

## Pharmacy and Therapeutics Committee Meeting Record

**Date:** 11/17/05    **Time:** 9:00 a.m. – 4:00 p.m.    **Location:** 3232 Elder Street, Conference Room D    **Moderator:** W. Terry Gipson, M.D.

**Committee Members Present:** W. Terry Gipson, M.D.; Bob Comstock, RPh; Catherine Gundlach, PharmD; Phil Petersen, M.D.; Rick Sutton, RPh; Stan Eisele, M.D.; Tami Eide, PharmD; Thomas Rau, M.D.; Steve Montamat, M.D.

**Committee Members Absent:** Cindy Bunde, P.A.; Richard Markuson, RPh

Agenda Item	Presenter	Outcome/Action
<p><b>CALL TO ORDER</b></p> <ul style="list-style-type: none"> <li>• <b>Roll Call</b></li> <li>• <b>Reading of Confidentiality Statement</b></li> <li>• <b>Committee Business</b></li> </ul>	<p>W. Terry Gipson, MD</p>	<p>Dr. Gipson called the roll. One voting and one non-voting member were not present.</p> <p>The confidentiality statement was read by Dr. Gipson.</p> <p>Dr. Gipson reviewed recently approved changes to the committee’s guidelines which included:  Removal of the psychiatrist requirement  Addition of Dr. Markuson as consultant as needed  Change of sponsoring bureau’s name to Bureau of Medical Care  Rewording of the officers section to reflect current practices  References to “Executive Committee” were to be changed to “Committee Chair”</p> <p>Dr. Gipson reported that the only change to the committee’s September recommendations was the grandfathering of Stattera for clients.</p> <p>2006 Calendar was reviewed. Dates and agenda topics are listed on the website.</p> <p>The minutes from September 16, 2005, Committee meeting was approved.</p>
<ul style="list-style-type: none"> <li>• <b>Approval of Minutes from September 16, 2005 Meeting</b></li> <li>• <b>Discussion of Key Questions for Upcoming EPC Drug Effectiveness Review Studies</b></li> </ul>	<p>Tami Eide, PharmD, BCPS, FASHP</p>	<p>The group discussed updated information on drugs used for ADHD, Alzheimer’s Disease, Antiplatelet agents, Sedative Hypnotics, and PPIs.</p>
<p><b>DUR OUTCOME PRESENTATION</b></p> <ul style="list-style-type: none"> <li>• <b>Urinary Incontinence</b></li> </ul>	<p>Heather Brandt, PharmD</p>	<p>Dr. Brandt presented a review of urinary incontinence in ID Medicaid population. Primary treatment for this condition is medication; Purpose of the review was to obtain information regarding the demographics of the affected population. The review demonstrated an increase in the number of Medicaid clients being treated for incontinence.</p>

		<p>Medicaid claims data demonstrated that the four medications previously selected by the committee have shifted and now are the four highest market share. These include: Ditropan XL, Detrol, Oxytrol, and oxybutynin.</p> <p>The review indicated that switch rates were only 10% after the implementation of the PA. Clients were receiving a good length trial before the switch was made. No negative outcomes were indicated by the data.</p>
<b>PUBLIC COMMENT PERIOD</b>	W. Terry Gipson, MD	<p>Eleven people signed up to speak during the public comment period. Public comment was received from the following:</p> <p>Dr. Alsey (self) – topical new modulators  Gloria Beri, NP—(self)—Aciclovire  Dr. Martin Tuback- (self) – antibiotics  Adam Shepeger (Shering/Plough)—antibiotics  Bob Snedker—(Ortho/Mcneil/Jensen Pharmaceuticals)—Fluroquinolones  Kathy Elchire, NP- (self)—antibiotics  Sue Heineman (Pfizer)—antibiotics and antifungals  Alan Kriste (Glasgow/Klein)—antibiotics  Dr. Johnson (Adventis Pharmaceuticals)—Macrolides/Ketolides  Andy Weis (Novartis)—anti-fungals  Jeff Benton (Roche Labs)-antivirals</p>
<b>DRUG CLASS REVIEW</b> <ul style="list-style-type: none"> <li>• <b>Cephalosporins and Related Antibiotics</b></li> </ul>	Steve Liles, PharmD	<p>Dr. Liles presented a view of Cephalosporins and related antibiotics. His presentation included indications, how the drugs work, the drug-drug interactions, resistance, dosing forms and frequency, clinical trial data and adverse affects. The following drugs were included in the review:</p> <p>amoxicillin/clavulante  cefaclor  cefpodoxime  ominicef  cefpodixime  cephalexin  Suprax  Ceflosporin</p>
<b>DRUG CLASS REVIEW</b> <ul style="list-style-type: none"> <li>• <b>Fluroquinolones, Oral</b></li> <li>• <b>Macrolides/Ketolides</b></li> <li><b>Antivirals</b></li> </ul>	Steve Liles, PharmD	<p>Dr. Liles presented a view of Fluroquinilones medications. His presentation included availability, a wide variety of indications, the drug-drug interactions, resistance, dosing forms, frequency/duration, drug interactions, warnings and adverse affects. The following drugs were included in the review:</p> <p>Levaquin  Tegquin  Avelox</p>

