



18 manufacturers were invoiced during the last calendar quarter, and 4 more manufacturers will be invoiced during this quarter. At this point, the Division is able to continue adding addendums to existing PDL contracts with manufacturers.

The Committee also asked for the schedule for the coming year for a final check prior to approval. The Drug Information Service has looked at the schedule and put it in the order that would best meet their needs. This schedule may still change due to the coming legislative schedule or other forces outside of the control of the Division. If any changes needed to be made, ample notice of at least 60 days would be given. Dr. Ward moved to accept the schedule as proposed. Dr. Miller seconded the motion. The motion was approved unanimously by Dr. Miller, Dr. Ward, Karen Gunning, Koby Taylor, Duane Parke, Kort DeLost, and Dr. Harris.

4. Leukotriene Antagonists: Dr. Erin Fox addressed the Committee. Three leukotriene antagonists are available in the United States: monteleukast as Singulair, zafirleukast as Accolate, and zileuton as Zyflo CR. All three agents are indicated for the treatment of chronic asthma. Monteleukast is indicated for children age 12 months and older, zafirlukast is for patients 5 years and older, and zileuton is for patients age 12 years and older. Monteleukast is also labeled for the prevention of exercise-induced bronchoconstriction in patients 15 years and older, the treatment of seasonal allergic rhinitis in patients 2 years and older, and the treatment of perennial allergic rhinitis in patients age 6 months and older. The University of Utah Drug Information Service conducted a literature search with an emphasis on identifying published randomized controlled clinical trials or meta-analyses evaluating comparisons between the leukotriene antagonists to address key clinical questions. Initially, 457 articles were identified, 226 abstracts were reviewed, and 89 articles were reviewed in detail. Few trials directly compared the leukotrienes to one another, so trials comparing the leukotrienes to other agents used to treat asthma, exercise induced bronchoconstriction, seasonal allergic rhinitis, and perennial allergic rhinitis were reviewed.

For the first clinical question of how does the efficacy of the leukotrienes compare in patients with asthma, few trials show that monteleukast or zafirleukast are more effective than other active therapies. Overall, trials show that inhaled corticosteroids and inhaled salmeterol are more effective than leukotriene antagonists for asthma symptoms. For asthma exacerbations, the number needed to harm is 26, which means that for every 26 patients treated with a leukotriene antagonist, 1 additional patient would have an exacerbation. For improving asthma control 20%, the number needed to treat for fluticasone is 7. One trial shows equivalent results with theophylline and zileuton, one trial shows monteleukast is more effective than cromolyn, and one trial shows that zileuton extended release is more effective than placebo. As far as efficacy in exercise-induced bronchoconstriction, one trial shows monteleukast, zafirleukast, and zileuton are as effective or more effective than salmeterol, budesonide, loratadine, or cromolyn at improving maximum FEV-1 fall after exercise. There are no trials available for zileuton extended release. For seasonal allergic rhinitis, comparative trials show that nasal corticosteroids are more effective in alleviating the symptoms of seasonal allergic rhinitis than zafirleukast or monteleukast. More patients treated with nasal fluticasone (42%) experienced significant improvement in symptoms compared to patients treated with monteleukast (24%). One trial found no differences between monteleukast and desloratadine in nasal symptoms. For perennial allergic rhinitis, one trial found no differences between cetirizine and monteleukast, one trial showed zafirleukast is more

effective than loratadine in improving nasal obstruction, and one trial showed greater improvement in nasal itching with cetirizine but improved night time sleep quality with monteleukast.

As far as compliance and patient preference, no trials directly compared the leukotrienes with one another. One trial showed better adherence with monteleukast compared to inhaled fluticasone, one trial showed equal adherence with monteleukast and nasal fluticasone, and one trial showed patients preferred salmeterol over monteleukast, and two trials showed that patients preferred moneleukast over inhaled cromolyn.

There are no comparative efficacy studies showing that any one agent is safer or more effective for a specific patient demographic, such as age, racial group, or gender. As far as adverse drug reactions, there are no studies comparing these agents directly. Short straw syndrome is a very rare side-effect estimated with an incidence of 60 cases per 1 million patient years for each agent. There are no cases reported with zileuton, but zileuton is used much less frequently than either of the other two leukotriene antagonists. Because of this, no conclusions can be drawn about the risk for zileuton. Rare cases of hepatic dysfunction have been reported with all 3 leukotriene receptor antagonists. The prevalence appears to be similar with all 3 agents, although there are no direct comparisons available. Current treatment guidelines consider zileuton the least desirable, because liver function monitoring is routinely required during therapy. As far as drug interactions, no trials specifically compared the interaction risk. Their effects on the cytochrome P450 isoenzymes differ. Zafirleukast inhibits the 3A4 and 2C9 isoenzymes, zileuton inhibits the 1A2, 2C9 and 3A4, and montekulast does not inhibit any of the cytochrome P450 isoenzymes, but is a substrate of the 3A4 and 2C9 isoenzymes.

In summary, treatment guidelines for asthma note that the leukotriene antagonists are not the preferred therapies, but can be used as alternative agents. Treatment guidelines for allergic rhinitis note that the leukotrienes may be the first line treatment for patients with concomitant asthma and rhinitis. There are no trials with statistical comparisons evaluating the efficacy of the leukotrienes with respect to each other. Overall, few comparative trials show that leukotriene antagonists are more effective than other available therapies. No trials specifically compared the risk of adverse events. Asthma treatment guidelines consider zileuton the least desirable of the leukotriene antagonists because of the need for liver function monitoring.

