7 July 2006

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
June 2006

The Uniform Formulary Beneficiary Advisory Panel commented on the recommendations from the DOD Pharmacy & Therapeutics Committee May 2006 meeting.

1. Contraceptive agents: The P&T Committee recommended that Seasonal, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary and that Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, Plan B and all generically available OCs remain on the UF. The P&T Committee voted to recommend an implementation period of 180 days.

Summary of Panel Comments:

- The Panel voted 10-1 to concur with the recommendation.
- The Panel voted unanimously (11-0) to concur with the recommended implementation period of 180 days.
- A Panel member stated that he believed that Plan B should have voted separately.

Director, TMA: BW

☑ These comments were taken under consideration prior to my final decision.

2. **Antiemetic Drugs:** The P&T Committee recommended that dolasetron be classified as non-formulary. The P&T Committee also recommended that granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine and trimethobenzamide remain on the UF. The P&T Committee voted to recommend an implementation period of 60 days.

Summary of Panel Comments:

- The Panel voted to unanimously (11-0) to concur with the recommendation.
- The Panel voted unanimously (11-0) to concur with the recommended implementation period of 60 days.

Director, TMA: BW

☑ These comments were taken under consideration prior to my final decision.

Uniform Formulary Beneficiary Advisory Panel

Meeting Summary
June 29, 2006
Washington, D.C.

Panel Members Present:

- John Class, Military Coalition, Chairman
- John Crum, TRICARE Network Provider
- Deborah Fryar, Military Coalition
- Marshall Hanson, National Military and Veterans Alliance
- Rance Hutchings, Uniformed Services Family Health Plan
- Lisa Le Gette, TRICARE Retail and Mail-Order Pharmacy Contract
- Jeffrey Lenow, Medical Professional
- Charles Partridge, National Military and Veterans Alliance
- Jan Prasad, TRICARE Network Provider
- Marissa Schlaifer, Medical Professional
- Robert Washington, Military Coalition

The meeting was held at the Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington, D.C. Major (MAJ) Travis Watson, the Designated Federal Officer (DFO), called the proceedings to order at 8:00 a.m.

MAJ Watson indicated this meeting of the Panel has been convened to discuss and review the recommendations of the Department of Defense (DOD) Pharmacy and Therapeutic (P&T) Committee meeting held on May 9 and 10, 2006, in San Antonio, TX.

Agenda

The agenda for the June meeting of the Panel is:

- Opening remarks and public comments
- Consideration of contraceptive agents drug class recommendations
- Consideration of antiemetic drug class recommendations
- Wrap-up comments

Opening Remarks

MAJ Watson stated that under 10 United States Code (U.S.C.) section 1074g the Secretary of Defense is required to establish a Pharmacy and Therapeutics (P&T) Committee for the purpose of establishing a Department of Defense (DoD) Uniform Formulary (UF) of pharmaceutical agents, review the formulary on a periodic basis and make additional recommendations regarding the formulary as the Committee deems necessary and appropriate.

10 U.S.C. section 1074g also requires the Secretary of Defense to establish a Uniform Formulary Beneficiary Advisory Panel (BAP) to review and comment on the development of the Uniform Formulary. The Panel shall include members that represent

non-governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. Comments of the Panel must be considered before implementing changes to the Uniform Formulary. The Panel's meetings are conducted in accordance with the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel are:

- To reviewing and comment on the recommendations of the P&T Committee concerning the establishment of the Uniform Formulary and subsequent recommended changes. Comments to the Director, TRICARE Management Activity (TMA), regarding recommended formulary status, pre-authorizations, and suggested dates for changing from "formulary" to "non formulary" status must be reviewed by the Director before making a final decision.
- To hold meetings in an open forum quarterly. The Panel may not hold meetings except at the call of or with the advance approval of the Chairman of the Panel.
- To prepare minutes of the proceedings and comments for the Director, TMA, regarding the P&T Committee's recommended changes to the Uniform Formulary. The minutes will be posted on the website.

As guidance regarding this meeting, MAJ Watson said the role of the Beneficiary Advisory Panel is to comment on the Uniform Formulary recommendations made by the P&T Committee at their last meeting. While the Department appreciates that the BAP may be interested in the drug classes selected for review, drugs recommended for the basic core formulary (BCF) or specific pricing data, these topics do not fall under the purview of the BAP.

The P&T Committee met for approximately 20 hours to consider the class review recommendations presented today. Since this meeting is considerably shorter, the Panel will not receive the same extensive information that is presented to the P&T Committee members. However, the BAP will receive an abbreviated version of each presentation and its discussion.

Detailed minutes of this meeting are being prepared. The BAP minutes, the DoD P&T Committee meeting minutes and Dr. Winkenwerder's decisions will be available on the TRICARE website in approximately four weeks.

MAJ Watson next reviewed the ground rules for conducting the meeting:

- All discussion takes place in the open public forum. There is to be no committee discussion outside the room, during breaks or at lunch.
- Audience participation is limited to private citizens who signed up to address the Panel.
- Members of the Pharmacoeconomic Center (PEC) and the P&T Committee are available to answer questions related to the BAP's deliberations. Should a misstatement be made, these individuals may interrupt to ensure that the minutes accurately reflect relevant facts, regulations or policy.

MAJ Watson introduced the members of the Beneficiary Advisory Panel present as well as individuals in the audience who might be participating in the session.

MAJ Watson then briefly reviewed housekeeping considerations.

Private Citizen Comments

MAJ Watson opened the meeting for private citizen comments. There were none.

Opening Remarks by the Chair

The new Panel Chairman, Mr. John Class, opened the meeting by publicly thanking Ms. Sydney Hickey for her hard work during her year as Chair of the Panel during its first year.

Mr. Class also sought to clarify the Panel's voting process, noting that questions were raised about it at the last meeting. Specifically, the need is to clarify the meaning of "concurring" and "nonconcurring." He noted that it is important to vote on the P&T Committee's specific recommendation. If the Panel believes that a change needs to be made in the recommendation, his opinion is that the Panel would vote to "nonconcur." He said the Panel has been concurring, but with stipulations. His concern is that, outside the Panel, that amounts to a "concur" vote. He is concerned that when the minutes of the P&T get signed and press releases go out, the Panel's comments or stipulations are not part of that. His feeling is that if the Panel wants to recommend additions or changes to the P&T Committee's recommendations, it should vote to "nonconcur" rather than "concur."

Mr. Hutchings agreed with the need to define the meaning of the votes. He said there have been instances in which he felt the Panel was all on the same page but voted differently because of the terminology. He said his main area of concern is with the implementation period recommendations. He believes the Panel has seldom had differences with the individual formulary recommendations.

Without further comment, Mr. Class said that the Panel would use that protocol as the basis for its future voting.

Presentation on Contraceptive Agents Drug Class Review

Major (Maj) Wade Tiller introduced the Pharmacoeconomic Center staff present today to make presentations to the Panel and answer questions.

Dr. Shana Trice made the presentation of P&T Committee recommendations regarding clinical effectiveness for the first drug class review: contraceptive agents.

[Insert script pages 1 through 10]

Panel Questions

Dr. Prasad asked to have the brand names of the drugs used instead of their generic names. He said it would make it easier to differentiate among the agents and make the recommendations easier to understand. Maj Tiller said that brand names are used in the presentation and the handout provides both. As far as additional use of brand names in the recommendations, Maj Tiller said the Agency would take the matter under advisement.

Dr. Lenow asked whether the PEC had come across any reports of conditions of extreme heat causing greater estrogen release in higher systemic levels with the patch. Dr. Trice said she hadn't seen any such reports, but noted that she hadn't been looking for them either.

Maj Tiller presented the P&T Committee's findings regarding the relative cost-effectiveness of agents in the contraceptive drug class.

[Insert script, pages 10 and 11].

Colonel (COL) Joel Schmidt next provided the Beneficiary Advisory Panel with the physician's perspective on the P&T Committee recommendations.

COL Schmidt, who announced that he is retiring soon after this meeting, characterized the recommendations to move four agents to non-formulary status as a "no brainer." He said that Seasonale is not more beneficial for its cost than those retained on the formulary. Ovcon-50 and Ovcon-35 are between two and three times more expensive than other brand names available and have a limited number of users. Estrostep Fe also offered no clinical advantages over the other agents available and was more expensive.

Panel Questions on Contraceptive Agents

Dr. Lenow commented that while he is now a family practitioner, his first residency was in obstetrics back when the profession used high-dose estrogen pills in the 1970s. He said he had made an informal survey of his colleagues at Jefferson, where he teaches, from young residents to seasoned veterans, as to whether they preferred brand agents or generic agents. Only about half of those surveyed knew about the HOPE trials. Two fought to the death to hold on to the old agents, but neither could make a good academic argument for doing so. He said if the profession is geared to principles of evidence-based medicine in the way it approaches safety and efficacy, it is hard not to recognize that there are a few drug classes where there are differentiating evidence-based trials for a select subset of patients. In these instances you could make a compelling case that the brand name drugs are different from generics. However, none of his colleagues was willing to "fall on their sword" over it. Most defer to the generic for insurance reasons. His point is that the profession and the P&T Committee have to be aware of these issues.

Dr. Lenow also said the he thought the breakdown of the drug class and the presentation of recommendations was excellent. He also pointed out that the number two agent, in terms of demand, is the patch, which has an enormous number of scripts. He asked that the Committee keep its eye on safety and efficacy data now moving forward. What he has been reading about the variable effect of the estrogen delivery under different temperature conditions makes him a little nervous and suggests the need to monitor the agent.

COL Schmidt said he thinks the novelty of the patch has worn off and that the utilization is dropping way down. The Committee does review the resale rate every time it looks at a drug. That is an indicator of tolerability and effectiveness.

Ms. Schlaifer asked, in regard to implementation of the non-formulary recommendation for Seasonale, whether there will be issues with refills too soon if patients are recommended to use

one of the alternative agents. Specifically, she asked if patients will be trying to get 28-day prescriptions filled every 21 days. Ms. Schlaifer pointed out that a patient would have to use up 75 percent of the prescription before getting a refill and that may be an incentive not to switch. Dr. Trice replied that she didn't anticipate that would be a problem since there are no special quantity limits on oral contraceptives. But she agreed with the point and will check on the matter.

Ms. Schlaifer also noted that her experience has been that in this class, more than any other, when you take a medication off formulary, only a very capable few can figure out the equivalent medication. She asked whether any information would be provided to the physician network to help with this and make recommendations for which formulary agents would be the most appropriate replacements. She is particularly concerned about Estrostep Fe more than Ovcon-35 and Ovcon-50.

Dr. Trice said there are probably very few people using Estrostep Fe because they need that specific agent. Beyond increasing the total amount of estrogen, the only reason she could find in the literature would be for manipulating breaks in the cycle. But she would think you could use anything for that.

Ms. Schlaifer said her experience suggests that physicians want to be told what to use instead in cases like this.

There was additional discussion with the staff in the audience regarding the matter of refilling prescriptions too early in the case of Seasonale.

Dr. Hutchings said that his organization has had some experience with the matter. Outside pharmacists, when they entered the prescriptions, didn't know they were getting a full pack and would actually list it as a 120-day prescription, thinking of it as a four-pack. His group had to put together a special presentation in the form of a hard edit to allow four packs.

Ms. Schlaifer said that in today's world, where they know they're going to get audited, they will always put in a 28-day supply of tablets, even if only 21 were active. Dr. Trice agreed that it requires a little bit of mental gymnastics to figure that four packs, not three, is a 90-day supply. She said the problem is fixable and they will definitely look at it.

Ms. Le Gette commented that the retail co-pay for the non-formulary would be $56 and the TMOP co-pay would be $22. Regarding Plan B, the background discussion indicated that Plan B is to be given within 72 hours. She said that to ameliorate access problems, it should be understood that there is probably no way that TMOP could ever deliver a prescription within 72 hours. Dr. Trice agreed and said the Committee wasn't thinking that TMOP would be able to deliver prescriptions in 72 hours.

An audience member said the regulation requires that when agents are dispensed on an emergency basis (such as Plan B), they are to be dispensed by a provider.

Dr. Hutchings asked, in relation to Depo-Provera, about injectable drugs and when they can be self administered and thus sold through the retail pharmacy. MAJ Watson replied that they had researched this issue and that Depo-Provera is an exception to the rule and can be dispensed through the retail pharmacy.