		<p>ciprofloxacin Noroxin Maxaquin Factive</p>
<p><b>DRUG CLASS REVIEW</b> <b>Macrolides/Ketolides</b></p>	Steve Liles, PharmD	<p>Dr. Liles presented a review of Macrolides/Ketolide medications. His presentation included indications, clinical trial data, drug interactions, frequency/duration, drug interactions and adverse affects. The following drugs were included in the review:</p> <p>Ketek Biaxin Zimax Zithromax</p>
<p><b>DRUG CLASS REVIEW</b> <b>Antivirals</b></p>	Steve Liles, PharmD	<p>Dr. Liles presented a review of antiviral medications. His presentation included indications, clinical trial data, pediatric indications, warnings, and CDC Guidelines.</p> <p>Acyclovir Amantadine Faicyclovir (Famvir) Ganciclovir Oseltamivir (Tamiflu) Rimantidine Valacyclovir (Valtrex) Valganciclovir (Valcyte) Zanamivir (Relenza)</p>
<p><b>DRUG CLASS REVIEW</b></p> <ul style="list-style-type: none"> <li>• <b>Oral Antifungal Agents</b></li> <li>• <b>Topical Antifungal Agents</b></li> </ul>	Steve Liles, PharmD	<p>Dr. Liles presented a review of antifungal agents. His presentation included indications, clinical trial data, indications, warnings, drug interactions, FDA health advisory.</p> <p>The following groups were reviewed:</p> <p>Azoles Non-Azoles Allylamines Ciclopirox Nystatin</p>
<p><b>CLINICAL DATA REVIEW</b> <b>Atopic Dermatitis</b></p>	Steve Liles, PharmD	<p>Dr. Liles's reviewed determined there was no clinical trial data for this class and no recommendations for one agent over another.</p>
<p><b>COMMITTEE CLINICAL DISCUSSIONS AND CONCLUSIONS FOR SELECTED THERAPEUTIC CLASSES</b></p>	W. Terry Gipson, MD	<p>COMMITTEES FINAL RECOMMENDATIONS FOR THERAPEUTIC CLASSES</p> <p><b><u>Cephalosporins and related antibiotics</u></b></p>

		<p>Consensus was to not require a prior authorization for these agents since there are many generics available for these agents.</p> <p><b><u>Fluoroquinolones</u></b>  Consensus was to not make a recommendation for a preferred agent at this time, but to bring this class back at a future meeting. Recommendation was made to add all agents in this class to the preferred drug list in the interim.</p> <p><b><u>Macrolides/Ketolides</u></b>  Consensus was to add all agents to the PDL (Preferred Drug List) and to require a PA for Ketek.</p> <p><b><u>Antivirals</u></b>  Recommendation was to add all agents to the PDL and have the committee bring it back for review in nine months.</p> <p><b><u>Antifungals, oral</u></b>  Recommendation was to add therapeutic criteria for Lamisil and Itraconazole , Grifulvin V. Tablets , Gris-Peg and griseofulvin and leave all agents on PDL</p> <p><b><u>Antifungals, Topical</u></b>  Recommendation was to add everything to the PDL except Penlac.</p> <p><b><u>Atopic Dermatitis</u></b>  Recommendation was to make no changes at this time.</p>
<b>PUBLIC MEETING ADJOURNED</b>	W. Terry Gipson, MD	<p>The next classes of agents to be reviewed by the Pharmacy and Therapeutics Committee on January 20, 2006 are Newer Sedative Hypnotics, Injectable Anticoagulants, Ulcerative Colitis Agents, Triptans and Beta Blockers.  Dr Gipson adjourned the public portion of the meeting.</p>
<b>SUPPLEMENTAL REBATE INFORMATION (CLOSED TO PUBLIC)</b>	Randy May, Medicaid Deputy Administrator	<p>Mr. May presented supplemental rebate information to the Committee members for their review and discussion. This review and discussion were closed to the public.</p>
<b>COMMITTEE FINAL RECOMMENDATION FOR THERAPEUTIC CLASSES</b>	W. Terry Gipson, MD	<p><b><u>Cephalosporins and related antibiotics</u></b>  Consensus was allow prescriber choice of agent within this class and not to require prior authorization for these agents.</p> <p><b><u>Fluoroquinolones</u></b>  Recommendation was made to add all agents in this class to the preferred drug list and allow prescriber choice within this class.</p> <p><b><u>Macrolides/Ketolides</u></b>  Recommendation was to add all agents to the PDL (Preferred Drug List) and to require a PA for Ketek to make it a second line agent.</p> <p><b><u>Antivirals</u></b></p>

		<p>Recommendation was to allow prescriber choice of agent by adding all agents to the PDL. Utilization patterns should be re-reviewed following the influenza season.</p> <p><b><u>Antifungals, oral</u></b> Recommendation was to add therapeutic criteria for Lamisil and Itraconazole , Grifulvin V. Tablets, Gris-Peg and griseofulvin.No agent would be designated as a preferred agent on the PDL.</p> <p><b><u>Antifungals, Topical</u></b> Recommendation was to add everything to the PDL as preferred except Penlac. No changes are to be made to the current Penlac PA criteria.</p> <p><b><u>A topic Dermatitis</u></b> Recommendation was to make both agents preferred at this time.</p>
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**Pharmacy and Therapeutics Committee  
Public Comment  
November 18, 2005**

**Dr. RYAN OWSLEY (self)--Modulators**

I am here to talk about the topical new modulators. I know they are up for review today and as a dermatologist, I would like to discuss what they mean to my practice. As one of the few dermatologists in town that accept Medicaid, I know most of my colleagues do not. They are very important to me since they provide an alternative to topical steroids. Topical steroids have a significant number of side effects, including skin atrophy, glaucoma and cataracts when used on the face.

I use them now first line for any inflammatory skin diseases of the face and in the diaper area because of those side effects. I find that they are very useful, especially in the pediatric population. I would hope that when you make your decisions today, you would consider them as a first line agent, especially in some of the inflammatory skin diseases of the face and the diaper area. Any questions?

