials. Captopril reduced end stage renal disease and death in patients with long-standing Type 1 diabetes.

The second key question was whether there are any differences in the ACE inhibitors in terms of adverse effects and safety. The adverse effects of ACE inhibitors include hypotension, dry cough, angioedema, hyperkalemia, and renal impairment. Other adverse effects include rashes, hepatotoxicity, distortions of taste, and neutropenia. The distortions of taste and neutropenia seem to be primarily with high-dose captopril. The angioedema that occurs is usually mild, but can be severe in some cases. It is usually treated with antihistamines and airway management. In the large trials, ACE inhibitors do increase angioedema fourfold, but that is from 1:1000 to 4:1000 patients in a large trial evaluating enalapril. The similar incidence were noted for similar drugs that were evaluated, including lisinopril and ramipril. In the head-to-head comparisons of ACE inhibitors that compared the rates, they looked at the different indications. Looking at hypertension, there were no important differences in adverse events in angioedema, hyperkalemia, and acute renal impairment. In recent MI, the adverse effect assessments were not adequately described in most of these trials. The adverse events were not defined in many of the studies, and there were potential confounders in many of the studies that were evaluated. In heart failure, there were 15 head-to-head trials. There were no difference shown between the trials, except that one study did report a 10% withdrawal rate due to hypotension in the enalapril group compared to 0 in the captopril group. The doses were not titrated in this particular study, which may account for the high rate of hypotension. This study appears to be an outlier. There is one other study that reported a significantly higher rate of systematic orthostatic hypotension in patients taking enalapril compared to those randomized to fosinopril. In the placebo-controlled trials, there was no clear pattern of one ACE inhibitor being superior to another in terms of adverse events.

The third key question is: Are there any subgroups of patients based on demographics, including age, race, gender, other medications, or comorbidities for which one ACE inhibitor is safer or more effective. There are no data to suggest that one ACE inhibitor is better than another for any demographic subgroups. Although the recommended initial dose fortrandilopril is higher in Black patients than in non-Black patients, they found no data suggesting that the efficacy is any different.

In summary, the evidence from head-to-head trials, especially in heart failure, shows that many of the ACE inhibitors are similar both in terms of efficacy and adverse events. Several

ACE inhibitors reduce mortality after MI in certain subgroups, but there is no definitive evidence that they differ in effectiveness for any of the major cardiovascular and renal endpoints. Across the indications, the evidence for mortality reductions is the strongest for captopril, enalapril, and ramipril.

There was no public comment for this class of drugs.

The Committee members asked the physicians about what frequency they see patients needing to change from an ACE inhibitor to an ARB. The physicians estimated this to be approximately 1 in 5 patients. Many people notice the cough, but it doesn't bother them enough to change medications. Cough was likely under reported in some of the earlier studies, because it was not a side effect that was asked about.

Dr. Ward made a motion that all of the members of the ACE inhibitor class are equivalent as far as safety. Duane Parke seconded the motion. The motion passed unanimously with votes by Dr. Harris, Dr. Miller, Dr. Bushnell, Dr. Ward, Dr. Gunning, Duane Parke, Kort DeLost, and Dr. Taylor.

The Committee asked about the differential cost of the various agents. Karen Gunning pointed out that some of the agents in this class may be dosed multiple times per day, and cause a drop-off in real world efficacy. Dr. Tyler stated that the only drugs that require multiple daily doses are enalapril and captopril.

Dr. Ward made a motion that among the ACE inhibitors, they are medically equivalent and the Department choose based on cost, with the caveat that there be agents included that are approved for pediatric use and for once-daily use. Kort DeLost seconded the motion. The motion passed unanimously with votes by Dr. Harris, Dr. Miller, Dr. Bushnell, Dr. Ward, Dr. Gunning, Duane Parke, Kort DeLost, and Dr. Taylor.