Dr. Hutchings noted that in the Committee action on oral contraceptives, Plan B was actually voted on separately. He said he sees Plan B as being a very different agent, even though it is chemically related to the others. He cited a recent FDA release to note that the agent actually prevents implantation even though it is touted as preventing ovulation. He said he personally has an ethical issue with that. There is a lot of buzz in the community regarding a pharmacist's right not to fill prescriptions they feel are not ethically correct. He asked whether it would be possible for the Panel to actually have a separate vote on Plan B.

Dr. Trice said one of the primary reasons the P&T Committee voted on Plan B separately was because she was concerned that the Committee would spend all of its discussion time on Plan B and not focus on the other 34 drugs in the class. Dr. Hutchings also noted that the vote was actually different on the two recommendations.

MAJ Watson stated that the recommendations are as presented. The Panel is obligated to take them up in the form presented. If there is something the Panel wants to disagree with, the process would be to nonconcur with the recommendation and include the objections in its comments.

COL Schmidt said that when Plan B first came up several years ago the vote was much closer and a lot of the voting then was based on personal beliefs. This time the vote was not close. The majority view was that Plan B is currently available, it is a TRICARE benefit, and the vote was just to continue its availability.

Panel Vote on Contraceptive Agents Recommendations

Formulary Recommendations

The Chairman read the P&T Committee recommendations for this drug class:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the contraceptive agents, and other relevant factors, the P&T Committee recommended that Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary pharmaceutical agents and that Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, Plan B and all generically available oral contraceptives be retained on the Uniform Formulary."

Without further discussion, the Panel voted on these recommendations. The result was 10 members voting to concur and one voting to nonconcur.

Dr. Hutchings commented that his nonconcur vote was because of the Plan B issue he raised earlier. He believes that Plan B should have been taken care of separately.

Implementation Recommendations

The P&T Committee's implementation recommendation is:

"The Committee voted to recommend an implementation period of 180 days."

The Chair commented that this is the maximum implementation period allowed.

There was no Panel discussion of the recommendations.

The Panel voted 11-0 to concur with the Committee's implementation recommendation.

Presentation on Antiemetic Drug Class Review

Maj Tiller introduced Dr. Dave Meade to present the clinical effectiveness review for the antiemetic drug class.

[Insert script, pages 12 through 18]

Maj Tiller then presented the relative cost-effectiveness review of the antiemetic drug class.

[Insert script pages 18 through 20]

COL Schmidt also presented the physician's perspective on the P&T Committee's review of this drug class.

He explained that the one vote against making Anzemet non-formulary was a provider who also voted in favor of making Kytril non-formulary, so it wasn't the case that the member thought the class should be kept totally open. The Committee thought that the clinical effectiveness of the newer antiemetics was similar. The Committee believed that it needed to keep the NK-1 antagonist Emend on because it is in a class by itself and has a niche for the high-risk patient. However, the Committee also agreed that the system does not need all three of the HT3 antagonists, particularly if there will be some cost savings. Two of the three are becoming generic in the near future and one of the two offered some cost differences.

COL Schmidt addressed the 808 users of Anzamet that will be moving to non-formulary. He said that treatment for some patients, such as cystic fibrosis patients can get quite expensive — the equipment can cost more than a car and the medicines can cost upward of $16,000 to $20,000 a year. He said he has stayed in the Army for 26 years because he can get his patients what they need. This will still be the case for any patient that really needs Anzamet.

Concerning the 60-day implementation period, COL Schmidt explained that it was a short period because there is no chronic use of this medicine.

Panel Questions on the Antiemetic Drug Class Review

Dr. Hutchings asked about Trans Scop, which he has only seen used twice for the treatment of nausea related to chemo or radiation in the past five years. He wondered whether there were any limitations discussed. COL Schmidt said there are quite a few off-label usages for the older agents in this drug class. For example, patients who are neurologically impaired and cannot handle oral secretions will be given one of these medicines to dry up the secretions.

Dr. Meade added that some of the drugs are administered as pre-op to patients, which saves money on the inpatient budget.

Mr. Hutchings asked whether Zofran was included in the cost analysis or was it pulled out because it's not going to become generic. Dr. Meade replied that it is going to become generic — at least four companies and maybe five will be making a generic version.

Panel Discussion of Formulary Recommendations for the Antiemetic Drug Class

Dr. Prasad asked whether the Committee's rationale — how it arrived at its conclusions — is made available to the providers so they can read about it. Maj Tiller replied that a complete listing of all of the P&T Committee meeting minutes is available on the PEC web page. Providers who know about this and have access can get information this way.

COL Schmidt added that providers don't have a lot of time to be looking at these things. The way it happens in actuality is that each Military Treatment Facility (MTF) has a pharmacy and therapeutics committee of its own that will review the actions that are taken here. These committees are made up of providers from each department and it is up to them to bring the decisions that impact them back to their specific departments.

Panel Vote on Antiemetic Drug Class Formulary Recommendations

The Chair read the P&T Committee recommendations for this drug class:

"Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the antiemetic drugs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that dolasetron be classified as a non-formulary pharmaceutical agent, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the Uniform Formulary."

The Panel voted 11-0 to concur with the recommendations.

Panel Discussion of Implementation Plan Recommendations

Mr. Partridge asked whether the pharmacy members of the Panel think the recommendation makes sense. If so, he has no problem.

Dr. Hutchings replied that there is no problem with this recommended time line from his perspective.

Mr. Class noted that there are only 808 patients affected by the Anzamet recommendation. For the record, he said he doesn't have much trouble with the 60-day recommendation in this case because the numbers are so low. Overall, however, the communication with retail providers is an issue that needs to be addressed. The associations have done a good job getting the word out, but he questions the use of minimum time frames.

Panel Vote on Implementation Plan Recommendations

The Chair read the recommendation:

"The Committee voted to recommend an implementation period of 60 days."

The Panel voted unanimously (11-0) to concur with the recommendation.

Additional Discussion and Closing Comments

Maj Tiller announced that the PEC is currently working on a communication system for network providers that will utilize the ePocrates downloadable formulary system. Under this plan, Military Health System (MHS) formulary data will be included in the ePocrates database and can be accessed and downloaded by providers electronically. It now looks like MHS will be able to upload its data to ePocrates, although there are details remaining to be ironed out.

Dr. Hutchings suggested that the P&T Committee, when it looks at implementation time periods, consider ways of staggering implementation dates so that several don't occur on the same date (or within a few days). From a logistical standpoint this would be helpful to the contractors. He suggested a two- or three-week staggering.

Dr. Lenow said he is excited to hear about ePocrates. He said it is an amazing development for those who use it. Users' personal digital assistants (PDAs) are updated automatically. He asked about the cost of formulary downloads. Maj Tiller replied that there is no cost to providers for downloading.

The Chairman asked if the Panel could get a briefing at its next meeting on the communication plan that the Panel has asked about in earlier sessions. He also asked if there had been any discussions with DoD about overlapping implementation dates and the phasing of implementation.

Maj Tiller said that the PEC has received input from people who like it both ways — those who like to do it all at once and get it over with and those who like to have a breather between implementation dates. He said the PEC would look into the question further. Commercial plans do it both ways.

Dr. Hutchings asked if there was a way to have implementation days occur on a set day each month to facilitate planning. Dr. Trice noted that the process already calls for implementation to be on a Wednesday, which is related to the formulary search tool. CAPT Richerson said the PEC tries to be sensitive to cost center buying, especially when there are a great many users who will be affected (as in the case of Norvasc). But he agreed that it might be useful to put it all on a spreadsheet and see how it plays out. Dr. Hutchings said it might be a matter of Dr. Winkenwerder signing off just a day or two earlier in some cases.

Ms. Fryar thanked the staff for the excellent work done on the read-ahead materials. She also asked that the news releases that come out after Dr. Winkenwerder makes his decisions be posted on the BAP web pages so that everything will be in one place.

She also suggested that TMA/PO consider, when setting up the next BAP date, publishing a backup date in the *Federal Register* in case bad weather forces a postponement.

The Chairman noted that the Panel received an excellent briefing at its last meeting on the results to date. He asked if the data could be updated at the next meeting since there were so many recommendations still in the process of being implemented in March. He said he is particularly interested in the shift from MTF to retail points of service.

Mr. Class also cited a recent article about Zocor stating that Merck was trying to lower the cost of their brand name to make it competitive with generics. He asked if this would cause DoD to take another look at its mandatory generics policy in order to get the best price. MAJ Watson said the way the regulation is written gives the Committee the ability to designate brand name products at a generic co-pay if it finds that it is more cost-effective. Mr. Class asked if the process is flexible enough to react quickly in such cases. MAJ Watson replied that paragraph (j), section 3 allows the P&T Committee to act. Ms. Schlaifer added that the headlines in the article said one thing and the full text said something different. She said that price of the drug has not been lowered.

Mr. Class asked if the charts, which are excellent and very helpful, could be standardized in terms of the information they present. CAPT Richerson agreed to try to standardize the charts.

MAJ Watson announced that the next P&T Committee meeting will be in San Antonio August 15-17. The next BAP meeting will be in Washington at the Naval Heritage Center, September 21st.

The meeting was adjourned at 11:20 a.m.

Appendix 1

6/29/06 Meeting Minutes

Brief Listing of Acronyms Used in This Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms used as acronyms are listed below for easy reference. The term "Panel" in this summary refers to the "Uniform Formulary Beneficiary Advisory Panel," the group whose meeting is the subject of this report.

- 5-HT3s — Type 3 serotonin receptor antagonists (an antiemetic drug subclass)
- ACOG — American College of Obstetrics and Gynecology
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CINV — Chemotherapy induced nausea and vomiting
- CMA — Cost-Minimization Analysis
- DFO — Designated Federal Officer
- DOD — Department of Defense
- ECF – Extended Core Formulary
- ER — Extended Release (a drug formulation)
- ESI — Express-Scripts, Inc.
- FACA — Federal Advisory Committee Act
- FDA — U.S. Food and Drug Administration
- HMO — Health Maintenance Organization
- MAUT — Multi-Attribute Utility Table (an analytical tool for quantifying effectiveness differences)
- MHS — Military Health System
- MTF — Military Treatment Facility
- NK-1 — Neurokinen-1 receptor antagonist (an antiemetic drug subclass)
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- OCs — Oral contraceptives (a drug subclass)
- ODT — Orally dissolving tablet
- OTC — Over the counter
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PA — Prior Authorization
- PDA — Personal digital assistant
- PEC — DOD Pharmacoeconomic Center
- PMDD — Premenstrual dysphoric disorder
- PMS — Premenstrual Syndrome
- PONV — Post-operative nausea and vomiting
- RCTs — Randomized Control Trials

- RINV — Radiation induced nausea and vomiting
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TRRx — TRICARE Retail Pharmacy Program
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs

29 June 2006 BAP Meeting Script

Good Morning,

I'm Major Wade Tiller, Deputy Director of the PEC. Joining me today from the PEC clinical operations staff are Drs. Dave Meade and Shana Trice, who are Staff Clinical Pharmacists. Our P&T Committee physician who is with us today is COL Joel Schmidt, who has been a member of the Committee for 5 years. He will provide the physician perspective for the decisions made by the Committee. The PEC Director, CAPT Richerson is also here.

The DoD Pharmacoeconomic Center (PEC) supports the DoD P&T Committee by conducting the relative (relative meaning in comparison to the other agents defined in the same class) clinical-effectiveness analyses and relative cost-effectiveness analyses of drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (UF).

Dave Meade, Shana Trice and I are here to present an overview of the analyses presented to the DoD P&T Committee. 32 Code of Federal Regulation (C.F.R.) establishes procedures for inclusion of pharmaceutical agents on a Uniform Formulary based upon both the relative clinical-effectiveness and the relative cost-effectiveness. The goal of this presentation is not to provide you with the same in depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee which include:

1) A brief overview of the relative clinical-effectiveness analyses considered by the DoD P&T Committee.
2) A brief overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.
3) The DoD P&T Committee's Uniform Formulary recommendation based upon its collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations of the Contraceptive agents and Antiemetic drugs.
4) The DoD P&T Committee's recommendation as to the effective date of the agents being changed from formulary tier to the non-formulary tier of the Uniform Formulary. Based on 32 C.F.R. 199.21, such change will not be longer than 180 days from the final decision date but may be less.

We've given you a handout which includes the Uniform Formulary recommendations for all the drugs discussed today; this is found on page two. There are tables and utilization figures for all the drug classes. We'll be using trade names, so you can refer to your handout throughout the presentation.