Question: So, should general practitioners use these as a first line agent?

Response: I definitely think so. Pediatricians need that as an option as well. In the past, with topical steroids, we have gotten in to trouble with atopic dermatitis and other inflammatory skin diseases. They provide a great use in diaper dermatitis, which pediatricians see all the time and family practitioners for that matter.

Questions: Are there any adverse effects or side effects in which indiscriminate use would be a problem?

Response: They have never been shown and there is the question of Lymphoma, but it has never been proven and there is not a black box warning to date. So, that has never been proven long-term and both companies are doing long-term studies on it. It has never been shown in humans.

Question: Has that possibility ever at all effected how you use it?

Response: For me, no.

Question: Do you have a favorite one?

Response: It depends on location. People do not like to use ointments on the face, so Protopic is not going to be used on the face. Elidel, I use that more for facial dermatosis, but Protopic is more effective than Elidel and so for moderate to severe cases, you're going to use Protopic. You need both. One is an ointment and one is a cream and you get more benefits. Like I said, an ointment on the face is not going to be satisfactory to patients, but ointments work better because they provide an emollient.

Question: Is this as important for first line in the adults as it is in pediatrics for you?

Response: I use it a lot in adults in off-label for dermatitis of the face and it has shown to be very effective even though it is not FDA approved for that use. They work incredibly well.

Question: Where do you practice?

Response: I have two offices. One is in St. Luke's Meridian and one in Nampa.

**GLORIA BEERY, NP (self)-- Valcyclovir**

I do general medicine, primarily for women. I have been working with Dr. Beverly Ludders of Boise Health Care for 26 years. I am here to talk about the usage of Valcyclovir for the treatment of Herpes Simplex virus. I have been in practice for 26 years, so I easily remember the times when I had nothing to offer patients, except warm soaks and Heat lamps to try to treat those symptoms. Then along came acyclovir to treat this and it was much improvement over the hot soaks and the heat pads that we had to give patients.

The biggest problem I saw with using Acyclovir is that it is a five times per day treatment. I don't know about you, but I can't remember my five fruits and vegetables a day, let alone carrying pills around in my pocket. So, we know from research that if you give a patient a once a day drug that you are going to get 90% compliance with that. If you increase the frequency to twice a day dosage, then you get down to 70% of people that will be compliant. Three times a day is 50% and four times per day is only 30% compliance. They didn't even do the research on five times per day, since it is such a rare occurrence to have it like that. So, when there is a break in the dosing with not being able to keep up with your five times a day dosing, you are going to have an increased risk of this disease continuing. These initial episodes of Herpes can be very debilitating. People feel flu like. They have fevers. They miss work and the whole event can last up to three weeks if it is left untreated. We do have research on Valcyclovir in terms of reducing the incidence or the length of time that people are sick with this. First of all it is a BID dosing or twice a day dosing, with the Valcyclovir, so you can reduce the length of these episodes by at least 30% plus you are talking about an improvement in about 70% compliance as opposed to maybe less than 30% with dosing five times per day. So to me, this is a much preferred route to treat. We know that the incidence of HSV is going up. The Haines study, the most recent one was 22% and the one prior to that was only 16%. We are doing a terrible job of treating and preventing it. My passion is to get people to take medications on a regular basis to prevent the spread of this disease. I am eagerly waiting for the time when we are going to have a vaccine to prevent the spread of this disease, but in the meantime, we owe it to society to decrease the spreading of this disease and more people getting infected and more time loss and more expense to the medical community.

#### **ADAM SHPRECHER (SCHERING)—Avelox & Cipro XR**

Avelox or moxifloxacin is a fourth generation fluoroquinolone and it is often dubbed a respiratory fluoroquinolone due to its advanced coverage with gram positive organisms. As far as its indications, all indications are at 400mg taken once daily. It is indicated for acute bacterial sinusitis for ten days and for acute bacterial exacerbation of chronic bronchitis for five days and for community acquired pneumonia including multi-drug resistant strep for seven to fourteen days and uncomplicated skin and skin structure infections taken for seven days and as of June 13<sup>th</sup> of this year, it is now indicated for complicated skin and skin structure infections if taken for seven to twenty-one days. All of these indications are a result of well controlled and well designed clinical trials. And its once daily dosing is due to an elimination half life, which is rather long at 12 hours. It has a lack of drug and drug-food interactions and this is due to a decreased ability to affect this cycle with peoples enzyme systems. It has no interactions with statins and it has no significant effects on moxy with interconazole or morphine or amantidine. It has no significant effects on oral contraceptives as well and it does not alter the metabolism of oral hypoglycemic agents due to not inhibiting cytochrome P 4503a4. It has an excellent bio-availability of 90% and it can be taken with food or meals or on an empty stomach and because of this bio-availability, the IV dose and the PO dose are the same. No dosage adjustment is required based on gender, age, race or in the presence of renal insufficiency and this include patients that are on hemodialysis and no dosage adjustment in those with hepatic insufficiency as well. Its' bacterial action is due to the equal inhibition of topoisomerase two or DNA gyrase as well as topoisomerase four, with two sites of activity that requires two mutations to become resistant and in vitro studies with resistance to moxy shows that it takes multiple steps for it develop resistance. It reaches good plasma and tissue concentrations, both well in excess of the MIC 90 for susceptible pathogens and it concentrates in the respiratory tissue and in fact the area with plasma concentrations as compared to the MIC90 achieve the best ratio for strep pneumonia of all the fluoroquinolone class. It is available as 400mg IV tablets or pre-mix IV 400mgs