Karen Gunning asked if the number needed to harm referred to the number of patients treated with leukotriene antagonists over corticosteroids. Dr. Fox stated that this was what she referred to, and it was from a systematic review.

Duane Parke asked if there was any reason to dose Singulair more than once daily. There is no reason for this.

The Committee asked why zileuton needed liver function monitoring. This is in the package insert.

Dr. Ward asked if there was any literature indicating that one leukotriene antagonists is superior over the other. There is nothing in the literature to indicate this, although there are no direct comparisons between the agents. There is also no evidence to indicate differences in safety, although one agent does require regular monitoring of liver

function. Monteleukast has the potential to be cleaner in terms of drug interactions because it does not inhibit any of the cytochrome p450 isoenzymes.

Lisa Hulbert asked about news stories concerning Singulair and suicidality. It is a rare side effect, and it has been noted with numerous agents, not just Singulair. Merck did update their package insert to reflect this, but zafirleukast and zileuton did not.

The Committee felt that an agent with a pediatric indication was needed. Compliance may be an issue with twice daily or four times daily dosing, although there is no hard proof for this in the literature. Dr. Harris noted that the monteleukast was frequently the only controller medication that a parent is willing to use. Karen Gunning also noted that the only area in which the leukotriene antagonists showed superior efficacy was exercise induced bronchoconstriction. The DUR Board may wish to take up appropriate use of this class.

Koby Taylor stated that he has two patients that are taking a combination of zileuton and monteleukast, in addition to other anti asthmatic agents. This is due to the difference in their mode of action, as noted on page 7 on the Drug Information Service's report.

Dr. Fran Kaiser, M.D. an endocrinologist, geriatrician, Executive Medical Director with Merck, and adjunct professor at St. Louis University and U.T. Southwestern addressed the Committee on behalf of Singulair. Asthma is a very complex disease that is very difficult to handle. Unfortunately, there is no silver bullet available that works all the time for every patient. Many patients respond very differently. There is huge variability regardless of the agent being used in the particular patient. The overwhelming majority of patients in Utah who are on Singulair are on it for asthma. The overwhelming majority of those patients are children. There are differences in control and response regardless of class. Children, and even adults, may not be able to use inhalers adequately or properly. No drug is good if the patient doesn't use it and use it correctly, regardless of cost. As was already mentioned, Singulair has a very unique spectrum in terms of its age profile, both in asthma and for allergic rhinitis. Many individuals don't get coded as having asthma, but do get coded as having allergic rhinitis, and there is a very tight correlation between the two. Over 60% of patients who have asthma have corresponding allergies. Physicians hate to brand a child for life as having asthma. Many of these children get cough variant symptoms, or allergic rhinitis coded in their chart instead of being labeled asthmatic, which is who and what they are. Looking at the usage data, the Committee should see that a majority of the use for Singulair, and the class as a whole, is for children under the age of 12. The updated guidelines from NHLBI and the National Asthma Education and Prevention Programs note that leukotriene receptor antagonists have a role in the treatment of mild to moderate asthma, especially when children are involved. Offering alternatives allows for consideration of treatment effectiveness, the characteristics of the individual patient's asthma, the patient's previous response to therapies, the ability of the patient and family to use the medications correctly, and the patient's and family's anticipated adherence to the treatment regimen. Granules in the pediatric age group that can be sprinkled on applesauce can be taken by anybody. The unique dosage availability, the unique age spectrum, the unique leukotriene receptor indication for Singulair for exercise induced bronchospasm that the other agents do not have make it an important addition. As for the issue of suicidality, the label has been updated to include anxiousness, suicidal thinking and behavior, including suicide. These additions are not based on clinical trial data. There was absolutely no signal in any of

the clinical trials, and it is not possible to base causality on post-marketing reports. Zyrtec, which is over the counter, actually has similar language in its label. The Committee is respectfully asked to keep Singulair on the PDL.

Karen Gunning asked how the company knows what the drug is being used for. This is difficult to determine. In states that have tried to restrict the use based on allergic rhinitis to lower cost OTC drugs, what ends up happening is that there are unintended consequences of restricting use. Physicians may turn to other agents that have worse adverse events. Karen Gunning stated that her specific concern is that over half of the patients in the 0-5 age group that are taking leukotriene antagonists are not on an inhaled beta agonist, or haven't received a prescription for it. Dr. Kaiser stated that a reduction of short acting beta agonists can occur with Singulair. Other Committee members stated that there is a lot of use of oral albuterol in this age group.

Dr. Ward moved that the Committee finds that none of the leukotriene antagonists have greater efficacy than any of the others or a substantially different safety profile. The Division should make a finding based on cost, and include an agent that has a pediatric indication down to one year of age. Dr. Miller seconded the motion. The motion was approved unanimously by Dr. Miller, Dr. Ward, Karen Gunning, Koby Taylor, Duane Parke, Kort DeLost, and Dr. Harris.

Next meeting set for July18, 2008.

Meeting adjourned.

Minutes prepared by Jennifer Zeleny