Shana Trice will now present the contraceptive drug class review

Relative Clinical Effectiveness

Background: This class of medications consists of prescription contraceptive products currently marketed in the U.S., including oral contraceptives, injectable contraceptives, the patch and the vaginal ring. The class does not include contraceptive devices such as IUDs and diaphragms.

For the purposes of evaluation, the 35 available contraceptive products were divided into 11 subgroups, primarily based on estrogen content, route of administration, and phasic formulation (which I'll explain in a moment). If you will look at Table 4 on pages 6 through 8 of your handout, you'll see the subgroups listed in the first column and the individual products listed in the second column. The third column shows available brand names for each of the products.

If you'll notice, the first seven of the subgroups are all oral contraceptives, with the first six being combinations of an estrogen component (which is almost always ethinyl estradiol) and a progestogen component (for example levonorgestrel). The monophasic, biphasic, and triphasic descriptions refer to whether or not, and how often, the levels of estrogen or progestogen change during the treatment period. For example, the first product listed under the triphasics, Ortho Tri-Cyclen Lo, provides a constant amount of ethinyl estradiol, but varies the levels of progestogen three times during the cycle.

If you look at the monophasic oral contraceptives – the first four subgroups – you'll see that the different subgroups are based on estrogen content. Over time, estrogen levels in combined oral contraceptives have decreased due to the risk of serious adverse events (such as blood clots and stroke). Most combination products now contain 20 to 35 mcg of estrogen. As you can see, utilization is low for the 50-mcg products, which are the highest estrogen products remaining on the market

The contraceptives have two major differences compared to most other drug classes. The first is the fact that generic contraceptives typically have brand names of their own – in other words, they are "branded" generics. In most cases, all of the brand names listed in the table for each product are generically equivalent to each other, although there are some exceptions to this. The second difference is that products that contain the same ingredients, but at different strengths, are considered to be separate products, which is not usually true in other drug classes (for example, Ortho-Novum 1/35 and Ortho-Novum 1/50 are two separate products). For the purpose of making formulary recommendations, the P&T Committee made its selections at the "product" level (column two), which is consistent with its approach in other drug classes.

The last three columns in the table are the FDA approval date for the initially marketed version of each product, the cost assessment group, and the number of Military Health System (MHS) prescriptions during calendar year 2005 for each product. Maj Tiller will talk more about the cost assessment groups during the cost effectiveness section, but if you notice, there are three groups – brand-only oral contraceptives, generically available oral contraceptives, and non-oral contraceptive products.

Relevance to MHS and utilization: During a twelve-month period ending 31 Jan 2006, a total of 552,272 MHS beneficiaries received one or more contraceptive prescriptions, accounting for about $80 million in annual expenditures.

Now, let's look at utilization. If you'll look at Figure 3 on page 9 in your handout, this shows that the number of prescriptions filled in retail network pharmacies is increasing, while those filled at MTFs are slightly decreasing. Very few contraceptive prescriptions are filled at mail order. One caveat here is that while this graph shows that almost as many contraceptive prescriptions are filled at retail as at MTFs, MTFs actually dispense considerably more 28-day packs (or cycles) than retail pharmacies do, since MTFs typically dispense 3 cycles at a time.

Figure 4 shows the breakdown among the subgroups of medications. This graph is based on cycles dispensed rather than prescriptions, with appropriate adjustments made for contraceptive alternatives that last longer than a cycle (for example, the injectable contraceptive Depo Provera, which is given about every 3 months, counts as 3 cycles). As you can see, monophasic oral contraceptives as a group represent the largest chunk of use, followed by triphasic oral contraceptives. Among the monophasics, low estrogen products (20-30 mcg of estrogen) represent most of the use. Alternative formulations, such as the contraceptive patch, vaginal ring, and injection, represent about 19% of all use.

Figure 5 shows the top 10 contraceptive products across the MHS, by number of prescriptions. Well, actually it's the top 12 based on use at the end of the time period – because that's how the products tended to split into groups. Note that the lines represent the originator product and all of its equivalents. As you can see, the most commonly used contraceptive product across the MHS is Ortho Tri-Cyclen and its generic equivalents, followed by Ortho Evra (the contraceptive patch), although utilization of the patch has dropped considerably over the last 6 to 9 months. (I'll address the patch in more detail later on.) For the next grouping of products, utilization is markedly increasing for the brand-name oral contraceptives Yasmin and Ortho Tri-Cyclen Lo, and the contraceptive vaginal ring, Nuvaring.

Figures 6 and 7 show the same data for MTFs only and retail pharmacies only. In general, the same pattern holds true for both, but, as you can see, the rate of increase for Nuvaring and the brand-name only oral contraceptives Yasmin and Ortho Tri-Cyclen Lo are steeper in retail than in MTFs. You can also see increasing use of some other brand-name only oral contraceptives in retail (Ovcon 35, Seasonale, and Estrostep Fe).

Data Sources: The relative clinical effectiveness analysis evaluated information primarily from published meta-analyses, systematic reviews, and head-to-head randomized controlled trials (RCTs) comparing two or more contraceptive products. A series of Cochrane reviews addressing various clinical questions concerning contraceptives were particularly useful.

Provider Input: Since many of the questions asked on the survey pertain directly to specific points that arose during the clinical review, I'm going to give you the provider results as we go along. Overall, we received a total of 79 survey responses in time to be tabulated for the review. The majority of physicians responding were family practice or obstetricians /gynecologists. A substantial number of responses were received from non-physician healthcare providers, including women's health nurse practitioners, family nurse practitioners, and certified nurse-midwives.

Clinical Effectiveness Review: I am first going to cover the potential points of difference between contraceptive products. These include estrogen content, progestogen content, regimen, phasic formulation, route of administration, and proven or potential usefulness for other conditions in addition to contraception. This will lay the groundwork for discussing relative clinical efficacy (both for prevention of pregnancy and for treatment of other conditions) and relative safety and tolerability.

Estrogen content – The specific estrogen included in combined contraceptive products is almost always ethinyl estradiol, although a few older products contain mestranol, which is converted to ethinyl estradiol in the body. How quickly estrogen is metabolized by the body tends to differ considerably both from patient to patient and over time in individual patients. This makes it difficult to predict how a specific patient will respond with regard to adverse effects (such as nausea) and what's referred to as cycle control – for example, whether break-through bleeding or spotting occurs during the treatment period or whether withdrawal bleeding fails to occur during the "off" period. In turn, this uncertainty contributes to the need for a wide array of contraceptive products with different levels of estrogen. Basically it's a trade-off—higher estrogen content equals better cycle control and possibly better contraceptive effectiveness, but may result in more adverse effects (such as nausea) and increased risk for thromboembolic events (such as blood clots) and other serious adverse events.

Complicating the issue is the fact that adverse effects and cycle control problems with all contraceptive products tend to occur more frequently in the first few cycles after starting treatment. So if women switch products within the first few cycles, they may falsely believe that they cannot tolerate certain products, when in fact they may have had the same problem with any product. A common recommendation is to continue with the same contraceptive product for at least 3 cycles before switching.

Progestogen content – Oral contraceptives available in the U.S. include a variety of progestogens. In general, the differences between products that may be due to their progestogen content have to do with the progestational activity of the progestogen (how well it binds to progesterone receptors), the amount of progestogen included, its androgenecity (or how well it binds to androgen receptors), its effects on other conditions, and its association with adverse effects. There are some data suggesting differences in adverse effects and/or serious adverse events related to progestogens belonging to different "generations," with these generations being based on chemical structure. I'll discuss these data in more detail later on.

Regimen – By this I mean the length of the treatment period before the "off" period. Most combined contraceptive products follow a 21-day on, 7-day off regimen, although this may be modified in clinical practice by either extending the active treatment period and/or shortening the medication-free "off" period. Extended treatment cycles (for example, 84 days on, 7 days off) or continuous (daily) use of oral contraceptives have been used clinically for many years to treat conditions which are associated with or which worsen during the menstrual period, including menstrual migraines, menstrual pain (dysmenorrhea), and endometriosis. Over time, extended or continuous use of oral contraceptives for practical or convenience reasons (reducing the frequency of, or eliminating menstrual periods altogether) has come into more common use. Trials evaluating extended or continuous use were evaluated by a 2005 Cochrane review, which concluded that such use appeared reasonable

for women without contraindications, based on the results of 6 such trials. More data are expected to become available in the near future as new contraceptive products are introduced.

There is only one contraceptive product, Seasonale, which is labeled and specially packaged for extended cycle use (84 days on, 7 days off). However, any oral contraceptive could be used for extended or continuous treatment by discarding the unneeded placebo tablets. In addition, if you'll look at the table—it's on page 6—you can see that the same contraceptive combination used in Seasonale is generically available in standard packaging.

A majority of DoD providers surveyed indicated that extended or continuous cycle regimens offered advantages over conventional dosing, with 29 citing convenience/lifestyle advantages and 36 citing advantages in treating menstrual-related problems. A total of 43 providers (out of 62 commenting) agreed that Seasonale (specifically) fails to provide any additional benefit compared to other oral contraceptives given on the same dosing schedule using standard packaging. The other 19 commented on the greater convenience of the special packaging. Many providers who reported no experience with Seasonale reported using other oral contraceptives on an extended cycle basis.

One more comment about regimens: the recently approved 20-mcg estrogen/0.3 mg drospirenone product Yaz is labeled for use as a 24-day on, 4-day off regimen. This is based on the idea that shortening the "off" period may decrease adverse effects and potentially provide a greater safety margin for contraceptive effectiveness. (The prospect of "shorter periods" is also appealing from a patient standpoint.) Yaz is actually the second 24-day product approved, but the other product will be considered at a future Committee meeting, since federal pricing was not available in time for this review.

Phasic formulations – Biphasic and triphasic oral contraceptives attempt to "mimic" changes in the levels of estrogen and progesterone seen during the normal menstrual cycle. By doing so, a lower total amount of hormone can be used. The introduction of these products was probably primarily a reaction to the controversy about the relationship between thromboembolic events and progestogens. The older biphasic oral contraceptives, which vary the progestogen content midway through the treatment period, were rapidly replaced by the triphasics, and are now very little used. It should be noted that Mircette and its generic equivalents is not one of the older biphasic products. It is listed as a biphasic product only because it provides a small amount of estrogen during 5 days of the 7-day "off" period.

Usefulness for other conditions – Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, reduction of acne and dysmenorrhea, and favorable effects on other conditions, such as endometriosis pain and menstrual migraines. A few contraceptive products do have FDA-approved indications in addition to prevention of pregnancy. I'll cover this in more detail later.

Alternative routes of administration – Contraceptive products offering alternative routes of administration include depot medroxyprogesterone acetate injections (Depo-Provera and equivalent), which are given every 11 to 13 weeks; the contraceptive patch (Ortho Evra), which is applied weekly for three weeks, followed by a "patch-free" week; and the vaginal ring (Nuvaring), which is inserted on a monthly basis and then removed after 3 weeks, followed by a 7-day ring-free period. Two formulations of Depo-Provera are available: 150 mg, which is generically available, given by deep intramuscular injection, and 104 mg

(Depo-subq Provera 104), given subcutaneously (or under the skin). The subcutaneous route of administration is less painful than intramuscular injections and potentially may allow patient self-administration.

Emergency contraception – The only product currently labeled as emergency contraception is levonorgestrel 0.75 mg (Plan B), which is given as one dose (1 tablet) within 72 hours after unprotected intercourse, with a second dose 12 hours later. A combination emergency contraception product (Preven) was discontinued in 2004. In addition to Plan B, the FDA has declared several brands of combined oral contraceptives to be safe and effective for emergency contraception. However, progestogen-only regimens such as Plan B have been shown to be more effective and better tolerated for emergency contraception than the combination products.

Efficacy

Contraceptive effectiveness – Basically, all of the reviewed contraceptives are highly effective at preventing pregnancy when used according to labeling. The progestogen-only oral contraceptives may be slightly less effective than combined oral contraceptives and for that reason have stricter use requirements. There is some question as to whether the lowering of estrogen content in combined oral contraceptives over time has resulted in a decrease in contraceptive effectiveness, although data are lacking. Use of injectable contraceptives, which reduces the potential for user error, is known to decrease "actual use" failure rates. With respect to the patch and vaginal ring, less frequent dosing appears to be associated with better compliance, but whether or not this results in a decrease in "actual use" failure rates remains to be seen. Drug interactions and patient weight may also affect contraceptive effectiveness.