And moxyfloxacin was the first quinolone approved for multi-drug resistant strep pneumonia. It is contraindicated in those with hypersensitivity amoxifloxacin or any member of the fluoroquinolone class and evaluated and selected at first events associated with some fluoroquinolones, such as seizure, pain in the Achilles tendon, tendon rupture, photoflexicity or elevation of liver tests. Moxifloxacin was comparable to comparator in over 4,000 patients and over 3,689 in the comparator arm. Moxifloxacin may increase the QT<sub>C</sub> in some patients. However, no cardiovascular morbidity or mortality attributable to QT<sub>C</sub> occurred with Moxy treatment in 7,900 patients in controlled clinical trials including 223 who were hypercholytic at the start of treatment and in addition, associated diarrhea including colitis has been reported with nearly all bacterial agents and therefore a class warning is in effect for all these drugs.

As far as Cipro XR, it is a quinoline with excellent coverage of gram negative organisms. Cipro XR is an extended release formulation containing two forms of ciprofloxacin. Ciprofloxacin hydrochloride and ciprofloxacin beitan and it is not a fine layer matrix design that provides convenient once daily dosing for urinary tract and it is indicated for patients 18 years of age or older for uncomplicated UTI with 500mgs once daily for 3 days and for complicated UTI at 1000mgs once daily for 7-14 days and acute uncomplicated pylonephritis at a 1000mgs once daily for 7-14 days. Cipro XR and Cipro immediate release tablets are not interchangeable as Cipro XR has a 40% higher C-max as compared to Ciprofloxacin given BID. Cipro XR is well distributed to the site of infection and is low protein binding and is highly concentrated in the urine within four hours. It is

contraindicated in persons with a known hypersensitivity to Cipro or any others in the fluoroquinolone class and patients who start therapy on Cipro IV per UTI may be switched to Cipro XR. As far as drug interactions, Cipro XR should be administered at least two hours before or six hours after antacids and it does have an interaction with theophylline as well. As far as warnings, colitis may occur and is a class warning and safety in patients in under 18 years of age or in women pregnant or lactating has not been established. No dosage adjustment is required for patients with uncomplicated UTI or elderly patients or patients with stable chronic cirrhosis. However, patients with complicated UTI or acute pyelonephritis dosage may need to be reduced from a 1000mg to 500mg daily. Thank you considering Avelox and Cipro XR for the formulary for Idaho Medicaid.

**DR. TUBACH (self)--Ketek**

I am an ENT specialist and I am here to talk on behalf of Ketek and would like to thank the Board for listening to my testimony. I have been in clinical practice for more than nine years now and that has given me the ability to observe the emergence of resistant strep pneumonia and ever since its emergence, it has been an important thing in the consideration for the treatment of sinusitis and otitis media for ear, nose and throat physicians. I have followed this closely and have done a lot of education in the community and been to many conferences on resistant strep pneumonia. Its an important consideration when we choose antibiotics for sinusitis especially because it is the most common pathogen for bacterial sinusitis and also the most virulent. So, with the emergence of resistant strep pneumonia and penicillin resistance rates hovering between 50 and 35% in the United States and around 25% in this area and resistance rates close to 30% for macrolide antibiotics to strep pneumonia and we have to choose very carefully what antibiotics we use that are going to be effective in sinusitis cases. There are several reasons for this. They are important for immediate care for first line treatment of sinusitis and as well as for treatment of chronic sinusitis, such as in the eye muscle involvement. In acute cases, we need to have an antibiotic that we know is going to cover the resistant strains. We need an antibiotic that is not going to provoke further resistance to the drug and we want a spectrum that not only covers the strep pneumonia, but the other common pathogens in sinusitis, such as H-flu and moraxella catarrhalis. First line for just acute sinusitis is just amoxicillin. However, in patients that fail treatment with amoxicillin or in patients that are penicillin allergic, we need a drug that fits that role. In the past, we have used macrolides, however with huge resistance rates of close to 30% for pretty much all the macrolidtes. That has been an area where we really need another drug to fill that gap. Ketek has been a drug that has been proven in Europe with millions of prescriptions and years of use and is very effective for strep pneumonia. This has been seen by clinical data, as well as MICs. By evaluating its unique mechanism of action, which actually makes it a bacteriocidal drug instead of bacteriostatic like the other macrolides. So, it is a drug that is very effective at completely killing the strains that lead to the disease process and in doing so, that prevents resistance because we don't have these resistance strains continuing on and it also reduces the chance of reoccurrence. So, we have an effective treatment and we know that there is less chance that it is going to come back.

As far as fluoroquinolones, they are also very effective and we use them commonly for sinusitis. However, we have seen some patterns for fluoroquinolones and we would like to save fluoroquinolones as much as possible, for the more resistant case and for cases that we really need something basically as a last antibiotic resort. This is not only my opinion, but also the opinion of my academy. So, I really feel like Ketek fits a good role for not only penicillin allergic patients, but also patients that fail other therapy in order to fill that space for treatment.

Question: Are you saying you would not recommend this as a first line agent?

Response: No, I think it should be available as a first line agent in cases where the person is either penicillin allergic or they are coming back to the physician because they failed amoxicillin or they have a history that makes them need something a little more potent or need broader coverage than amoxicillin. So, in many cases in immediate care or acute setting for sinusitis, it would be first line treatment. Augmentin is another one. I hold Augmentin and Ketek in very similar places.

Question: And what would you recommend for a second line choice?

