Pharmacy and Therapeutics Committee Meeting Record

Date: 5/13/05 **Time:** 9:00 a.m. – 5:00 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; Cindy Bunde, P.A, Phil Petersen, M.D.; Richard Pines, D.O.; Rick Sutton, RPh; Stephen Montamat, M.D.; Tami Eide, PharmD; Thomas Rau, M.D.

Committee Members Absent: George Pfoertner, M.D.; Mic Markuson, RPh.

Agenda Item	Presenter	Outcome/Action
CALL TO ORDER	W. Terry Gipson, MD	
• **Roll Call**	Linda Edson	Ms. Edson called the roll. One voting and one non-voting member were not present.
• **Reading of Confidentiality Statement**	W. Terry Gipson, MD	The confidentiality statement was read by Dr. Gipson.
• **Approval of Minutes from March 18, 2005 Meeting**		The minutes from the March 18 2005, Committee meeting were approved.
• **Discussion of Key Questions for Upcoming EPC Drug Effectiveness Review Studies**	Tami Eide, PharmD, BCPS, FASHP	The draft key questions for antiepileptics, antihistamines, inhaled corticosteroids, agents for overactive bladder, and statins were discussed.
DUR PROPOSED OUTCOMES STUDIES	Chris Owens, PharmD	Dr. Owens presented utilization data on calcium channel blockers and statin drug classes and requested P&T input on meaningful outcome studies that the DUR Board should pursue.
PUBLIC COMMENT PERIOD	W. Terry Gipson, MD	Nine people were listed to speak during the public comment period. Public comment was received from the following: • Richard Ensign, PharmD, Pfizer – Aricept® • Ann Speiser, PhD, Ortho McNeil – Galantamine® (Reminyl® /Razadyne®) • Calvin Harris - Namenda™ • Betsy Woodall, Wyeth – Premarin®/Premarin® Vaginal Cream • Richard Ensign – Detrol® LA • Anton Nguyen, Ortho McNeil – Ditropan® XL • Laura Kososki, MD, Odyssey – Sanctura® • Andy Weis, PharmD, Novartis – Enablex® and Exelon® • Allen Christie, GlaxoSmithKline – Vesicare® • Allen Han, MD, Forest – Namenda®
DRUG CLASS REVIEW • **Alzheimer's Drugs**	Selma Gearhardt, PharmD	Dr. Gearhardt presented a review of Alzheimer's drugs including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: <u>Cholinesterase Inhibitors</u> • Tacrine (Cognex®) • Donepezil (Aricept®)

		• Rivastigmine (Exelon®) • Galantamine (Reminyl®) N-methyl-D-aspartate (NMDA) Receptor Antagonists • Memantine (Namenda®)
CLINICAL DATA REVIEW • **Alzheimer's Drugs**	Richard Hansen, PhD	Dr. Hansen attended via conference call and presented the RTI-UNC Evidence-Based Practice Center's report comparing the Alzheimer's drug class. This report was finalized in March of 2005. The Committee accessed and reviewed a copy of the report prior to the meeting.
CLINICAL DATA REVIEW • **Estrogens**	Marian McDonagh, PharmD	Dr. McDonagh attended via conference call and presented the Oregon Evidence-Based Practice Center's report comparing the estrogen drug class. This report was finalized in July of 2004. The Committee accessed and reviewed a copy of the report prior to the meeting.
DRUG CLASS REVIEW • **Urinary Incontinence**	Mary Wheatley, RPh	Ms. Wheatley presented an updated review of the urinary incontinence drug class including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: • Darifenacin (Enablex®) • Flavoxate (Urispas®) • Oxybutynin (Ditropan®, Ditropan®XL, Oxytrol™) • Solifenacin (VESIcare®) • Tolterodine (Detrol®, Detrol® LA) • Trospium (Sanctura®)
DUR PRESENTATION • **Triptans Outcome Study** • **PPI Outcomes Study**	Heather Brandt, PharmD	Dr. Brandt presented clinical and financial outcomes on the triptan and PPI drug classes relative to EPAP implementations. No negative outcomes could be attributed to use of the preferred agents.
PPI THERAPEUTIC REQUIREMENTS REVIEW	Tami Eide, PharmD, BCPS, FASHP	Dr. Eide presented the recommended therapeutic requirements for the PPI drug class to the Committee. The Committee agreed with the requirements and recommends implementation.
COMMITTEE DISCUSSION AND CLINICAL CONCLUSIONS FOR SELECTED THERAPEUTIC CLASSES	W. Terry Gipson, MD	Alzheimer's Drugs The Committee determined Tacrine should not be included in a preferred drug list. All other agents should be available with a diagnosis for a dementia disease state, however Namenda could be a second line agent. Recommendation was made to have a DUR educational intervention on combination therapy with an anticholinesterase inhibitor and Namenda®. Estrogens The Committee determined that no new information was received regarding estrogens. Urinary Incontinence The Committee determined that agents in this class are equally efficacious and safe.
PUBLIC MEETING ADJOURNED	W. Terry Gipson, MD	The next classes of agents to be reviewed by the Pharmacy and Therapeutics Committee on July 15, 2005 are antiplatelet agents, statins, calcium channel blockers, long acting opioids, and skeletal muscle relaxants.