6. ACE Inhibitors vs. ARBs (Informational Discussion): Dr. Beckwith addressed the Committee. This report looks at the indications covered in the Oregon-based documents, and compares the efficacy of the classes based on the available clinical trials. Looking at these two classes of agents, they have similar labeled and off-label uses between the two. Both classes have agents available that are labeled for use in children. For the question of efficacy for hypertension, the Agency for Healthcare Research and Quality released a systematic review in November 2007, that evaluated 69 comparative trials between these two classes. They found that blood pressure lowering was similar between the two classes of agents. There were also similarities between the agents for patients who had treatment success with a single antihypertensive agent, effects on left ventricular mass and function, and effects on proteinuria. They did not assess differences between the two classes in death or cardiovascular events because the event rates were too low. Neither class had any significant effect on quality of life, lipid profile, blood glucose, or renal function.

How did the two classes compare for reducing morbidity and mortality in heart failure patients? For all-cause mortality, it is similar between the two groups with the ARBs at about 14% and the ACEs at 13%-14% in a large meta-analysis. Hospitalization rates for the two groups are also similar at between 15%-16%. Looking at whether combination therapy is better than monotherapy, all-cause mortality was similar between ACE inhibitor monotherapy and ACE inhibitor combination therapy with ACEs and ARBs (18% in both

groups). For hospitalizations due to heart failure in both groups, combination therapy does reduce this anywhere from 18%-24% of patients hospitalized on combination therapy versus 17%-28% on ACE inhibitor monotherapy. In the individual trials, it compared those, and in the systematic review it was statistically significant.

In patients with diabetic nephropathy, how did the two classes compare for slowing progression? Neither class has any significant effect on renal function. For proteinuria, both classes reduce proteinuria by up to 80% when given as monotherapy. When given as combination therapy with the two classes together, it is more effective than monotherapy with either class alone. There are no trials comparing the two classes of agents for effects on mortality or effect on end-stage renal disease.

For progression of non-diabetic nephropathy, how did the two classes compare? Effects on proteinuria are similar for both classes. Again, combination therapy with both ACEs and ARBs appeared to be more effective than monotherapy of either class alone. Neither class has any significant effect on renal function as measured by GFR or creatinine clearance. There are some trials that have evaluated effects on end-organ damage, so the composite endpoint was doubling of serum creatinine, end-stage renal disease, or death. With trials that compared losartan to enalapril, this endpoint occurred in 16%-30% of losartan patients and 18%-31% of enalapril patients. The comparisons between the two groups were not statistically significant. In all trials reviewed, there were no significant changes in creatinine clearance. However, this one trial that appears to be an outlier did find that both classes of agents decreased creatinine clearance significantly from 80%-90%, but it may be that the patients were different in this study. The study found that 81% of patients treated with ARBs progressed to end-stage renal disease, compared to 53% of patients on ACEs. This was statistically significant. However, because of some of the other results that this study found that were so different from the other trials, that may be an outlier. With combination therapy versus monotherapy, combination therapy is more effective. Fewer patients progress to end-stage renal disease or doubling of serum creatinine on combination therapy versus monotherapy with either class alone.

How did these two classes compare in causing regression of left ventricular hypertrophy? The ARBs are at least as effective as the ACE inhibitors. There are not many trials available, and some of the trials found were not able to assess comparative differences because of power limitations. Combination therapy is significantly more effective than monotherapy in patients with this disease. There are some questions about whether left ventricular hypertrophy regression is an appropriate endpoint to evaluate. This came out of a life study and was used as a surrogate marker that may not predict long-term morbidity and mortality.

For reducing morbidity and mortality due to cardiovascular disease, how did these two classes compare? There are three direct head-to-head trials that have evaluated this. In patients who have acute MI and heart failure, losartan was equivalent to captopril. There were some endpoints for which it was more effective; however, there were others where it was equivalent. For valsartan in patients with MI and left ventricular dysfunction or heart failure, valsartan and captopril have equivalent efficacy. In patients with coronary artery disease, candesartan plus an ACE inhibitor is equivalent to ACE inhibitor monotherapy. Overall, one trial evaluated effective age, and they found that no matter what, all-cause mortality increased with patient age. It was 4 times higher in patients at least 85 years old compared to younger patients.