Response: Augmentin has been a stand by we've used for many years and is very effective. In my specialty, we have patients that have been on multiple different drugs sometimes and sometimes you need several options for treatment for resistant strains of sinusitis. Also, we need something that is very effective when a patient is penicillin allergic.

Question: Do primary care workers use this as a second line if the patient is penicillin allergic?

Response: I think they are fairly equivalent as far as choices. The choice would have to depend on things such as price and the tolerability of the drug. I think they are fairly similar and I think most patients have an easier time taking Ketek since it is once a day and where Augmentin, especially the XR which is more effective and has better MICs for

resistant strep pneumonia, is two very large pills twice a day. It is very difficult to get a lot of patients to take. It is a very effective treatment as well as Ketek. In a lot of cases where a patient has tried Augmentin and they haven't tolerated it well and have had side effects such as diarrhea, you need something besides just Augmentin to be available and if they are allergic to that stuff.

#### **BOB SNEDIKER (Ortho/McNeil/Janssen)--Levaquin**

I am here to represent Levaquin as an addition to your formulary. Some thoughts on Levaquin include that it has been available in the United States since 1996 with over 300 million patients being treated with the drug. It is available both in oral tablet, IV solution, as well as oral solution. There are 11 indications for Levaquin which include: Acute bacterial exacerbations of chronic bronchitis, nosocomial pneumonia, uncomplicated and complicated soft tissue infections, chronic bacterial prostatitis, complicated UTI, acute pyelonephritis, as well as uncomplicated urinary tract infection. As you can see from that list of indications, Levaquin is widely distributed within the body including the urinary tract. Some of the newer indications for Levaquin, which I will highlight, include short course therapy for community acquired pneumonia and that would be 750 milligrams daily for five days. Also, more recently the latest indications we've received was for short course acute bacterial sinusitis, again 750 milligrams daily for five days. We have also had indication for multi-drug resistant strep pneumonia, as well as post exposure inhalation Anthrax. Levaquin was the first fluoroquinolone approved for multi-drug resistant strep pneumonia, as well as short course community acquired pneumonia therapy which is high dose five day therapy. In addition, it has been indicated for both typical and atypical in community acquired pneumonia. Let me give you some thoughts behind the high dose, short course therapy. The first thing that I would just like to dispel is that we did not go for the high dose, short course because the 500 hundred milligram dose is ineffective, but the latest thinking on antibiotic therapy is To provide maximum killing power with measures such as area under the curve, C-max relationships which promote more rapid killing and thus shorter course therapy. The high dose therapy was developed to maximize concentrated killing by achieving higher c-max and area under the curve values, increased sinus and lung penetration. Fifty percent increase in the dose of Levaquin results in a doubling of the tissue concentrations for both lung and sinus. There is a more rapid and complete bactericidal activity, essentially the bacteria are killed over a shorter period of time. There may be a slowing in the development of resistance and an additional cost savings may be realized from a more rapid switch from the intravenous formulation to the oral formulations. The bio-availability of the oral formula is equivalent to the intravenous therapy. Lastly, there may be a decrease in the length of stay to the hospitalized patient. Regarding efficacy, in looking at short course therapy compared to standard dose therapy, 750 mgs of Levaquin administered daily for five days versus 500mgs for ten days showed a clinical success rate of 92% versus 89% respectively for sinusitis. Short course therapy for community acquired pneumonia clinical success rates for the 750mg dose, given for five days was equivalent to the 500mg dose administered for ten days. Regarding multi-drug resistant strep pneumonia 95% clinical and bacteriological success has been seen with the treatment of Levaquin and the importance of this can't be underestimated in the multi-drug resistant strep pneumonia. It occurs in about 20% of cases and the most common antibiotics used to treat strep pneumonia generally fail in this circumstance including Penicillin, Erythromycin and Trimeth. Safety as it looks as drug related from ADR is from clinical trials is about 6.7% with a low discontinuation rate of about 4% and the most common side effects include nausea, diarrhea, vaginitis all occurring in less than 2% of patients. Drug interactions and side effects are minimal for the 750mg. One last point, there has been no shift in the MIC's in the last eight years of surveillance and MIC 90 has remained at one MIC per ml and the susceptibility of strep pneumonia has been 99% over this time period.

#### **KATHY ALKIRE, NP (Self)--Zmax**

About 25% of my patients are Medicaid patients, but what I want to say today really doesn't matter at to whether this is Medicaid, Blue Cross or any one else I would be speaking too. I would just like to comment on patient compliance with medications. It has been my experience that the shorter course therapies seem to decrease patient return visits. They are better tolerated and we see less return in patients who are telling us, particularly in sinusitis, that they are not getting better. There are basically three drugs that are available that are shorter course therapies (first line therapies). The new Zmax, which is a one time agent; the Zithromax pack and then the Ketek pack. I am here really to not basically talk about a lot of statistics, but basically more of my own practice. I see very few patient returns for the three of those drugs. With the new Zmax, the one time dose particularly with patients that we wonder if they are going to comply with even five day therapies, the Zmax is basically guaranteed compliance because we can have them take it in the office provided there is not a high level of nausea or anything else going on. So, I would like to encourage you to keep the short course therapies on as first line agents. In acute sinusitis particularly, and that I believe that it will not only be effective against pathogens, but will also decrease spending in the long run as far as repeat visits to their providers.

I was a little late this morning because I had a young woman come in who had been treated two weeks ago with amoxicillin course for acute sinusitis and she came and the mom who was with her said, "We had asked the provider to use Zithromax first line because we know it always works for her." The provider hadn't wanted to do that, because there is good evidence that says amoxicillin should be used first course and back she came. She wasn't a Medicaid patient, but if she had been a Medicaid patient that would have been another visit cost to the program.