		Dr Gipson adjourned the public portion of the meeting.
SUPPLEMENTAL REBATE INFORMATION *(CLOSED TO PUBLIC)*	Randy May, Medicaid Deputy Administrator	Randy May presented supplemental rebate information to the Committee members for their review and discussion. This review and discussion were closed to the public.
COMMITTEE FINAL RECOMMENDATION FOR THERAPEUTIC CLASSES	W. Terry Gipson, MD	<u>Alzheimer's Drugs</u> The Committee recommends the following: • The use of these agents be limited to individuals with an approved dementia diagnosis (approved diagnosis is indicated by NDC). • The use of these agents be subject to the use and documentation of an objective dementia rating scale such as the Mini-Mental State Examination (MMSE). • Aricept® be designated as a preferred agent for mild to moderate dementia ratings. • Namenda® be designated as a preferred agent for moderate to severe dementia ratings. • All other agents in this class (Exelon®, Reminyl®/Razadyne™) become designated as non-preferred agents subject to additional PA criteria. • Individuals with an approved diagnosis who are currently stable on a non-preferred agent will not have to transition to the preferred agent. (Stable patients with an approved diagnosis will be grandfathered into the PA criteria.) <u>Estrogens</u> The Committee recommends no change to the May 21, 2004 recommendations. <u>Urinary Incontinence</u> The Committee recommends that Oxybutynin, Detrol LA®, Enablex®, Oxytrol®, and Sanctura® be designated as preferred agents. All other agents in this class will require prior authorization.