As far as adverse effects compare, cough is much less common with the ARBs. Frequency of cough is variable with the ACEs at 5%-80% and 0%-50% for ARBs. However, in many trials that compared the individual ACEs with the individual ARBs, cough was statistically significantly less likely with the ARBs than with the ACEs. There are very few trials that directly assess angioedema as an endpoint; however, angioedema seems to be much less common with ARBs than ACEs. Overall, with both of these side-effects, patients who have had the side effect of cough or angioedema on an ACE inhibitor are more likely to have the side effect with an ARB. The Agency for Healthcare Research and Quality Review also assessed these facts and looked at persistence (how long a patient is expected to stay on a particular drug). With ACEs, the median persistence was 50% of patients, ranging from 31%-82%. With ARBs it was 62% median with a range of 33%-89%. More patients were likely to stay long-term on the ARBs versus the ACEs. Similarly, discontinuation rates were about 19%-20% with ACE inhibitors compared to 10% for the ARBs. Looking at the separate question of whether combination therapy is better than monotherapy, patients who are on combination therapy are more likely to discontinue medication due to side-effects than patients on monotherapy.

Overall, there are no significant differences in efficacy for the indications examined between these two classes of agents. For combination therapy, it may have some positive effects on some patients with diabetic nephropathy, nondiabetic nephropathy, and left ventricular hypertrophy. However, in the other indications, combination therapy has not been shown to be more effective than monotherapy. Adverse events may differ between the two classes.

7. Antihypertensives - Aliskiren (Information Discussion): Dr. Tyler addressed the Committee. Aliskiren is the first direct renin inhibitor approved by the FDA. It is approved for the treatment of hypertension as monotherapy or in combination with other antihypertensives. A direct renin inhibitor effects the renin-aldosterone pathway very early on in the process. ACE inhibitors work in the middle of the pathway, and ARBs effect the pathway at the direct receptor level. In the development of this drug, it was thought that targeting the pathway very early would have more efficacy. In clinical trials, it has shown equal efficacy to the other antihypertensives that it has been compared to. There have been six randomized controlled clinical trials comparing the efficacy of aliskiren to other antihypertensives, including amlodipine, HCTZ, irbesartan, losartan, valsartan, either as combination therapy or as monotherapy. The labeled doses of aliskiren have been 150mg-300mg. There have been higher doses used in some of the trials, but higher doses do not show any additional efficacy. All of these displayed similar effects on blood pressure to the other agents. In a single trial, aliskiren 300mg per day was more effective than irbesartan 150mg per day for lowering diastolic blood pressure and helping patients achieve blood pressure control. The efficacy was similar between the aliskiren 150mg/day and irbesartan 150mg/day. In another trial, valsartan 160mg-320mg per day lowered the diastolic and systolic blood pressure more than aliskiren 150mg per day. The aliskiren 150mg-300mg per day lowered diastolic mean blood pressure by a mean 2.2-12 mmHg and the mean systolic pressure by 10-15 mmHg in monotherapy groups. In the comparator groups, the diastolic blood pressure was reduced by 5.5 -11.3 mmHg and the systolic blood pressure was reduced by 10-16 mmHg. Aliskiren produced additional blood pressure control when used along with HCTZ, irbesartan, and valsartan. Aliskiren combined with either HCTZ or valsartan lowered the blood pressure by 10-14 mmHg and the systolic blood pressure by 15-21 mmHg. The most common adverse effect associated with aliskiren is diarrhea. Other serious adverse effects include head and neck angioedema and hypotension. Only 2% of patients discontinued therapy due to an adverse event. Because the renin inhibitors do not effect substance P or bradykinine

concentrations, aliskiren is not expected to cause angioedema and cough that is commonly associated with ACE inhibitors. Aliskiren also does not inhibit or induce cytochrome P450 enzymes, so it does not cause some of the same interactions as some of the others. The starting dose is 150mg daily with or without food, and it may be increased the 300mg daily if necessary. In summary, this is the first direct renin inhibitor on the market.

Next Meeting Set for Friday, January 18, 2008. The Committee requested that the University of Utah Drug Information Service include information about ease of device use and inert propellant contents for the February presentation on inhaled beta agonists.

Meeting Adjourned.

Minutes prepared by Jennifer Zeleny