**SUE HEINEMAN (Pfizer)—Zmax and Vfend**

I am going to speak on Zmax and Vfend today. Just real briefly, we have heard a lot of statistics and data, but what you have heard throughout the previous speakers is that there has been a common theme. We are moving towards higher dosages of the anti-infective, the anti-bacterial and anti-vials and anti-biotic and shorter courses of therapy. The CDC and the WHO knows that there is a problem with resistance and a problem with patients hoarding medications. My husband is one of them. In fact, he is going through some pulmonary problems right now, because he didn't finish his medications. So, it is a true issue. So, appropriate use and taking the full course of therapy is pertinent. Zmax is a new formulation and the previous speaker mentioned how she uses it in her practice and how it is different from Zithromax. Zmax is an extended release formulation and they are in encapsulated micro spheres so that it bypasses the stomach and you don't get all the nausea and vomiting that you do with Zithromax. You would think that this is a two gram dose and generic azithromycin will soon be available, so why not use that. Well, the thing is that using two grams of immediate release azithromycin, you've got 50% side effects right there. Most of them are nausea, vomiting and diarrhea. With this new formulation with Zmax, two gram dose, you take it right there and it is an oral suspension and you've just reduced your side effects. You've increased patient compliance to 100%, because there is just that one dose. Azithromycin is a favorite of Medicaid prescribers. 82% of your macrolide and ketolide prescriptions are Zithromax, so you know that it works. Otherwise the prescribers would not continue to use it. Zmax offers that additional benefit for mild to moderate acute bacterial sinusitis or community acquired pneumonia, you have something that you can take just one dose. The killing that occurs, the bacterial static killing that occurs with macrolides, is true. Zmax acts a little bit different, instead of being a time dependent time of mechanism, so with the time dependent antibiotics you want to have the level to be about two to four times the minimum concentration. With Zmax, that is a concentration dependent killing, so we want to make sure the area of the curve divided by the MIC is high and because of that, you do see azithromycin being more effective even in light of the macrolide resistance that is occurring. One last comment with Zmax, it was studied against the azithromycin 500mg dose (the tri-pack) and what you saw within the first 24 hours was three times higher concentrations than the 500mg dose and at 72 hours, it was twice as high a concentration which is key. It is very key to have those concentrations in the lungs and in the sinuses. So again it is approved for the mild to moderate acute bacterial sinusitis and community acquired pneumonia.

Then, real quick with Vfend or voriconazole for the anti-fungal class. This is a relatively new triazole antifungal and has a very broad spectrum, covering Aspergillus, Scedosporium and Fusarium which are very life threatening diseases. I would imagine that most of the Medicaid population would be going out of state either to Washington or down to Salt Lake since they are the transplant population. You are going to see more of the IV's of Vfend being used out of state, but when they come back into the state there needs to be that oral formulation that is available for them to continue on in therapy. In fact Vfend is the only anti-fungal that has both IV and oral formulation that is approved for first line indication for various mold and yeast species. There is a better survival benefit over the amphotericin and fluconazole, so there a lot of advantages to Vfend. The majority of your claims are with fluconazole, which is still a good agent. But again, Vfend does provide that first line indication which the other ones don't for invasive aspergillosis and some of the other yeast infections.

Question: What is the age parameter on the Vfend?

Response: Let me check on that. I think it is 16, but it has been used in investigational studies in Denver on children under the age of 16. The approval is not for under that age.

**ALLEN CHRISTIE (SmithKlineBeecham)—Augmentin XR & Valtrex**

I am here to do a little two step to talk about Augmentin XR and Valtrex. So we have heard quite a bit already about bacterial resistance and Augmentin XR was designed specifically with bacterial resistance in mind, particularly strep pneumonia resistance which is really a growing problem with serious complications and preventing mortality. In community acquired pneumonia and in acute bacterial sinusitis, the idea previously mentioned is that time above the MIC for antibiotics is the key predictor for clinical efficacy and bacteriological eradication. With the unique formulation of Augmentin there are two formulations of Augmentin, the hydrate form and the anhydrous form which allows for immediate release, as well as, sustained release delivery of amoxicillin. It gives a prolonged time of high levels of drug to exposure from bacteria. If you look at what is considered to be susceptible or even immune resistant strep pneumonia, with MICs of four or less, Augmentin can provide more than 49% of the dosing involved with adequate levels of drug, which would predict a cure. That has been demonstrated in various clinical trials in comparison with Levaquin or other formulations of amoxicillin showing eradication of resistant strep pneumonia and with a decreased susceptibility of penicillin of greater than 95% in acute bacterial sinusitis and greater than 85% in community acquired pneumonia. This information has really been used to change some guidelines and third party recommendations including the Sanford Guide as well as the Sinus & Allergy Health Partnership which have placed a high dose amoxicillin concentration which is Augmentin XR in the first line choice for areas where there is high levels of strep pneumonia resistance and for people who have mild or moderate disease prior to exposure. The problem is sort of when we created this is to address the issue to show eradication of strep pneumonia that has decreased susceptibility to penicillin. That has been done. That's it for Augmentin.