Pharmacy and Therapeutics Committee
Public Comment
May 13, 2005

Richard Ensign, PharmD, Pfizer – Aricept

Dr. Ensign: My name is Richard Ensign, I'm a pharmacist with Pfizer Pharmaceuticals and [unintelligible], so I will try to keep it as short and painless as possible. Pfizer is the maker of Aricept [unintelligible]. As you know [unintelligible] disease is a very devastating disease involving patients and their caregivers [unintelligible] the goal of therapy is obviously to make the patients and keep them home with their families and loved ones as long as possible. I know later today you're going to look at the [unintelligible] report, and I encourage you to look carefully at the evidence that is presented in that report. Aricept [unintelligible] the most evidence with fourteen placebo controlled trials. At the time the majority of those are in Oregon reported, there are a couple that are not there but the majority of the evidence is there. Look carefully at the head to head trials because that is obviously where [unintelligible] differences between them. And the three head to head trial that are in Oregon that reported, two out of the three showed significant benefit for Aricept over the competitors in both efficacy and tolerance parameters. So it is difficult when you [unintelligible] that evidence closely to say there is no difference between those agents. And that is backed up a little bit by the usage data in Idaho I'm going to talk about in a minute. As we know patients with Alzheimer's are on multiple medications and any opportunity we have to streamline their therapy can be beneficial. One of the advantages with Aricept is the once daily dosing and the ease of [unintelligible] for these patients. Aricept [unintelligible] and Estrace inhibitor if they actually start on a therapeutic dose a 5mg dose they have [unintelligible] get to 10 mgs for the maximum efficacious dose. If you look at the actual [unintelligible] statement in Medicaid, and this is available from the CMS website, for the first three quarters of 2004, based on the number of prescriptions Aricept accounts for about 75 % of prescriptions, Exelon is 13 % and Revinal is 12%. Demonstrated in Idaho and similar areas nationwide, Aricept is the first choice by physicians based on the evidence that is available. What you might find interesting if you look even closer at the data and the different dosages that were used there are some more interesting observations. In the state of Idaho with Aricept 67% of patients are on the 10 mgs [unintelligible] effective dose. Exelon has 35% on the 12 mg dose, and Revinal has 10% on the 24 mg per day dose. [Unintelligible] maximum efficacious dose again based on prescription data. Why is this important? Well, what is says is all the patients [unintelligible] treated in Idaho who are on a Aricept are on the effective dose with two out of three being on the maximum effective dose. Whereas in the competitor is only one out of three and Exelon only one out of ten with Revinal [unintelligible] the comparable doses in the study. So again when we look at the evidence it doesn't necessarily translate to how these drugs should be used in Idaho, so keep that in mind as well. [Unintelligible] the way of looking at it is if anyone made the switch based on therapy with interchange patients would probably not receive the equivalent dosing that they had currently receive on Aricept. Now I did not include [unintelligible] analysis because at least from the data it appears that a lot of these patients when actually use a combination of therapy not a mono-therapy so it couldn't [unintelligible] it out. A lot of this information along with what you gain from the scientific review later on I would ask you to consider Aricept as a preferred choice for the Idaho Medicaid based on the efficacy, the tolerance, the [unintelligible] and the fact that it is a very valuable option for patients.

Committee: Any questions? Thank you.

Ann Speiser, PhD, Ortho McNeil – Galantamine

Dr. Speiser: Good morning and thanks for the opportunity. My name is Ann Speiser; I'm with Regional Scientific Services with Janson Ortho McNeil. I want today to provide and update on Galantamine. This is information that is new since the information was complied for the systematic review from LHSU. Galantamine remains the same molecule but has a new name and a new formulation. It was previously known a Reminyl it is now Razidine. There were some prescribing errors between Reminyl and Amaryl, and since this can be a life threatening prescribing error Johnson and Johnson has agreed to change the name from Reminyl to Razidine. The other new information is that Galantamine is now available in a once daily dose. Again this is the exact same molecule it is Galantamine [unintelligible] dosing, this is just an addition of a rate controlling membrane that allows the drug to be delivered over the course of a day rather the needing a BID dosing. This [unintelligible] string is called Razidine ER. The clinical data for Razidine ER show that, in terms of semen and [unintelligible] curve and two formulations are bioequivalent there are slight differences in Cmax and Tmax although these are not believed to be clinically relevant. In a study

with 971 patients with them evenly divided into three groups. So, a placebo group, a Galantamine immediate release group and a Galantamine extended release group there was significant [unintelligible] Galantamine groups over the placebo and no difference in efficacy in the two Galantamine groups. There were also similar tolerability profiles although there is mounting evidence that with the ER formulation a greater number of patients are able to go on to the 24 mg dosing. So, the proportion of patients who reach that maximum dose is greater with ER than it is with the immediate release formulation. So, I will try to keep the short and sweet, the Tako message is going to mean it is now available in once daily dosing; its name change is to Razidine and Razidine ER. It is the same molecule so all the history we have with its safety, tolerability and efficacy remains valid, but there is now a new choice in once daily [unintelligible] inhibitors. Any questions I can answer? Thank you.