Overall, the Committee concluded that the differences in contraceptive effectiveness among the reviewed products appear minor, with no reliable evidence to suggest substantial differences based on progestogen content, phasic formulation, or regimen.

Acne – All combined contraceptives are likely to have beneficial effects on acne, based on several potential mechanisms, including decreased production and increased binding of free testosterone, blocking androgen receptors, and inhibiting conversion of testosterone to dihydrotestosterone in the hair follicles and skin. Clinically, progestogens with relatively low binding to androgen receptors have been preferred for patients with androgenic adverse effects—such as acne or hirsutism (or "hairiness")—although actual differences between products are unclear. A 2005 Cochrane review reviewed 14 head-to-head contraceptive trials focusing on acne (9 different comparisons); unfortunately, most products included in the review are not currently available in the U.S. and the remaining three trials are not sufficient to draw conclusions.

Contraceptive products with an additional FDA-approved indication for acne include Ortho Tri-Cyclen, which is now generically available, and Estrostep Fe. The vast majority of DoD providers surveyed (76/79) agreed that other oral contraceptives work as well for acne as Ortho Tri-Cyclen, despite its FDA indication. (Providers were not asked about Estrostep Fe, which is not widely used at MTFs.)

Notably, trials with products containing drosperinone, which has anti-androgen properties, have reported comparable to somewhat superior results in clinical trials comparing them to

Ortho Tri-Cyclen and to a product containing cyproterone (a progestogen traditionally favored in the UK for acne treatment, but not available in the U.S.).

Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD) – Several clinical trials with drospirenone-containing oral contraceptives have reported favorable effects in PMDD, which is basically a severe form of PMS, especially with regard to fluid retention and weight fluctuations ("bloating"). In addition, extended or continuous use of oral contraceptives can decrease premenstrual symptoms by reducing the number of menstrual periods.

Endometriosis pain – Oral contraceptives with higher progestational activity may be preferred in patients with endometriosis pain. In addition, continuous use may be useful, since symptoms tend to fluctuate with the menstrual cycle. The two formulations of Depo-Provera are associated with improvements in endometriosis; the 104 mg formulation (Depo-subq Provera 104) has an FDA-approved indication for endometriosis pain.

Heavy menstrual bleeding and dysmenorrhea (menstrual pain) – Combined oral contraceptives have been used to treat dysmenorrhea and heavy menstrual bleeding since their introduction in 1960. Most of the available literature addresses older contraceptive products with a higher estrogen content ($\geq$ 50 mcg ethinyl estradiol) and does not support conclusions about the comparative efficacy of currently used low estrogen products.

Safety and Tolerability

Serious adverse events/contraindications – Use of combined oral contraceptives is associated with increased risk of several serious conditions, including myocardial infarction (heart attack), venous thromboembolism (blood clots), stroke, hepatic cancer and gallbladder disease; however, the absolute risk of these events is very low in women without additional risk factors. Absolute contraindications to the use of combined contraceptives include: previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, or valvular heart disease with complications; major surgery with prolonged immobilization, severe hypertension; headaches with focal neurologic symptoms; known or suspected estrogen-dependent tumors; liver disease; cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use; pregnancy; undiagnosed abnormal uterine bleeding; and women over age 35 years who smoke.

Much of the available epidemiological data was obtained from studies using higher estrogen and progestogen doses than those currently in use; the effect of long-term, low-estrogen oral contraceptive use has yet to be determined. Safety risks with the patch and vaginal ring are presumed to be similar to those of combined oral contraceptives, although epidemiological data are not yet available for these newer products.

The issue of whether so-called third-generation progestogens are associated with increased thromboembolic risk compared to second-generation progestogens (levonorgestrel or norgestrel) or first-generation progestogens (norethindrone or ethynodiol diacetate) has been controversial. However, many sources now appear to agree that there is a modestly increased risk with products containing the third generation product desogestrel, compared to those containing the second generation product levonorgestrel. This modest increase in risk appears to be of limited concern in women who are at low risk for thromboembolism – for example, women younger than 35 who do not smoke. The risk of venous thromboembolism with

norgestimate, which is sometimes described as a third-generation product and sometimes as a second generation product, appears similar to levonorgestrel and lower than desogestrel, based on limited data. Epidemiological data for drospirenone, which remains unclassified, is not yet available, although postmarketing surveillance data does not suggest an excess risk compared to products containing levonorgestrel or other progestogens.

Common adverse effects – In general, adverse effects of oral, transdermal, or vaginal ring contraceptives may include: breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.

Estrogen content and adverse effects – Logically, very low estrogen products (for example, 20 mcg or less) would be associated with a lower risk of estrogen-related adverse effects and a lower risk of thromboembolic events (although data are limited). However, this must be balanced against a greater vulnerability to compromises in contraceptive effectiveness due to missed doses or drug interactions, a potential decrease in non-contraceptive benefits, and a higher incidence of cycle control problems such as, breakthrough bleeding. As we stated before, determination of the "best" estrogen dose is complicated by considerable variability in estrogen metabolism.

Progestogen content and adverse effects – There is considerable difference of opinion among providers concerning the extent to which the choice of progestogen affects tolerability. Products containing third-generation progestogens appear to have fewer androgenic effects than the first- and second-generation products and may be favored in patients complaining of acne or hirsutism ("hairiness"), although all combined oral contraceptives reduce free testosterone levels and therefore tend to have favorable effects on acne. According to a Cochrane review, second- and third-generation products may offer some advantage over first generation products with respect to cycle control, but the magnitude of the difference is unclear.

A word about drospirenone: in addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney, resulting in a diuretic effect. As a consequence, drospirenone reduces fluid retention and weight fluctuations ("bloating"), but, like spironolactone, may cause concerns about elevated potassium levels in patients with a predisposing condition or on other medications that increase potassium levels. Women receiving daily, long-term treatment with medications that can increase potassium should have their serum potassium levels checked during the first treatment cycle. Overall, however, while precautions are indicated, there appears to be little evidence of clinically significant problems related to increases in potassium caused by drospirenone, given worldwide exposure to date (about 14 million women).

Alternative routes of administration – In general, the Committee agreed that availability of products offering alternative routes of administration were necessary to offer broad clinical coverage.

With respect to the patch (Ortho-Evra), the Committee noted the following:

- Based on a comparative trial, adverse effects of the transdermal patch appear similar to a combined oral contraceptive, with the exception of a higher incidence of reactions at the application site, breast symptoms (such as breast tenderness), and dysmenorrhea.

- About 5% of patches used during clinical trials had to be replaced because they fell off or partially detached. A small study cited in labeling showed a relatively small percentage of patches falling off under conditions of heat, humidity, or exercise; anecdotal reports and survey results from deployment sites suggest a much larger percentage.
- The decline in utilization of the patch is likely related to results of a pharmacokinetic study, which reported about 60% higher overall systemic estrogen exposure with the patch compared to a combined oral contraceptive with 35 mcg ethinyl estradiol and 0.25 mg norgestimate, although peak concentrations were about 25% lower with the patch. This information has caused some uncertainty regarding potential safety, especially with respect to thromboembolic risk. Unfortunately, epidemiological data available to date are too limited to draw conclusions about relative safety.
- The patch may have compliance advantages. Based on pooled data from North American pivotal trials, perfect compliance (21 days of drug-taking followed by 7 drug-free days) was reported in 79% of cycles for patients receiving comparator oral contraceptives vs. 98% of cycles in patients using the patch.
- DoD providers cited advantages of the transdermal patch as being improved compliance with infrequent dosing and availability of a different dosing option; disadvantages included the patch coming off, the uncertainty regarding estrogen exposure and thromboembolic risk, the incidence of skin reactions, and weight limitations (the patch has shown reduced contraceptive effectiveness in women weighing more than 198 lbs).

With respect to the vaginal ring (Nuvaring), the Committee noted the following:

- Adverse effects with the vaginal ring appear low compared to rates typically reported with combined oral contraceptives. Specific to the vaginal ring are issues such as vaginal symptoms, interference with intercourse, premature expulsion, and difficulties with insertion and removal.
- Storage requirements for the vaginal ring represent a potential disadvantage. Refrigeration is required prior to dispensing; after dispensing, the product may remain at controlled room temperature for up to 4 months, but should not be exposed to excessive heat.
- DoD providers surveyed cited advantages of the vaginal ring as being improved compliance with infrequent dosing and a good adverse effect profile; disadvantages included a substantial number of patients who are not comfortable with the method and deployment limitations related to storage requirements.

With respect to the injectable contraceptives (the two Depo-Provera formulations), the Committee noted the following:

- Women receiving injectable medroxyprogesterone may lose significant bone mineral density, an effect which may not be completely reversible. It is unclear whether use during adolescence or early adulthood reduces peak bone mass and increases the future risk of fracture. Depo Provera and its equivalents carry a black box warning advising that it be used as a long-term birth control method (e.g., longer than 2 years) only if other birth control methods are inadequate.

- Other factors that may discourage use include: reports of progressive and substantial weight gain, irregular menses and unpredictable spotting/bleeding in the first several months of use, lack of bleeding (amenorrhea) in a high percentage of users with continued use (which actually may be an advantage or a disadvantage), and lack of immediate reversibility after discontinuation (10 months to return to baseline fertility).
- On the other hand, the reduced chance for user error and the every 12-week administration schedule are desirable characteristics in patient populations that tend to be poorly compliant (in adolescents, for example) and/or patients for whom pregnancy would represent a health risk or who would not be able to sustain a pregnancy.

Drug interactions – A large number of medications may interact with hormonal contraceptives, and oral contraceptives may also affect levels of other medications. However, similar drug interactions probably apply to all combined contraceptives. Data do not suggest differences in clinically significant drug interactions based on differences in progestogen content, phasic formulation, regimen, or route of administration.

Overall Clinical Effectiveness Conclusion

Overall, the Committee concluded that: 1) contraceptives vary in estrogen and progestogen content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in metabolism and response; 3) products may differ with regard to safety, adverse effects/tolerability, convenience/ compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) based on survey results, providers desire a wide variety of choices based on estrogen and progestogen content, consistent with variable patient response and the clinical niches for which multiple choices are required; 6) the alternative formulations are required for adequate clinical coverage, 7) none of the reviewed contraceptives are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone.

Maj Tiller will now present the next portion of the contraceptive presentation.

Contraceptive Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the contraceptive agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

The cost effectiveness review used the same classification system overall as the clinical review – these are the 11 subgroups in Table 4. However, for the initial cost assessment, the contraceptives were stratified into three broad groups: 1) oral contraceptives available only as brand-name products; 2) oral contraceptives available generically; and 3) non-oral contraceptives. Generically available oral contraceptives were found to be more cost-effective than brand-name oral contraceptives and non-orally administered contraceptives, based on the average weighted cost per cycle across the MHS. In addition, the opportunity exists to obtain lower prices for generically available agents through DoD/VA national pharmaceutical contracts. For these reasons, the Committee concluded that all generically available contraceptives should be maintained on the UF.

The Committee also concluded that despite a somewhat higher average weighted cost per cycle for non-orally administered contraceptives compared to generically available oral contraceptives, these agents should remain on the UF to ensure clinical coverage for patients who need these methods of administration. The Committee also concluded that Plan B should remain on the UF because of its clinical advantages compared to the use of combined oral contraceptives for emergency contraception.

By process of elimination, this left only the brand-only oral contraceptives to be considered—Estrostep Fe, Ovcon-35, Ovcon-50, Yasmin, Yaz, Ortho Tri-Cyclen Lo and Seasonale. A cost-minimization analysis and a budget impact analysis were performed to determine the relative cost-effectiveness of these agents, compared to products within the same subgroup (as defined by the clinical review).

The results of each category-specific cost minimization analysis were incorporated into a budget impact analysis to account for other factors and costs associated with a potential decision to recommend non-formulary status for one or more brand-name contraceptive agents, including market share migration, cost reductions associated with non-formulary cost shares, and medical necessity processing fees. Based on these results, and taking into account the results of the clinical effectiveness review, the Committee agreed that Yasmin, Yaz and Ortho Tri-Cyclen Lo offered clinical and/or economic value for retention on the UF. They noted that, in each of these cases, the price reductions offered by manufacturers through the UF process based on formulary status offered overall cost reductions, even after taking into account the likelihood of shifts in utilization from generically available oral contraceptives. The Committee agreed that Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe should be non-formulary because the cost minimization analyses showed clinically similar alternatives were available at a significantly lower cost.