Valtrex, you heard earlier that Valtrex that compliance is a major issue and I have to agree that it certainly is. I can't remember to take anything once a day. So, the idea being Valtrex was really an innovation on top of what we knew about Acyclovir. The problem with Acyclovir certainly was compliance and with the new formulation of Valcyclovir we are able to reduce the number of doses in patients and increase compliance. Gloria mentioned something about in her practice that it was more along the lines of treating acute episodes of recurrent genital herpes or first episode genital herpes. I would like to spin this a little bit differently and that is to talk about long term use suppressive therapy. Gloria also mentioned that 22% of the general public was positive based on serology for herpes simplex virus. There is also a study that was done in a suburban setting showing that greater than 25% of people are HSV serum positive. This is an epidemic. It's not being reduced. It's increasing. There is a study that was done with Valcyclovir once a day, 500mgs to look at the transmission of the virus. That is probably the only way you are going to inhibit this growing epidemic of herpes simplex virus in the community now is to reduce the transmission from HSV positive patients to negative patients. Since we know that 70% of the time, transmission occurs in asymptomatic patients you can't change their behaviors if they don't know that anything is going on. So, the only way to completely interrupt this is to change behaviors as well as to suppress the virus. In this study, published in the New England Journal in 2004, were able to show that once daily Valtrex over an eight month period of time reduced the risk of transmission of symptomatic general herpes by 75% and total acquisition of Herpes by almost 50%. In addition, we can see a 73% reduction in total shedding and 64% reduction in mean asymptomatic viral shedding at that is the dangerous time. This kind of data has been taken into consideration and incorporated into third party guidelines on recommended use of antivirals including the American College of Obstetrics and Gynecology and talking about how to treat pregnant women in reducing exposure to Herpes Simplex Virus of the neonate. While you can assume that other anti-viral agents would do the same thing, there is no data at all on Acyclovir or Vancyclovir to reduce transmission and also the once daily type of treatment is convenient for patients and helps ensure long term adherence to a regimen that would allow for a reduction of or reducing the risk of transmission of Herpes Simplex.

#### **DR. JOHNSON (AVENTIS)--Ketex**

Basically, we have heard a lot on resistance and most of the information we have heard on erythromycin and Ketek, since it is a new class of antibiotics called Ketolides has been that we have been able to show effectiveness in five days. There has been some talk on concentration dependent killing and independent killing and the truth is concentration dependent killing like we have with erythromycin is probably only working in bacterial endocarditis or meningitis. The bigger question here really is in community acquired pneumonia. This is where we can see a lot of health outcomes and money saved. We know that data published this year by the CDC and Dr. Klugman has shown that there is emergent strep pneumonia. The number one cause for hospital admission is due to respiratory tract infections as community acquired pneumonia. So, the question is are we doing what we can to take care of our patients. Erythromycin still has its own problems. We do inhibit cytochrome P450 and therefore it is a problem with staph as a first line agent. It is not all of them. For example, it does not interfere with Pravochol and it doesn't interfere with Crestor or Simvastatin. We have also had our same problems with other macrolides and other antibiotics on increasing intervals and causing torsades. By far, macrolides do not inhibit IKR channels like fluoroquinolones do. Well, how are we getting resistance? Resistance is being emerged because of high dose and over utilization of macrolides, especially over use of amoxicillin. Collateral damage and resistance is occurring because of excessive use of fluoroquinolones. This has actually been demonstrated in the Vandercoy study that was published this year on clinical and infectious disease. It demonstrated that patients that were on a macrolide for three months before coming onto subsequent therapy had anywhere from 23 to a 53% increase in strep pneumonia resistance. So, the question comes as, is Ketek going to be a highly utilized drug and my answer is: I don't think so. I think that the patients who the physicians choose to use this drug in, who have thought about it, this is your ENT doctor, your allergists, your pulmonologists, these are the people that will actually think about whether or not this drug will be helpful for this patient population. The patients that you will see that actually have resistance or develop it are your patients that have primary deposition. The ones that have poorer follow up for compliance, that's your Medicaid patients. This drug being allowed on the formulary gives the opportunity for your physicians to have a choice. I'm not blocking it. Infectious disease is not something that you can go back and look at after a month or two months to review how a patient is doing. It has to be taken care of then, immediately. So, if you think of what am I doing that is in the best interest of the patient. Are we improving patient care? Is this the best thing for our community? Do we wait until strep pneumonia is like it is down south where it is 40% before we do something in the Pacific Northwest. We actually should have viable choices and having a targeted specific antibody for specific bugs and for resistance is what we always said. We have always felt that bacterial antibiotics has been overused and that we have taken a shot gun approach, so that now we have utilization of antibiotics that is really targeted for specific processes. I think that is where we fit in. Physicians who do again use it or have thought about it, there won't be just randomly choosing to use this drug. It will be used because they thought about the process. That I think is what is in the best interest for improving patient care in the Pacific Northwest and what is best for our communities. Any questions on Ketek?

#### **ANDY WEIS (Novartis)—Terbinafine & Famvir**

I'm going to speak to you today on two different subjects. I thank the committee for allowing me to appear this morning. I'm Andy Weiss, Scientific Pharmaceutical Director for Novartis. When this was approved by the FDA for the treatment of chronic mycosis it indicated that an appropriate tissue specimen should be obtained and confirmed by a laboratory to confirm a diagnosis.