Calvin Harris

Mr. Harris: Dr. Han is not here right now, he had and engagement with one of his patients. My name is Calvin Harris [unintelligible] Laboratories, but I will speak as a caregiver on Namenda. My mother has had Alzheimer's for the past five years, she has severe dementia and as I've seen what all my mother has been able to before this. Just starting with she has been as I say, with Alzheimer's the past five years, she has declined as the disease does normally does decline. And she has been in long timers unit where she has to perform, well not perform, but take care of herself. Literally eat by herself, walk and take care of her own self. With Namenda she has been able to stay in that long timers unit. Before Namenda came out they had moved her from that secured Alzheimer's unit to one of the out facilities because she had quit feeding herself and [unintelligible] to a vegetative state. Now with Namenda she has been able to go back into the long timers unit and today be able to feed herself and be more active and participate in her own care with Namenda. Namenda is a unique drug. It's not [unintelligible] so it is unique in its characteristics also it is for moderate to severe Alzheimer's unlike the other placebo [unintelligible] which are for mild to moderate. We're unique. [Unintelligible] for the more severe patients with Alzheimer's. And it is the only drug out there right now for moderate to severe Alzheimer's. So, with that being the case we are just asking that the committee consider adding an addition to the formulary for that. Thank you.

Committee: Thank you. Any questions?

Betsy Woodall, Wyeth – Premarin/Premarin Vaginal Cream

Ms. Woodall: Good Morning. I'm here to discuss Premarin and Premarin Vaginal Cream. My name is Betsy Woodall and I'm a pharmacist, I work in Global Medical Affairs Department at Wyeth Pharmaceuticals. Last year the Food and Drug Administration along with the North American Medical Society and the American College of Obstetricians and Gynecologists issued public statements stating estrogens, all of them should be used for the lowest dose and the shortest duration of time [unintelligible] each woman's individual risks and goals, their individual rights, patient therapy. Now Premarin tablets are indicated for moderate to severe treatment of these and other symptoms as well as moderate to severe treatment of [unintelligible] and the prevention of post menopausal osteoporosis. Premarin vaginal cream is indicated in the treatment of vaginal atrophy [unintelligible]. Continued use of Premarin and Premarin vaginal cream as preferred drug agents on the Idaho state formulary will continue to give health care practitioners these options for individualizing patient care and the resolution of their symptoms. [Unintelligible] some of the accuracy for both of these products. The Women's Health Osteoporosis progesterone and estrogen study or Women's Hope Study, was the pivotal trial that allowed for the approval of low dose [unintelligible]. It also provided supporting information for the previously commercially available Premarin .3mg strength which continues today. This is a randomized double blind placebo controlled clinical trial inducted at many sites over the United States. The mean age of the women involved in this trial was 53. And this trial did indeed show that all doses of Premarin were effective in relieving basal motor symptoms in symptomatic women. Additionally it showed that all doses down to .3 and .45 mg of Premarin, in addition to .65 effectively prevented post menopausal osteoporosis. Now keep in mind that health care practitioners are encouraged to consider non estrogen medications if their only using Premarin in the treatment of post menopausal osteoporosis. Additionally the Women's Hope trial also noted that all doses of Premarin were effective in relieving symptoms of vaginal atrophy. And again, if a woman is not experiencing hot flashes and the only symptom is vaginal atrophy health care practitioner are really encouraged to use topical products first. Reading into that, we have a study I would like to discuss with you on Premarin vaginal cream. Just last year a study published by Romundo and Colleagues looked at two consecutive cycles of cyclic administration, three weeks on, one week off, of Premarin vaginal cream administered in one gram dosed containing .625mgs of conjugated estrogens. This study was intended to look at changes in vaginal maturation index, which is the clinical marker for vaginal atrophy, and compared to baseline at the end of the two cycles, we noticed a significant increase in numbers [unintelligible] superficial and intermediate cells and significant decrease in the number of [unintelligible] cells. Exactly what you would like to see.

Most of these products have been available for over 60 years and there is a whole host of safety and efficacy information. But I would like to highlight the safety information specific to, probably what we are most familiar with, women's health initiative, which has lead to class labeling for all estrogen products whether or not the contain a progestin. And this is actually detailed [unintelligible] the sheet that was handed out ahead of time. This is a randomized double blind placebo controlled [unintelligible] clinical trial. The mean age of these women was in fact 63 years old. And the intention of this particular trial was to look at the overall risks and benefits of using Premarin therapy. The primary efficacy outcomes was to see if Premarin decreases the risk of [unintelligible] disease, primary safety was to see if it increased the risk of breast cancer. The trial was stopped prematurely in 2002 again leading to class labeling issues in 2003 and 2004. Briefly I've shared with you just some of the information describing some of the safety and efficacy of Premarin and Premarin vaginal cream. I hope that you as well as the Food and Drug Administration, the American College of Obstetricians and Gynecologists, and the North American Medical Society, as well as Wyeth, consider providing healthcare professionals with these products to allow the individual [unintelligible] of therapy to provide them with the lowest dose for the shortest duration of time. Further details are provided for you in the handout that was given to you ahead of time. At this time I can answer any questions that you have.