Conclusion & Committee Action: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the UF cost effectiveness analysis. The P&T Committee concluded that Seasonale, Ovcon 35, Ovcon 50, and Estrostep Fe were not cost-effective relative to other contraceptive agents with similar clinical attributes. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness reviews and other relevant factors, and based on its collective professional judgment, P&T Committee, voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary under the UF, with Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104 and all generically available contraceptives (and equivalents) being added to the UF. In a separate vote, the P&T Committee recommended addition of Plan B to the UF (12 for, 1 opposed, 3 abstained, 2 absent).

Implementation Plan: On an annual basis, about 23,000 patients obtain prescriptions for Seasonale, Ovcon-35, Ovcon-50 or Estrostep Fe. Although this is a small percentage of the total number of DoD beneficiaries who receive contraceptive prescriptions, a high proportion of these beneficiaries (about 11,000) are receiving Seasonale, which necessarily requires dispensing of a 90-day supply because of the way it's packaged. Accordingly, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period, to begin immediately following approval by the Director, TMA.

Dave Meade will now present the clinical effectiveness review for our last drug class, the antiemetics.

The next class we will review are the anti-emetic agents or agents used to treat nausea and vomiting. I will break these down into groups of newer and older agents. A list of these agents can be seen in table 2 on page 3 of your hand out. The newer agents will be further subdivided into the type 3 serotonin receptor antagonists or 5-HT3s antagonists, and the neurokinin-1 receptor antagonist or NK-1 antagonist. The number/letter designation indicates where on the nerve the drug acts. The 5-HT3 antagonist drugs include Zofran, generically named ondansetron, Kytril, generically named granisetron, and Anzemet or dolasetron. The only NK one receptor antagonist on the market at this time is Emend, generically named aprepitant. None of the newer antiemetics are available in generics.

The older agents have been around for a number of years, and in the case of promethazine, since the 1940's and are used in other conditions besides nausea and vominting. We will discuss later some of the other indications for which these agents are used. The older antiemetic subclass is further divided into four subclasses. The first of four subclasses is the cannabinoids. Marinol is the only drug in this subclass and is generically named dronabinol. The second subclass is the phenothiazines, which includes Compazine, generically named prochlorperazine and Torecan, also named as thiethylperazine. The third subclass is the antihistamines. The antihistamine class is the most popular antiemetic class in DoD. The two drugs in the class are Antivert, or meclizine, and Phenergan, or promethazine. Promethazine is the most commonly prescribed antiemetic in the MHS. The final subclass of older agents is the anticholinergics. This subclass includes Tigan, generically named trimethobenzamide, and scopolamine patches, with the patented name Transderm Scop. Of the older agents, Transderm Scop, Marinol and Torecan do not have generic forms available.

Let's look at the cost of these medications and utilization in the MHS. This class accounts for approximately 37.4 million dollars annually and is ranked number 48 in the MHS drug class expenditures. If we look at the subclasses, we spend approximately 28 million dollars on the newer agents and approximately 9.4 million on the older agents. If you'll turn to figure 1 on page 4 of your handout, you can see the utilization in the MHS of the newer agents. Zofran tablets and Zofran oral disintegrating tablets are the most commonly prescribed newer agents. Zofran tabs are prescribed on average 3,500 prescriptions per month. We will discuss the characteristics of the oral dissolving tab later. In figure 2 on page 5 of your handout, the utilization of the older antiemetics is shown. You will see that promethazine is the most frequently prescribed nausea medication in the MHS, prescribed tenfold more than the leading newer agent, at about 40,000 prescriptions per month. Not shown in these graphs is that approximately 50% of the use is in the retail section, 49% is in the military treatment facilities, and only about 1% of the prescriptions are filled in the mail order setting. Antiemetics are need immediately and patient's can't for the prescriptions to arrive in the mail. Although not shown in figure 2, also of note is that Torecan averaged only 4 prescriptions per month throughout the entire MHS.

Before we talk about the DOD P&T recommendations, first we want to go over the sources of nausea and vomiting. We most commonly experience nausea and vomiting due to such general things as the flu, motion sickness, or food poisoning. This general type of nausea and vomiting is usually self-limited, and if treatment is desired, older agents can be prescribed with success outcomes. Every once in awhile, nausea and vomiting can become protracted, older agents fail, and newer agents may be required.

There are four categories of severe nausea and vomiting where the newer antiemetics are used. Patients with cancer who are treated with chemotherapy many times experience chemo induced nausea and vomiting, or CINV. If they are treated with radiation for cancer, they may experience radiation induced nausea and vomiting or RINV. Certain surgeries can lead to nausea and vomiting after the surgery has been completed. This is known as post operative nausea and vomiting or PONV. Nausea and vomiting in pregnancy is a continuum that has mild nausea on one end and a severe form called hyperemesis gravidarum on the other. If not treated, CINV and RINV patients may refuse further courses of therapy. Also, CINV and RINV can lead to dehydration and nutrition problems. Patients that experience PONV may have complications from vomiting, including risk of aspiration or choking, or tearing out stitches. Excessive nausea and vomiting in pregnancy can have detrimental effects on the baby, and in extreme cases women may terminate a pregnancy to avoid the associated nausea and vomiting.

I'm going to give the conclusions first, then go back and discuss the differences between the drugs used to treat nausea and vomiting. Based on the relative clinical effectiveness review, the DOD P&T committee concluded the following points:

1. The 5-HT3 antagonists Zofran, Kytril, and Anzemet have shown similar complete response rates in patients with chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV), and post operative nausea and vomiting (PONV).

2. Emend, the NK-1 antagonist, serves a unique role in preventing CINV caused by regimens that have a high or moderate likelihood of causing nausea and vomiting.

3. For nausea and vomiting in pregnancy, Zofran should be reserved as third line therapy in women requiring IV hydration who have not responded to other therapies.

4. There is insufficient evidence to suggest that there are major differences in the adverse effect profiles of Zofran, Kytril, Anzemet and Emend. Headache and GI effects, such as diarrhea, are the most common reported adverse events

5. Of the newer antiemetics, Emend has the most clinically important drug interaction profile due to the fact it is extensively metabolized in the liver.

6. There are differences among the newer antiemetics in terms of number of different oral formulations available, approval for use in children and the number of FDA approved indications.

7. None of the newer agents are sufficiently less clinically effective than any of the other newer agents to be classified as non-formulary on the Uniform Formulary.

8. None of the older antiemetics are sufficiently less clinically effective than the other older antiemetics to be classified as non-formulary on the Uniform Formulary.

The DOD P & T Committee's conclusion was determined after answering the following key questions based on the Relative Clinical Effectiveness Review:

1. What are the differences in efficacy, safety and tolerability among the newer antiemetic drugs?

2. Are there differences between the antiemetic drugs in other factors, such as, different types of oral formulations available, approval in pediatric patients, number of FDA-approved indications, and differences in provider opinion, that are likely to affect outcomes?
3. Would any of the older antiemetic regimens be candidates for non-formulary placement on the Uniform Formulary based on their clinical attributes alone?

To answer these questions, the relative clinical effectiveness analysis evaluated information from meta-analyses, systematic reviews, published head-to-head randomized clinical trials and placebo-controlled trials. The published clinical trials were found using a MEDLINE Search, searching major medical journals table of contents, and manufacture press releases. The FDA web site was monitored for updates.

Key question #1: What are the differences in efficacy, safety and tolerability among the anti-emetic drugs? We want to answers this question, as it pertains to CINV, RINV, PONV and nausea and vomiting in pregnancy.

To determine efficacy, the term "complete response" is used to define a successful outcome. Complete response is an outcome comprised of two or more of the following components: the patient has experienced no emesis or vomiting, no nausea, and no need for rescue medication.

In CINV, several head-to-head trials comparing the 5 HT-3 antagonists show no difference in efficacy between intravenous and oral routes, and no consistent difference in efficacy between Zofran, Kytril and Anzemet treated patients. A head to head trial between oral Kytril and oral Zofran showed response rates of 47% vs. 48% respectively. Another head to head trial between oral Anzemet and oral Zofran showed response rates of 76% vs. 72% respectively. Clinical practice guidelines from four national professional groups consider the 5-HT3 antagonists therapeutically interchangeable for CINV.

Emend, the NK-1 antagonist, is approved for preventing nausea and vomiting associated with chemotherapy regimens that have a high or moderate chance of causing nausea and vomiting. In four studies, Emend was used with 5-HT3 antagonists and a steroid, Decadron. A significantly higher number of patients achieved complete response with the Emend/Zofran/Decadron combination versus the regimen that only had Zofran/Decadron plus placebo. The main

conclusion here is that Emend is effective, but it will be added on to a regimen of Zofran or another 5-HT3 antagonist, and won't replace the 5-HT3 antagonists. Emend serves a role in that it will be used in a unique subset of patients with CINV.

In the treatment of radiation induced nausea and vomiting, systematic reviews indicated no evidence of consistent differences between the efficacy of Zofran, Kytril, and Anzemet. There are no head-to-head trials comparing 5-HT3 antagonists in the treatment of RINV. One indirect comparison of Zofran and Kytril showed that 27% vs. 28% of patients had complete control of vomiting, compared to none of the patients in the control group. Clinical practice guidelines from 3 physician led professional organizations and 1 pharmacist led professional organization, indicate that the 5-HT3 antagonists are interchangeable as first-line prophylaxis or prevention, for RINV. Emend is not approved for RINV, so was not evaluated here.

For post operative nausea and vomiting -PONV- there is very few efficacy studies published evaluating oral medication. Most of the studies are with drugs given by the IV route, or not continued when the patient was discharged from the hospital. A systematic review found no differences between the 5HT3 antagonists when studies compared either the oral or IV routes. In one review compared use of IV formulations in the treatment (vs the prevention) of PONV. There were no significant differences between the three agents, and the number needed treat for a successful outcome was similar among the agents. Emend is not approved for PONV.

In the treatment of nausea and vomiting in pregnancy, none of the newer agents are FDA approved for this indication. But, in a data base review, 21% of the Zofran in the MHS was most likely prescribed for the treatment of nausea and vomiting in pregnancy. An evidence based review concluded that there is insufficient data to recommend use of Zofran as a first-line agent for this indication. There are no head-to-head trials comparing any of the oral dosage forms of the newer antiemetics amongst themselves or with older antiemetics in the treatment of this indication. There is only one case report published on the use of oral Zofran in the treatment of nausea and vomiting in pregnancy which did show that Zofran was effective. Guidelines from the American College of Obstetrics and Gynecology state that Zofran may be used IV as third line therapy if dehydration is present and the patient has failed multiple older antiemetics. The older drug, promethazine, is recommended as first line therapy.

We will now look at safety and tolerability.

First, let's look at major or severe adverse events. Zofran, Kytril and Anzemet all carry warnings of potential cardiac problems. This risk appears to be very small and occurs rarely. All the 5-HT3 antagonists have a rare potential to cause anaphylaxis, a severe allergic reaction. Zofran and Kytril can rarely cause bronchospasm or breathing problems. Emend has been noted to cause Stevens-Johnson syndrome (a severe allergic reaction) and angioedema (swelling similar to hives, but the swelling is beneath the skin rather than on the surface). While these two adverse events were noted, a clear association between the events and Emend use has not been established.

Next, we will look at minor adverse events for the newer antiemetics. Headache occurs in 8-18% of patients; fatigue, constipation and increases in labs that monitor liver function also occur

with an incidence of greater than 5%. Emend has been associated with diarrhea, dizziness and hiccups.

Finally, we will look at drug interactions of the newer antiemetics. All the newer agents metabolize through the liver. The 5-HT3 antagonists are metabolized by multiple pathways in the system. However, there are no recommendations to adjust dosages of 5-HT3 antagonists due to drug interactions. Emend has a significant drug interaction with Decadron. The manufacturer recommends that the Decadron dose be reduced by 50% when the drugs are given together.

We are going to move away from the efficacy, safety and tolerability and look at key question #2. Key Question #2 asks "Are there differences between the antiemetic drugs in other factors, such as different types of oral formulations available, approval in pediatric patients, number of FDA-approved indications, and differences in provider opinion, that are likely to affect outcomes?"

Zofran has the most oral dosage forms, including tablets, solution and an oral dissolving tablet. The oral dissolving tablet or ODT is dissolved on the tongue and swallowed without any additional liquid. The advantage of this is that additional liquid could trigger vomiting. An oral solution is also an advantage, since some patients will find it easier to swallow a liquid instead of a tablet. Kytril comes in a tablet and solution. Anzemet is only available in capsules.