Based on liver function tests that are obtained in most patients with existing liver disease, which should be cautioned to report any signs or symptoms of exacerbation or other conditions by the prescriber. Recent iron clad trial investigated the safety and efficacy of twelve weeks of oral terbinafine therapy at a dose of 250mgs per day without masetermial debridement in the treatment of onychomycosis. This was a 48 week open label study with a 12 week treatment period followed by a 36 week follow up period. Patients aged 18 to 75 years old with a clinical diagnosis of moderate to severe onychomycosis confirmed by positive tissue. Mycology samples received terbinafine 250mgs per day for 12 weeks with or without gross debridement. Patients with pre-existing liver or kidney disease or liver transaminases above normal ranges were excluded. Prominent medication therapy could continue, unless the examiner felt it unwise to do so. These patients in the debridement received this treatment at 6, 12 and 24 weeks. Liver function tests including AST and ALT were performed base line in weeks 6 and there after at the investigators discretion. Primary efficacy variable was complete cure was defined as microbiological cure; negative potassium hydroxide and culture and 100% toe nail clearing. The second efficacy variables were clinical cure, 87.5% toe nail clearing, clinical effectiveness (Defined as microbiological cure) and more than 5mm of new toe nail growth and micrological cure...was also administered in the form of a completed questionnaire prior to debridement and a baseline in weeks 6, 12 and 24...for patients were re-examined and 84% or 425 completed the study. In general, patients in both treatment groups with or without debridement improved over the course of the study. That study was a trend in favor of terbinafine with debridement that did not reach statistical significance. Micrological cure was achieved in 67% of patients in the terbinafine and debridement arm versus 62% in terbinafine alone, but that did not achieve statistical significance. Complete cure or 100% was achieved in 37.8% of patients in the terbinafine and debridement arm versus 32.5% with tribinufene alone. Once again that did not reach statistically significant levels. Adverse events or those related to the liver were continuously assessed throughout the study. No clinically significant increases in liver transminases were observed and no clinically apparent drug interactions were reported even with 14.5% of the study population over the age of 65. Despite the wide use of prominent medications across many different classes in many patients and the largest number of patients were ages 65 or over. Now, if a patient had elevated AST or ALT greater than two times the upper limit of normal. Typically, this two times the upper limit of normal in these tests would be considered abnormal. 29 patients did have increases in ALT or AST, but none were over this level. In closing, Tribinufene is well established clinically with a demonstrable track record of efficacy in treating onychomycosis. It has an admirable safety profile when compared to other orally administered anti-fungal medications and data from this most recent iron clad trial underscores its place in patient therapy.

Finally, I will speak to you about Famvir. I won't bore you with any details about its FDA labeling, because you already know that. There are some differentiating factors. The first is post herpetic neuralgia. It's the only anti-viral approved to shorten the duration of post herpetic neuralgia. It shortened the duration by 100 days versus placebo. In patients 50 years of age or greater, meeting time to resolution was 63 days versus 163 days for placebo. Additionally, patients healed 30% faster with five days for recovery versus 7 days with placebo. Viral shedding was 1.8 days with Famvir versus 3.4 days for placebo. Finally, recurrent mucocutaneous Herpes Simplex infection in HIV patients was studied in a randomized, double blind, multi-center and multi-national trial in 293 HIV patients with mucocutaneous Herpes Simplex virus infection. This included genital herpes and oral labial herpes. Patients were treated with Famvir, 500mgs twice a day, for seven days or oral Cyclovir, 400mgs five times per day. Therapy was initiated within 48 hours of lesion onset. These two therapies were comparable in reducing the lesion formation leading to complete healing.

#### **JEFF BENTON (Roche Laboratories)**

I am to discuss the anti-vials. First of all I would like to say that before Tamiflu came to market, there were two anti-vials already on the market. One was amantadinee, which is an m-2 inhibitor and it was used for treatment of influenza A and it had a rather high incidence of CNS side effects, but was still used pretty widely. In 1992, Forest Pharmaceuticals launched rimantadine, also known as Flumadine. It two was an m-2 inhibitor used to treat influenza A. Now recently there was a study published in the Lanset that said that influenza A is becoming increasingly resistant to these older antibiotics. In fact, the study results show that resistance increased to 12.3% in 2003/2004 from 0.4% in 1994/1995. Now, Tamiflu or oseltamivir was brought to market in 1999 by Roche Laboratories and it has a different mechanism of action. It is a neurometanasase inhibitor and because of its different mechanism of action, it treats not only influenza A, but also influenza B well. It has not seen the resistance that amantidene and rimantadine have.

Now, Tamiflu is indicated for both the treatment and prevention of influenza A and B and it is approved all the way down to the age of 1 for treatment and down to the age of 13 for prevention. It comes in a 75mg pill or capsule I should say and is dosed BID for five days for treatment and for the children, there is a suspension that is dosed 2mg/kg twice daily for five days. That can also be used for adults who can't swallow. The Tamiflu for prevention, the dose is 75mg QD for 7 days. The drug is rapidly absorbed and achieves plasma concentration within 30 minutes and achieves maximum concentration in 3-4 hours and has a long half life of 6-10 hours which allows for convenient BID dosing. Benefits to the patient are that it decreases the severity of symptoms by about 38% and shortens the duration to about half. The most commonly seen side effects are normally headaches, nausea and vomiting in right around 10% and those are pretty much mild and transient. The drug can be taken with or without food, when it is taken with food it has been shown to decrease the side effects. The overall benefit to your patients is not only are they going to feel better, but they are not going to be sick as long and it is going to help stop the spread to other family members, co-workers and friends. Every year, we used to be in the hospitals a lot with this stuff and the emergency departments and you can tell

when flu season hits. Those emergency departments just got packed. People were in there in their bath robes and in lying on the floor all cuddled up. Tamiflu is going to help keep, at least, a majority of the family out of the emergency rooms if this drug is available to these folks. Does anyone have any questions?

Question: What about availability?

Response: I'm glad you brought that up. There will be plenty of Tamiflu available. The company is taking all the necessary steps to make sure that there is an adequate supply to treat this year's influenza.