Committee: The study that you referred to early was that submitted to Oregon Health Sciences?

Ms. Woodall: The Women's Hope trial?

Committee: Yes.

Ms. Woodall: Yes.

34.7 No sound on tape. Pick up on side to 15.0

<u>Richard Ensign, PharmD – Detrol LA</u>

Dr. Ensign: Pfizer does make their [unintelligible] because of some of the thing we will find out about a little later on. First of all Detrol LA, the long acting [unintelligible] Medicaid PDL and hopefully based on the evidence [unintelligible]. Mentioned earlier when we talked about the [unintelligible] criteria and the inappropriate use [unintelligible] the DUR Board was [unintelligible] in Idaho Medicaid. And as you are aware the short acting Oxybutynin, while it's inexpensive is on that list and not recommended to patients over age of 65. So I was excited to see [unintelligible] that information. If you look at why patients stop using these medications it's usually due to side effects. [Unintelligible] constipation. And that is where there are significant differences between these agents. For one, the long acting formulations tend to be a lot better than the shorting acting. In the case of Detrol and Detrol LA, the Detrol LA formulation is considerably better both in efficacy and in tolerance parameters. And so that's why [unintelligible] only product that is currently promoted because that is the best option for the patient out there. After you compare the long acting formulations to each other [unintelligible] and see some of the differences and there are significant advantages with the Detrol LA [unintelligible] compared to the other agents. If you just look at the package inserts, for instance, comparing the Ditropann XL package insert for [unintelligible], Detrol LA is 23%, 60% for Ditropann XL, constipation, 6% Detrol LA, 13% for Ditropann XL. We all know the weakest element you have out there is package insert as a comparison that's usually what you start with. But now we have [unintelligible] based on the update of the Oregon report several head to head studies looking at tolerance. There are two studies in there number 31 and 32 and both show significant fewer side effects with Detrol LA compared to the Ditropann XL. And while you will be looking at some new additional medications today that have been evolved over the last year with the FDA none of these have shown better tolerance compared to Detrol LA. In fact, in a recent study with Detrol they found if you give it at bedtime the incidence of dry mouth was 9% and constipation was 3%. Nationwide due [unintelligible] Detrol LA continues to be the number one medication for over active bladder, as well as in the state of Idaho [unintelligible] CMS data up until [unintelligible] last year based on this efficacy and safety data it was the first choice by physicians. So I would ask you to consider the evidence and give the patients in Idaho Medicaid access to an effective, the best tolerated and valuable therapeutic [unintelligible] bladder. Questions? Thank you.