With regards to special populations, all 5-HT3 antagonists are approved for use in pediatrics in either the oral or IV forms. Emend currently does not have the pediatric indication, but the manufacturer is pursuing a pediatric indication with the FDA.

If you turn to table 3 on page 4 of your handout, this shows the FDA approved indications for the newer antiemetics. Zofran has the most indications, while Emend has only one indication, CINV, which talked about previously.

We used a new survey tool to query providers and obtained 241 responses from providers in the MHS. Responses came from MTF providers and military providers training in civilian institutions. Providers preferred Zofran primarily due to familiarity with this drug over the other 5-HT3 antagonists. The cancer docs identified the need for Emend for patients treated with chemotherapeutic agent regimens that have a high potential to cause nausea and vomiting.

Efficacy conclusion for the newer antiemetics: The committee concluded that there is not enough evidence to suggest that the 5-HT3 antagonists differ significantly from one another in terms of ability to control or prevent nausea and vomiting. Zofran, Kytril and Anzemet show clinical efficacy for CINV, RINV and PONV, and show similar response rates. In the MHS, Zofran has significant use in nausea and vomiting associated with pregnancy, though national guidelines recommend third line use. Emend has shown efficacy as an adjunct, which means added on, to 5-HT3 antagonists for chemotherapy regimens that have a high or moderate probability of causing nausea and vomiting. There are no major differences in the side effect profiles of the newer antiemetics. Zofran has the largest number of oral dosage forms. All three 5-HT3 antagonists are indicated for treatment of pediatric patients. Emend is currently pursuing a pediatric indication.

Now let's move on to the older antiemetics. The final key question asks whether any of these older agents are candidates for non-formulary placement on the Uniform Formulary based on clinical attributes alone.

The subclass of older antiemetics includes Marinol, meclizine, promethazine, prochlorperazine, Torecan, Trimethobenzamide, and Transderm Scop. As we discussed earlier, Promethazine is the most widely prescribed antiemetic overall in the MHS, at approximately 40,000 prescriptions per month. Meclizine and prochlorperazine also have significant use in the MHS. On the other end of the spectrum, Marinol and Torecan have very little use.

In terms of efficacy, it is difficult to compare the older antiemetics, since some of them were approved in the 1950s and 1960s, when the requirements for getting a drug on the market were not as strict as today. However, the older antiemetics are still commonly used for nausea and vomiting, and motion sickness. Many of the older agents are still included in national guidelines for the treatment of CINV and PONV. Several of the older antiemetics are used for conditions other than nausea and vomiting. Prochlorperazine is also used in the treatment of anxiety and may be used in treating schizophrenia. Marinol is used in the treatment of glaucoma, AIDS and chemo related anorexia, and spasticity associated with multiple sclerosis.

In terms of safety, all the older antiemetics are associated with drowsiness and dizziness. The newer antiemetics don't cause drowsiness, so they are sometimes preferred over the older drugs. Provides specifically commented that newer agents are prescribed to avoid drowsiness and to get active duty members back to work. In rare cases, older agents can cause severe temperature fluctuations, involuntary movement disorders, seizures and significant changes in white blood cell counts. Marinol has been associated with confusion, hallucinations and severe paranoia on rare occasions in large doses. Many of the older antiemetics are used as rescue agents, or as a last resort, when the newer antiemetics don't adequately control nausea and vomiting.

In terms of other factors, several of the older agents are available in different dosage forms, which is helpful in patients where the oral route can't be used. Promethazine, prochlorperazine and trimethobenzamide are available in suppository form, and Transderm Scop comes in patches. Transderm Scop can't be used for treating nausea and vomiting, due to delayed absorption of the drug from the skin, but is useful for preventing nausea and vomiting. For pediatrics, promethazine, prochlorperazine and trimethobenzamide can be used in children over the age of two. For patients age of 2 years and younger, promethazine should only be used if absolutely necessary due to respiratory depression. Marinol is a drug enforcement agency controlled scheduled III substance, as it is the active ingredient in marijuana.

Conclusions for older antiemetics: The older antiemetics are frequently used for nausea and vomiting and several are used for other indications. As noted in the graphs in the handout, older agents are widely prescribed in the MHS. All of the older agents can cause sedation and dizziness. The availability of non-oral dosage forms is useful for rescue therapy.

Overall clinical effectiveness conclusion: The DOD P&T committee concluded that there was insufficient evidence to suggest that any of the 5-HT3 antagonists were different than the others

at treating nausea and vomiting. Emend is a useful adjunct, or add-on therapy to 5 HT3 antagonists when treating patients with chemotherapeutic regimens that have a high or moderate probability of causing nausea and vomiting. Based on national guidelines for nausea and vomiting in pregnancy, Zofran can be used third line. There are no major differences in the side effect profiles of the newer agents. Drug interactions can be an issue with Emend. There are some minor differences among the 5HT3 antagonists in the number of oral formulations, approval for use in children, and FDA-approved indications. Based on clinical issues alone, there is nothing to recommend that any of the newer agents be designated non formulary.

The older antiemetics can be used both in the prevention of nausea and vomiting and as rescue when new agents fail. The primary problem with the older agents is that all of them can cause sedation and dizziness. The older agents have a wide variety of dosage forms not offered by the newer agents, such as patches and suppositories. Based on clinical issues alone, there is nothing to recommend that any of the older agents be designated non formulary.

This concludes the antiemetic clinical effectiveness section. MAJ Tiller will discuss the cost effectiveness section of the antiemetics.

Antiemetic Drugs Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the antiemetic drugs in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class.

As you have already heard from the clinical presentation, the antiemetic drug class is composed of three subclasses: the 5HT-3 drugs, NK-1 antagonists, and the older miscellaneous antiemetics. We will discuss the cost analyses of the three subclasses in that order.

First, let's talk about the 5HT-3 drugs. The conclusion of the evidenced based relative clinical effectiveness evaluation was that there was insufficient evidence to suggest that the agents within the 5HT subclass differ in regards to efficacy, safety and tolerability. Because there is little clinical difference among the agents, a cost-minimization analysis (CMA) was used to evaluate the drugs in this subclass. The PEC performed CMA under two sets of conditions, a literature based analysis and a data driven "real world" analysis.

The literature based CMA used recommended dosages from the literature to evaluate the potential cost of each 5HT-3 antiemetic drug in the treatment of chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV), and post-operative nausea and vomiting (PONV). These three conditions were the only conditions evaluated because they were the only conditions for which there was strong evidence in the literature for recommended dosages. In the analysis, the amount of drug needed for each recommended dosage (mg per treatment episode) was calculated, and a weighted average cost per treatment episode was determined for each of the 5HT3 antiemetic drugs.

The "real world" CMA utilized data from the Prescription Data Transaction Service (PDTS) and the MHS Management Analysis and Reporting Tool (M2) database to evaluate the utilization and dosages of 5HT-3 antiemetics for a variety of conditions. The analysis was a one-year sample based retrospective database analysis. In this study, patient subsets were defined by their diagnosis prior to treatment with a 5HT-3 drug. Five major categories of diagnoses were

compared: CINV, RINV, PONV, nausea and vomiting of pregnancy (NVP), and all other diagnoses combined. Actual dosages (mg per treatment episode) were calculated, and a weighted average cost per treatment episode was determined for each 5HT-3 antiemetic drug.

The results of the CMAs were incorporated into a budget impact analysis (BIA). The BIA accounted for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. Four different UF scenarios were considered with a budget horizon of one to three years.

The results of the BIA showed that scenarios that removed Anzemet from the UF were ultimately more cost-effective for the DoD MHS. The manufacturer of Kytril submitted competitive pricing and was determined to be the most cost-effective of the 5HT-3s in the short term. Moreover, Kytril is projected to be available in a generic as early as December 2007, thus making a cost-effective treatment alternative in the long term. In regard to Zofran, although the CMAs showed that Zofran was more costly relative to the other agents, a sensitivity analysis conducted around expected generic pricing showed Zofran was the most cost effective agent once a 15% reduction in cost is acheived through generic pricing. Zofran is scheduled to be available in a generic by December 2006, and there are already several companies approved to market generic versions. Ultimately, it was recommended that Zofran be maintained on the UF for two reasons: 1) Cost reductions resulting from generic competition may eventually make this drug the most cost-effective 5HT-3, 2) Once generically available, this drug would provide the first and only 5HT-3 antiemetic drug for the generic copay.

Now, let's discuss the pharmacoeconomic analysis for the neurokinin-1 (NK-1) inhibitor Emend. Emend, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic chemotherapy. A cost-effectiveness analysis (CEA) was performed to assess the incremental costs and effectiveness of adjunctive treatment with Emend compared with current treatment, or treatment without Emend, to provide an estimate of the efficiency or value of the Emend compared with current treatment. The CEA was a decision analytic model for a two hypothetical cohorts of 1,000 patients treated with and without adjunctive Emend. The results of the CEA showed that adjunctive treatment with Emend was more cost-effective relative to a regimen without adjunctive treatment with Emend for highly emetogenic CINV, when total health care costs are considered.

Finally, the Committee evaluated the effectiveness and costs of the older antiemetic drugs. This subclass is composed of several different chemical entities and dosage forms. The results of the clinical review showed that while there is little difference in antiemetic efficacy between the older antiemetic agents, each has a place in therapy that may make it clinically useful as a "niche product". The cost analysis showed that the older antiemetics account for less than 25% of the total MHS antiemetic drug spend, and that 72% of this cost was incurred in the retail point of service (POS). In addition one third of the retail expenditures were for promethazine, which has long been available generically. Because DoD currently has no influence over generic drug selection in the retail POS, it was determined that there is little to be gained by placing one of these agents in the non-formulary tier of the uniform formulary.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the antiemetic cost-analysis presented by the

PEC. The P&T Committee concluded that: Anzamet (Anzemet) was not cost-effective relative to the other 5HT-3 agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the antiemetics, and other relevant factors, the P&T Committee recommended Uniform Formulary status for the antiemetic class.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 2 absent, 1 abstain) that Anzemet be classified as non-formulary under the UF, with Kytril, Zofran, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF.

Implementation Plan: Due to the low number of beneficiaries who would be affected by this formulary action (808 patients known to have taken Anzemet across the MHS in the twelve months evaluated), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval of the Director, TMA.

Committee Action: The P&T Committee voted (14 for, 1 opposed, 2 absent, 1 abstain) to recommend an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

DECISION PAPER:

May 2006
DEPARTMENT OF DEFENSE PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

1. **CONVENING**
2. **ATTENDANCE**
3. **REVIEW MINUTES OF LAST MEETING**
4. **ITEMS FOR INFORMATION**
5. **REVIEW OF RECENTLY APPROVED AGENTS**

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee, therefore Uniform Formulary (UF) consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a schedule of four weeks on treatment followed by two weeks off treatment. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or drug-related adverse effects, and due to the dosing regimen. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

COMMITTEE ACTION: The DoD Pharmacy and Therapeutics (P&T) Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TRICARE Mail Order Pharmacy (TMOP) Program of 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRICARE Retail Pharmacy Network (TRRx), the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days. (See paragraph 5 on pages 10-11 of the P&T Committee minutes).

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant, with a recommended daily maximum of four or fewer units ("lollipops") per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain

should be reevaluated. The Committee agreed that a quantity limit of 120 units per 30 days, 360 units per 90 days should be established for Actiq, based on the daily maximum of four per day recommended in product labeling, in order to address potential concerns of overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion.

COMMITTEE ACTION. The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for oral transmucosal fentanyl citrate (Actiq). (See paragraph 6A on page 11 of P&T Committee minutes for rationale).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. Rizatriptan (Maxalt, Maxalt MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days, which is consistent with the maximum recommended dose in product labeling. However, rizatriptan tablets are now available in packages of nine rather than six tablets. The Committee agreed that the 30-day quantity limit for rizatriptan tablets should be increased to 18 tablets, but that the 90-day quantity limit should remain at 36 tablets. This quantity limit would take into account the fact that a substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days, allow for dispensing of whole packages, and avoid increasing the 90-day limit to 54 tablets (3 times 18), which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

COMMITTEE ACTION. The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days. (See paragraph 6B on pages 11-12 of P&T Committee minutes for rationale).