Anton Nguyen, Ortho McNeil – Ditropann XL

Mr. Nguyen: Good Morning Board Members. My name is Anton Nguyen. I am a pharmacist with Ortho Neurology [unintelligible]. I am here to speak to you on behave of Ditropann XL [unintelligible] for over active bladder. Specifically today I would like discuss dosing, safety and tolerability. As you are aware Ditropann XL is available in three strengths, 5, 10 and 15 mgs. This is important because it allows for six different dosing regimens. As with most patients that are on anticolonergents if is important to receive an optimum dose that balances all [unintelligible] and again with six different dosing regimens, let me back up, starting at the most common dose of 10mgs. patients [unintelligible] to an effective dose or conversely taken be taken down to a more tolerated dose, would give them that flexibility on Ditropann XL dose was allowed for [unintelligible] appropriate therapeutics. As for safety, Ditropann XL is the only long acting [unintelligible] that has an indication for pediatric patients 6 years and older. Specifically the indication is for patients with over active [unintelligible] muscles and this is seen with a neurological disorder. The dosing measure for this specific indication is 5 [unintelligible] mgs. Again pediatric populations are difficult [unintelligible] caution, so with this indication [unintelligible]. As you've heard earlier today prior to 2003, Oxybutynin was on this list as an IR product as of the 2003 update Ditropann XL was excluded because it does not present the same inappropriate potential as the IR. So again, please consider that when you are looking at the use of Ditropann XL. Similarly with pediatric [unintelligible] population is one that we are really more concerned with dosing and [unintelligible]. Again exclusion from the [unintelligible] to Ditropann XL's safety and tolerability. A recent update to our UPI and [unintelligible] associated with the PI and as of 2004 [unintelligible] the update has [unintelligible] that 10mgs. is the most commonly prescribed medication for [unintelligible] dose and hence [unintelligible]. With the 10mg dose being the most common UPI has shown a decrease in incidences of side effects of dry mouth [unintelligible] 29% which is comparable to the other long acting products available on the market. In addition, patients that are on the long acting products who do experience dry mouth typical within the 5 to 30mg dosing range only 1.2 % of those are seen to discontinue. Most of the patients that do experience dry mount it is a mild form and don't [unintelligible] discontinuation. In conclusion, with the tolerability and pediatric limitation and the safety profile [unintelligible].

Laura Kososki, MD, Odyssey – Sanctura

Dr. Kososki: Good Morning. I'm Dr. Laura Kososki from Odyssey Pharmaceuticals. I'm a physician, medical science liaison for the company and I'm here to talk about Sanctura [unintelligible]. This is a new product in this class as of last Friday. Sanctura [unintelligible] is an important addition to the Idaho Medicode [unintelligible] formulary due to its unique [unintelligible] in this [unintelligible] class of drugs for urinary incontinence. [Unintelligible] option in this class the choice being compounds [unintelligible] molecular structure. All of the other first line tertiary means in this class have three substitutions the ammonia molecule so this product has a novel chemical entity. These characteristics [unintelligible] receptor binding [unintelligible] penetration, metabolism, [unintelligible] action and these are [unintelligible] tolerability and safety advantages for [unintelligible] along with it's established efficacy. I will talk about all of these during the [unintelligible]. Sanctura lacks the typical anticoallrgic [unintelligible] side effects very often seen with this class of drugs. Sanctura inability to penetrate the blood/brain barrier is widely supported in the literature by such venerable authors as Alsfinder, Peietscon, Pack, and Zena. The typical [unintelligible] such as dizziness, confusion and somulance as a highly substantiated by the lack of these agents in Sanctura's clinical studies. Sanctura has no known drug/drinking reaction. Sanctura is not metabolized by the same [unintelligible] metabolic pathway as are the other tertiary means first line agents in this class. As a result the patients that take Sanctura [unintelligible] with many of the other commonly prescribed products that [unintelligible] metabolism that are not at risk for [unintelligible] interactions. Sanctura has no known drug/drug interactions. Its metabolic pathway is comprised of estohydrolosis which is [unintelligible] five [unintelligible] and this has no known drug/drug interactions. This is an important safety feature in this class and is unique as none of the other products offer this safety advantage. Sanctura is not highly protein bound and as a result there are no known plasma protein binding drug/drug interactions. In terms of efficacy, a very important feature is that Sanctura has rapid onset of action that occurs within the first seven days. Our two [unintelligible] large scale U.S. clinical trials demonstrated that for failed both the primary [unintelligible] reduction in frequency and reduction of urgent incontinence that patients had meaningful differences with onset of actions starting in the first seven days. For frequency reduction this occurred in the first three days. This type of [unintelligible] is very important when looking at compliance rates at it does [unintelligible] compliance for this class of drugs especially since side effects tend to occur early. And final Sanctura has a favorable tolerability profile; especially admitted is Sanctura's lack of [unintelligible] side effects, the lack of dizziness, confusion, insomulance, day time somulance, as well as no blurred vision. In summary Sanctura offers distinct safety and tolerability and the on set of action improvements in this class and we highly recommend that you do consider it for your formulary here. I will now answer any questions about Sanctura.

Committee: Thank you.

Andy Weis, PharmD, Novartis – Enablex and Exelon

Dr. Weis: I'll be talking to you about [unintelligible]. We'll just start with the info in alphabetical order. I would like to thank the committee for letting me appear this morning. Enablex which is also known also by it's generic name Darifenacin is highly selective [unintelligible] separate antagonist which was recently approved by the FDA for treatment of over active bladder, with symptoms of urgent urinary incontinence, urgency, and [unintelligible]. M3 receptors are found principally in urinary bladder detrusser muscle and in salivary glands and to a lesser extent in other parts of the body. [Unintelligible] M3 receptors when demonstrated between 9 and 12 fold more selective for M3 than for M1 and M5 receptors, respectively. The 59 fold more selective for M3 than for M2 and M4 muscular [unintelligible] receptor types. M3 receptors are also found in the salivary glands and dry mouth is commonly found in patients treated with [unintelligible]. In [unintelligible] performed in patients with involuntary urinary bladder detrusser contractions increased bladder capacity was demonstrated by increased volume threshold for unstable contractions and the [unintelligible] frequency of unstable detrusser contractions after Darifenacin extended release tablet treatment. Clinical [unintelligible] treatment of over active bladder was demonstrated by [unintelligible] double blind placebo controlled studies. Efficacy was measured not only by mean number of [unintelligible] per day but also by number of incontinence episodes [unintelligible] urine pasted. [unintelligible] double blind placebo controlled study which examined the effects of [unintelligible] Darifenacin [unintelligible] concluded that, we quote, "At the dose of study [unintelligible] did not result in QT, QTC prolongation of any time period in the study state while [unintelligible] treatment resulted in the mean increase from base one QTC up of about 7 milocycles when compared to placebo. It is important to note that within this study [unintelligible] dose of 75mg of Aroplenicin which is ten times the current FDA approved starting dose. Just like other systemic anticholinergic agents [unintelligible] is confident in getting patients with known urinary retention, gastric retention or uncontrolled uroangle glaucoma in patients who are known risk for these conditions. So it is also currently indicated for patients who have hypersensitivity [unintelligible]. Caution should be used in patients taking known medications to inhibit [unintelligible] therapeutic index. This includes tricycline, antidepressants, [unintelligible]. Caution should also be used in patients taking known inhibitors aside from [unintelligible] Ketacarnazole, Detracarnazole, [unintelligible] and Fazadone. [Unintelligible] systemic and anticholinergic agents caution should be used in patients taking medication with known anticholinergic side effects. The dose in [unintelligible] Enablex is initially 7.5mgs QD and can be increased to 15mgs QD after two weeks. Patients with [unintelligible] such as [unintelligible] class C or receiving medication which inhibits [unintelligible] P415 particularly the 3 day [unintelligible] form such as those previously mentioned should receive a daily dose of 7.5mgs according to the FDA per the package insert. In summary, [unintelligible] to patients in a highly convenient once daily dosing form as documented advantageous and safe [unintelligible] with over active bladder, with urgent urinary incontinence [unintelligible] and frequency. Now I will switch gears and become a neurologist. I'm going to talk to you today about Exelon also known as [unintelligible]. Its reversible [unintelligible] for up to ten hours. Evidence suggests that both of these enzymes play a play a role in regulating levels of asatolcolene in the brain with Alzheimer's disease patients [unintelligible] of both enzymes make [unintelligible]. It is approved by the FDA for the treatment of mild to moderate dementia of the Alzheimer's type. [Unintelligible] prepared a placebo which demonstrated in three typical clinical trials. The three studies where 26 weeks in duration and used perspective randomized double blind placebo controlled parallel group design. Subject enrolled in these studies had mild to moderately severe cognitive impairment based on many mental status examination scores between ten and twenty-six inclusively. Subjects receiving [unintelligible] experienced either significant improvement or relative preservation of cognition based on the [unintelligible] scale [unintelligible] compared with those receiving placebo. A sub analysis of one pivotal trial found initiating treatment with Exelon later on in the study failed to achieve the same benefit as those starting Exelon earlier. Additionally studies and analyses have found Exelon to be affective with control and several behavioral disturbances associated with Alzheimer's disease measured by the Behave AD and MPI scales. [Unintelligible] analyses of pivotal trials indicate Exelon is associated with long term cognitive benefits for up to five years. [Unintelligible] unique linear dose response to maximize efficacy [unintelligible]. There are known [unintelligible] drug interactions with the compound acid as with other [unintelligible] the most common [unintelligible] events are nausea, vomiting, anorexia, [unintelligible]. Traditionally it has been shown to be effective in patients no longer responding to Aricept therapy. [unintelligible] study in 200 patients with mild to moderate Alzheimer's disease, 17% of patients who responded poorly to treatment with Aricept responded to Exelon as measured by Global functioning scales, particularly the CGIC scale. These studied are consistent with benefits seen in previous [unintelligible] six months study [unintelligible] patients with mild to moderate Alzheimer's disease who were treated with [unintelligible] after discontinuing Aricept therapy. In these patients in this study, 56% of the patients who discontinued Aricept responded to Exelon. Other studies have indicated that Exelon can be used safely in combination with Remenda and [unintelligible] of colon estrace is not affected by [unintelligible] administration. Studies have also shown that Exelon can decrease the need