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

7. ANTIEMETIC DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness and cost-effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) that: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting (RINV), and post-operative nausea and vomiting (PONV); (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for adequate clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring intravenous hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone; (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness , or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

Based on the results of the cost-effectiveness analysis (CEA) and other clinical and cost considerations, the Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that granisetron and ondansetron were the more cost effective 5HT-3 antiemetic drugs; that it is also cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee voted (14 for, 1 opposed, 2 absent, 1 abstained) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF. (See paragraphs 7A and 7B on pages 12-18 P&T Committee minutes)

In addition, the P&T Committee agreed that the current quantity limits for the newer antiemetics should remain unchanged; it also agreed that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed to assist military treatment facilities (MTFs).

Director, TMA, Decision: BW ☑Approved ☐Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of dolasetron (Anzemet) and the conditions for establishing medical necessity for a non-formulary medication provided in the

UF rule, the P&T Committee recommended (15 for, 0 opposed, 1 abstained, 2 absent) medical necessity criteria for the antiemetics. (See paragraphs 7C on page 18 of the P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P & T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend an effective date no later than the first Wednesday following an implementation period of 60 days. The implementation will begin immediately following the approval of director, TMA. (See paragraph 7D on pages 18-19 of the P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost-effectiveness analysis, the P & T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to recommend oral and rectal promethazine as the Basic Core Formulary (BCF) agent. (See paragraphs 7E on page 19 of the P&T Committee minutes)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. A total of 36 products were divided into 11 subgroups, based on estrogen content, phasic formulation, and route of administration. The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) contraceptives vary in estrogen content, progestin content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices (based on both estrogen and progestogen content), patient response is variable, and there are clinical niches for which multiple choices are required; 6) the alternative formulations (vaginal ring, patch, intramuscular and subcutaneous injection) are required for adequate clinical coverage; 7) none of the reviewed contraceptives are sufficiently less clinically effective than others to be classified as non-formulary based on clinical issues alone.

Based on the results of the CEA and other clinical and cost considerations, the P&T Committee agreed (15 for, 0 opposed, 0 abstained, 3 absent) that: 1) all generically available oral contraceptives (OCs) should remain on the UF, because they are generally more cost-effective than brand name contraceptives and non-orally administered contraceptives and because further opportunity exists to negotiate lower prices for generic agents through contracting; 2) all of the non-oral products (Nuvaring, Ortho Evra, Depo Provera and equivalents, Depo-subq Provera 104) should remain on the UF to ensure clinical coverage for patients who need these methods of administration; 3) the brand-only products Yasmin, Yaz, and Ortho Tri-Cyclen Lo should remain on the UF, because they offer clinical and/or economic value; and 4) the brand-only products Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be classified as non-formulary under the UF, because clinically similar alternatives are available at a significantly lower cost. The P&T Committee also agreed (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue on the UF because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception.

In addition, the P&T Committee voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP, with a quantity limit of one Plan B package per co-pay applying to purchased care prescriptions.

A. COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) be classified as non-formulary under the UF and that the brand-only products Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically-available products listed in Table 1 (on pages 18-19 of the P&T Committee minutes) be classified as formulary on the UF. The P&T Committee voted (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF. (See paragraphs 8A and 8B on pages 19-30 of P&T Committee minutes)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

B. COMMITTEE ACTION: Based on the clinical evaluation of the contraceptive agents and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) medical necessity criteria for the contraceptive agents. (See 8C on page 30 of P&T Committee minutes for criteria.)

Director, TMA, Decision: BW ☑ Approved ☐ Disapproved

Approved, but modified as follows:

C. COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. (See paragraph 8D on pages 30-31 of P&T Committee minutes for rationale)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

D. COMMITTEE ACTION: Based on the relative clinical and cost effectiveness analyses, the P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following products as the BCF agents.

- EE 20 mcg; 3 mg drospirenone (Yaz)
- EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- EE 30 mcg; 3 mg drospirenone (Yasmin)
- EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
- EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- EE 25 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
- EE 35 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

(See paragraph 8E on pages 31-32 of P&T Committee minutes for rationale.)

Director, TMA, Decision: BW ☑Approved ☐ Disapproved

Approved, but modified as follows:

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

APPENDIX A – TABLE 1: Implementation status of UF Decisions

APPENDIX B – TABLE 2: Newly Approved Drugs

APPENDIX C – TABLE 3: Abbreviations

DECISION ON RECOMMENDATIONS

Director, TMA, decisions are as annotated above.

William Winkenwerder, Jr., M.D.
Date: 26 July 2006

Department of Defense
Pharmacy and Therapeutics Committee Minutes

11 May 2006

1. CONVENING

The Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee convened at 0800 hours on 9 May 2006 at the DoD Pharmacoeconomic Center (PEC), Fort Sam Houston, Texas.

2. ATTENDANCE

A. Voting Members Present

CAPT Patricia Buss, MC, USN	DoD P& T Committee Chair
CDR Mark Richerson, MSC, USN	DoD P& T Committee Recorder
CAPT Bill Blanche, MSC, USN	DoD Pharmacy Programs, TMA
Maj David Carnahan, MC	Air Force, Internal Medicine Physician
Maj Michael Proffitt, MC	Air Force, OB/GYN Physician
LtCol Brian Crownover, MC	Air Force, Physician at Large
LtCol Charlene Reith *for* LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
CDR Brian Alexander, MC	Navy, Physician at Large
LCDR Joe Lawrence MSC *for* CAPT David Price, MSC	Navy, Pharmacy Officer
COL Doreen Lounsbery, MC	Army, Internal Medicine Physician
MAJ Roger Brockbank, MC	Army, Family Practice Physician
COL Joel Schmidt, MC	Army, Physician at Large
LTC Peter Bulatao, MSC *for* COL Isiah Harper, MSC	Army, Pharmacy Officer
CDR Vernon Lew, USPHS	Coast Guard, Pharmacy Officer
CDR Jill Pettit, MSC, USN	TMOP COR
Mr. Joe Canzolino	Department of Veterans Affairs

B. Voting Members Absent

LCDR Chris Hyun, MC	Navy, Internal Medicine Physician
LCDR Scott Akins, MC	Navy, Pediatrics Physician
CAPT David Price, MSC	Navy, Pharmacy Officer
LtCol Everett McAllister, BSC	Air Force, Pharmacy Officer
COL Isiah Harper, MSC	Army, Pharmacy Officer

C. Non-Voting Members Present

COL Kent Maneval, MSC, USA	Defense Medical Standardization Board
Mr. Lynn T. Burleson	Assistant General Counsel, TMA
Mr. John Felicio *for* Ms Martha Taft	Health Plan Operations, TMA
Major Peter Trang, BSC, USAF	Defense Supply Center Philadelphia

D. Non-Voting Members Absent

None	

E. Others Present

CAPT Don Nichols, MC, USN	DoD Pharmacoeconomic Center
Col Nacy Misel, BSC, USAF Reserve	IMA DoD Pharmacoeconomic Center
Lt Col David Bennett, BSC, USAF	DoD Pharmacoeconomic Center
Lt Col James McCrary, MC, USAF	DoD Pharmacoeconomic Center
Maj Wade Tiller, BSC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
SFC Daniel Dulak, USA	DoD Pharmacoeconomic Center
Mr. Dan Remund	DoD Pharmacoeconomic Center
Ms Shana Trice	DoD Pharmacoeconomic Center
Mr. David Bretzke	DoD Pharmacoeconomic Center
Ms Angela Allerman	DoD Pharmacoeconomic Center
Mr. Eugene Moore	DoD Pharmacoeconomic Center
Ms Julie Liss	DoD Pharmacoeconomic Center
Ms Elizabeth Hearin	DoD Pharmacoeconomic Center
Mr. Dave Flowers	DoD Pharmacoeconomic Center
Mr. David Meade	DoD Pharmacoeconomic Center
Ms Harsha Mistry	DoD Pharmacoeconomic Center
Ms Elaine Furmaga	Department of Veterans Affairs

3. REVIEW MINUTES OF LAST MEETING

A. Corrections to the minutes – February 2006 DoD P&T meeting minutes were approved as written, with no corrections noted.

B. February minutes approval – Dr. William Winkenwerder, Jr., M.D. approved the minutes of the February 2006 DoD P&T Committee on 26 April 2006.

4. ITEMS FOR INFORMATION

TMA and DoD PEC staff members briefed the P&T Committee on the following:

A. Interim Fluoroquinolone Basic Core Formulary (BCF) Administrative Action: CAPT Buss and CDR Richerson briefed the DoD P&T Committee on the justification and process employed for the 16 March 2006 fluoroquinolone administrative change to the BCF (replacement of gatifloxacin with levofloxacin).

B. **Tikosyn Availability in the TRICARE Mail Order Pharmacy (TMOP) Program:** Ms. Libby Hearin briefed the DoD P&T Committee that, as of 24 April 2006, Tikosyn is now available through the TMOP. This drug is an anti-arrhythmic which is subject to a controlled distribution program.

C. **Beneficiary Advisory Panel (BAP) Briefing:** CAPT Buss, CDR Richerson, and CPT Dacus briefed the members of the DoD P&T Committee regarding the 30 March 2006 BAP meeting. The Committee was briefed on BAP comments regarding DoD P&T Committee's Uniform Formulary (UF) and implementation recommendations.

D. **Implementation Status of UF Decisions:** Mr. Dave Bretzke briefed the members of the Committee on the progress of implementation for drug classes reviewed for UF status since August of 2005. The Committee made the following observations:

- Utilization in all UF classes continues to remain stable, suggesting continued access to drugs within the reviewed classes.
- Collective utilization of UF agents across all reviewed drug classes and points of service (military treatment facility (MTF), TMOP, TRICARE Retail Pharmacy (TRRx) Network) continues to increase as a percentage of prescriptions dispensed, while utilization of non-formulary agents has decreased. Based on the UF decisions that have been fully implemented since the first UF DoD P&T meeting in February 2005, there has been a 27% reduction in the use of non-formulary agents. Based on all drug classes reviewed by the Committee to date, including those classes where implementation has only just begun, there has been an 18% reduction in the use of agents designated as non-formulary.
- Success in terms of generating increased market share for UF agents (while decreasing market share for non-formulary agents) varies by class and by point of service.
- Market shares by point of service continue to reflect the degree of utilization management applied to each point of service. The more highly managed points of service (i.e., MTFs) are generating higher market shares of UF agents than the unmanaged points of service (i.e., TMOP and TRRx).
- For drug classes fully implemented, MTFs have reduced the use of non-formulary drugs by 81% as projected, but the decrease in the use of non-formulary medications at mail (-2%) and retail (-13%) is significantly less.
- It appears that more beneficiaries are electing to receive non-formulary medications through TMOP. It is unclear at this time whether these beneficiaries are former MTF patients or former TRRx patients.

5. REVIEW OF RECENTLY-APPROVED AGENTS

The P&T Committee was briefed on six new drugs that had been approved by the Food and Drug Administration (FDA). None of the medications fall into drug classes already reviewed by the P&T Committee; therefore, UF consideration was deferred until the corresponding drug class reviews are completed. The Committee reviewed one new drug for quantity limits. Sunitinib (Sutent) is an oral multi-kinase inhibitor approved for treatment of patients with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumor (GIST). It is available in 12.5, 25 and 50 mg capsules and is administered once daily for a period of four weeks followed by two weeks off treatment. Dosage reductions are recommended in 12.5 mg intervals, if needed. There is no 37.5 mg capsule available. Quantity limits were recommended for sunitinib since there is a risk of discontinuation of therapy due to poor patient prognosis or

drug-related adverse effects, and likelihood of changes to individual dosing regimens. Other oral chemotherapy drugs (imatinib, erlortinib, sorafenib) also have quantity limits.

One of the new drugs, mecasermin rinfabate (Iplex), is a new version of a medication for which a prior authorization (PA) is already in place. Mecasermin rinfabate was added to the existing PA criteria and forms for mecasermin.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 2 absent) to recommend that sunitinib (Sutent) have quantity limits in the TMOP for 60 capsules for the 50 mg formulation, 120 capsules for the 25 mg formulation, and 180 capsules for the 12.5 mg formulation per 84 days. In the TRRx, the recommended quantity limits were 30 capsules for the 50 mg formulation, 60 capsules for the 25 mg formulation, and 120 capsules for the 12.5 mg formulation per 30 days.