for psychotropics and narcoleptics in Alzheimer's disease patients. Once our study found patients initiating treatment with Exelon were 60% less likely to be prescribed antipsychotics than for patients not on colon estrace inhibited therapy. Now this study found that 60% of patients initiating Exelon therapy discontinued or reduced the use of antipsychotic agents, 58% discontinued or reduced the use of [unintelligible] agents, and 29% discontinued or reduced the use of antidepressants, and 27.9% discontinued or reduced the use of hypnotic agents as well. I would like to ask if there are any questions.

Public: Yes, I have a question. You mentioned a study of people who were, you said one time had failed to respond to Aricept, the second time you said had changed from Aricept to Exelon. Is that two different statements or…

Dr. Weis: There were two different studies. One study was done in patients who no were no longer responded, they responded [unintelligible] treatment, and then the other study was done, one study in 270 patients who had responded poorly to treatment with Aricept and responded to Exelon and then the other study was in 382 patients [unintelligible] the study done before where the patients were discontinued, were treated with [unintelligible] after discontinuing Aricept therapy. On, specific to those studies, I don't have in terms of what was meant by responding. I can only say that [unintelligible] to the studies that we saw I can provide further information to you. [Unintelligible].

Public: Question was unintelligible.

Dr. Weis: I don't believe that they were published [unintelligible].

Allen Christie, GlaxoSmithKline – Vesicare

Mr. Christie: Good Morning. My name is Allen Christie I'm a Pharmacologist for GlaxoSmithKline. [Unintelligible] I'm going to spend a few minutes talking to you about Vesicare and it is a relatively new compound that [unintelligible]. There are three things I would like to point out. Three numbers I would like you to remember 51%, 10.9% and 81%. [Unintelligible] 51% is the number of patients that were considered included in [unintelligible] in a 12 week trials. So of course it was the ultimate measure for patients undergoing LAB treatment [unintelligible] function. 10.9% represents the rate of dry mouth for these patients that are on 5 mg which is considered the efficacious starting dose. That is considerably less than what you would for other [unintelligible]. And lastly 81%. This is the percent of patients that actually stayed on drug for a total of 52 weeks. [Unintelligible] this is really a measure of patient's efficacy and tolerability of the medication; it really adds a conservative composite number of the 51% that are considered to be dry as well as [unintelligible] side effect profile. [Unintelligible] provides patients with the safety they are looking for as well as tolerability. The last thing that is not included in the [unintelligible] unpublished and will be soon in the Journal of Pharmacology. [Unintelligible] head to head study compared to [unintelligible] 5mg Tolterinin extended release [unintelligible]. Zahirapin study over 1300 patients in this study [unintelligible] the best you could do was show you were not inferior [unintelligible].

Allen Han, MD, Forest – Namenda

Dr. Han:

Public: Unintelligible (recorder not working properly).