6. QUANTITY LIMITS:

A. ORAL TRANSMUCOSAL FENTANYL CITRATE (ACTIQ) – Actiq is indicated only for breakthrough cancer pain in patients already receiving opioids and who are opioid tolerant. Based on safety recommendations in product labeling, the daily limit for Actiq is four or fewer units ("lollipops") per day. If consumption increases to more than four per day, the dose of the long-acting opioid for persistent cancer pain should be reevaluated. The product is available in multiple strengths—200, 400, 600, 800, 1200, and 1600 mcg—to accommodate individual patient needs and increases in opioid requirements associated with long-term opioid treatment.

The major potential concerns with Actiq are overuse (i.e., use in lieu of appropriate increases in long-acting opioid treatment) and diversion. Actiq is costly; average wholesale price per unit ranges from $17.40 to $51.40 per lollipop, with a federal supply schedule price of $4.89 to $14.56.

The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling. The Committee noted that Express Scripts, Inc. (ESI), the contractor for the TMOP and TRRx programs, has established procedures to deal with circumstances that may require temporary overrides of quantity limits (e.g., increases in dose).

COMMITTEE ACTION: The Committee voted (13 for, 1 opposed, 1 abstained, 3 absent) to recommend that a quantity limit of 120 units per 30 days, 360 units per 90 days be established for Actiq, based on the daily maximum of four per day recommended in product labeling.

B. RIZATRIPTAN (MAXALT, MAXALT MLT) – The current quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) is 12 tablets per 30 days, or 36 tablets per 90 days. Based on safety recommendations in product labeling, the safety of treating more than four migraine attacks in a 30-day period has not been established. Doses may be repeated after two hours if the first dose is ineffective, with no more than 30 mg taken in any 24-hour period. Based on this, a quantity limit of 12 tablets per 30 days would allow use up to the recommended maximum, assuming that 10-mg tablets are prescribed. However, rizatriptan packaging has been changed to packages of nine rather than six tablets.

The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend that the quantity unit for rizatriptan tablets and orally disintegrating tablets be increased to 18 tablets per 30 days, 36 tablets per 90 days, based on the following reasoning:

- A substantial number of patients currently fill prescriptions at the maximum quantity limit of 12 tablets per 30 days.
- The proposed quantity limit allows for dispensing of whole packages of rizatriptan tablets.
- Although the proposed quantity limit does violate the usual rule-of-thumb that 90-day limits will be three times 30-day limits, it is technically feasible to implement and avoids increasing the 90-day to 54 tablets, which is in excess of safety recommendations and not consistent with quantity limits for other triptans.

COMMITTEE ACTION: The Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to recommend changing the quantity limit for rizatriptan tablets and orally disintegrating tablets (Maxalt, Maxalt MLT) to 18 tablets per 30 days, or 36 tablets per 90 days.

7. ANTIEMETIC DRUG CLASS REVIEW

A. Antiemetic Relative Clinical Effectiveness: The P&T Committee evaluated the relative clinical effectiveness of the antiemetic agents marketed in the United States. The drugs in the class were broken into two subclasses, the newer and older antiemetics. The newer agents include the type 3 serotonin receptor (5-HT3) antagonists ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet); and the neurokinin-1 (NK-1) receptor antagonist aprepitant (Emend). The older antiemetic subclass is comprised of the cannabinoid dronabinol (Marinol); the phenothiazines prochlorperazine and thiethylperazine (Torecan); the antihistamines meclizine and promethazine; and the anticholinergics transdermal scopolamine (Transderm Scop) and trimethobenzamide. The clinical review included, but was not limited to, the requirements stated in the UF Rule. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in Military Health System (MHS) drug class expenditures.

1) Newer Antiemetics

A. Efficacy

Efficacy Measure – The Committee evaluated efficacy of the newer antiemetics in chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV), post-operative nausea and vomiting (PONV) and nausea and vomiting in pregnancy. Complete response was the primary efficacy measure considered. Complete response is a composite outcome of two or more of the following components: no emesis; no nausea; or no need for rescue medication.

When reviewing efficacy trials in nausea and vomiting, direct comparisons of trials is difficult due to large heterogeneity in the trials. Trials conducted in the setting of CINV and RINV are differentiated by the type of chemotherapy administered, emetogenicity potential of the chemotherapy regimen, number of chemotherapy or radiotherapy courses given, and type of malignancy; and show widely varying outcomes. For trials conducted in the setting of PONV, differences in the type of surgical procedure, duration of surgery, and type of anesthesia make direct comparisons difficult.

Chemotherapy-induced nausea and vomiting (CINV)

5-HT3 antagonists – For CINV, there are several head-to-head trials comparing the three 5-HT3 antagonists which overall have shown no differences in efficacy between the intravenous (IV) and oral routes and no consistent differences in efficacy between ondansetron, granisetron and dolasetron. However there is large heterogeneity between the trials.

5-HT3 antagonists – Head-to-head trials and national guidelines: In two head-to-head trials comparing oral 5-HT3 formulations, the complete response rates, as measured by no nausea or emesis or need for rescue therapy, were similar between granisetron and ondansetron (47% vs. 48%), and dolasetron and ondansetron (76% vs. 72%). There were no trials comparing oral dolasetron with oral granisetron, but a trial comparing IV formulations of these two drugs reported no differences in efficacy. Clinical practice guidelines from four national professional groups consider the 5-HT3 antagonists therapeutically interchangeable for CINV.

Aprepitant – The NK-1 receptor antagonist aprepitant is approved for preventing nausea and vomiting associated with highly emetogenic chemotherapy regimens, including high dose cisplatin. Aprepitant has been evaluated in four active-controlled trials in patients undergoing highly emetogenic chemotherapy regimens. When aprepitant was used as adjunctive therapy to 5-HT3 antagonists plus dexamethasone and older antiemetics, a significantly higher percentage of patients achieved complete response rates, vs. placebo.

Radiation-induced nausea and vomiting (RINV)

Systematic Reviews – Systematic reviews state that the evidence shows no consistent differences in efficacy for ondansetron, granisetron and dolasetron for RINV.

Head-to-head trials and national guidelines – There are no head-to-head trials comparing the 5-HT3 antagonists for RINV. One indirect comparison of ondansetron 8 mg and granisetron 2 mg with a historical control group in the prevention of RINV found no differences between the two 5-HT3 antagonists in achieving complete control of emesis (27% with ondansetron vs. 28% with granisetron vs. 0% in the historical control group). There are no published studies evaluating aprepitant for RINV. Clinical practice guidelines from four national professional organizations state that the three 5-HT3 antagonists are therapeutically interchangeable as first-line prophylaxis for RINV.

Post-operative nausea and vomiting (PONV)

Prevention of PON – The majority of studies evaluating prevention of PONV used intravenous (IV) therapies, and rarely continued oral medication after hospital discharge. There are seven head-to-head trials comparing the efficacy of IV formulations of the 5-HT3 antagonists for prevention of PONV; five trials comparing dolasetron with ondansetron, and two trials comparing granisetron with ondansetron. Although the heterogeneity between the trials was large, overall the complete response rates were similar between ondansetron, granisetron and dolasetron. There are no head-to-head trials of oral formulations of the 5-HT3 antagonists for prevention of PONV. A systematic review of four placebo-controlled trials comparing either oral or IV 5-HT3 formulations allowed indirect comparisons between oral dolasetron, IV dolasetron, and IV granisetron. The complete response rates were similar between drugs.

Treatment of PONV – Treatment of PONV most commonly occurs with IV therapy, and is of minor importance to this review. There are no head-to-head trials comparing efficacy of the 5-HT3 antagonists for treatment of PONV. Three systematic reviews of active and placebo controlled trials of the 5-HT3 antagonists in the treatment of PONV provided numbers needed

to treat (NNT) to obtain complete control of further nausea and vomiting (complete response). In one review, no statistically significant differences were found between dolasetron and ondansetron in treating PONV occurring within 6 hours of surgery (NNT of 2.0-3.5 with ondansetron vs. 4.2-6.1 with dolasetron). In the same review there were no significant differences between granisetron and ondansetron in treating PONV occurring < 24 hours after surgery (NNT of 3.3-6.3 with ondansetron vs. 2.4-3.3 with granisetron). The NNTs from all three reviews were similar for ondansetron, granisetron, and dolasetron. There are no published studies evaluating aprepitant for PONV.

Nausea and vomiting in pregnancy

Systematic reviews and MHS utilization – No newer antiemetics are FDA-approved for treating nausea and vomiting in pregnancy. An evidenced-based review concluded that there is insufficient data to recommend use of ondansetron as a first-line agent for this indication. A database linking prescription data with diagnosis codes shows that 21% ondansetron usage in the MHS is for nausea and vomiting in pregnancy.

Clinical trials and case reports – One trial compared IV ondansetron 10 mg with IV promethazine 50 mg in 30 women hospitalized with hyperemesis gravidarum. No differences were found in any outcome measure. One published case report showed that ondansetron 8 mg IV given twice daily was effective at reducing emesis, and that ondansetron 4 mg orally given three times daily for 25 weeks was also effective.

National guidelines – Guidelines from the American College of Obstetricians and Gynecologists (ACOG) state that ondansetron may be used IV as third line therapy if dehydration is present, and IV fluid replacement and dimenhydrinate, metoclopramide, or promethazine have failed to control symptoms. The 5-HT3 antagonists and aprepitant are rated as pregnancy category B by the FDA.

B) Safety / Tolerability

Major adverse events – Ondansetron, granisetron and dolasetron all carry a class warning regarding potential prolongation of the QTc interval. The risk is dose dependent. All three 5-HT3 antagonists can rarely cause anaphylaxis; ondansetron and granisetron can rarely cause bronchospasm. Aprepitant has rarely been associated with Stevens-Johnson Syndrome and angioedema.

Minor Adverse events – For the newer antiemetics, the most commonly reported adverse effect is headache, occurring in 8-18% of patients. Asthenia/fatigue, constipation, and increases in liver enzymes also occur with an incidence of greater than 5%. Aprepitant is associated with diarrhea, dizziness, hiccups and increases in liver enzymes, all occurring in <6% of patients. No dosage adjustments are necessary for the four newer antiemetics in patients with renal dysfunction. The maximal dose of ondansetron should be limited to 8 mg in patients with severe hepatic dysfunction.

Drug Interactions – All three 5-HT3 antagonists are metabolized by varying degrees through the Cytochrome P450 (CYP450) enzyme system. The 5-HT3 antagonists are metabolized by multiple pathways within the system. Ondansetron is metabolized to the greatest extent, followed by dolasetron and granisetron; however, there are no requirements for ondansetron dosage adjustments when given with CYP450 inducers. Aprepitant can inhibit Cytochrome P450 3A4 (CYP3A4) enzymes, and is associated with the most clinically important drug interactions of the newer antiemetics. Aprepitant increases concentrations of dexamethasone up

to two and half times, and if administered concomitantly with dexamethasone, the dexamethasone dose should be reduced by 50%.

C) Other Factors

Available formulations – Ondansetron is available in several oral formulations, including an oral tablet, oral solution, and orally dissolving tablet (ODT). Ondansetron ODT may be swallowed without the need to consume additional liquid that could trigger vomiting; however, it should be used with caution in patients with phenylketonuria, as it contains aspartame. Granisetron is available in an oral tablet and oral solution.

Pediatrics – Ondansetron and dolasetron are approved for prevention of CINV in pediatrics. Ondansetron is approved for use in children as young as four years of age, while dolasetron is approved for use in children as young as two years. The oral formulation of granisetron is not approved for use in children; however the IV formulation is approved for use in children older than two years. Aprepitant is not approved for use in the pediatric population.

FDA indications – Of the newer antiemetics, ondansetron has the most FDA-approvals (CINV, RINV, and PONV). Granisetron is approved for CINV and RINV, and dolasetron is approved for CINV and PONV. Aprepitant is approved for prevention of CINV caused by moderately or highly emetogenic chemotherapy regimens.

Quantity Limits – There are existing quantity limits in place for the four newer antiemetics, which take into account FDA-approved indications and dosing recommendations for CINV, RINV, and PONV. Quantity limits may be overridden for individual patients if greater quantities are determined to be medically necessary. A frequent reason for medical necessity is severe nausea and vomiting associated with pregnancy (i.e., hyperemesis gravidarum).

MHS Utilization – The most widely prescribed newer antiemetic in the MHS is ondansetron, with 3,500 prescriptions per month. Over 51% of the MHS usage of the newer antiemetics is for CINV; nausea and vomiting in pregnancy accounts for 15% of the usage of the newer antiemetics, RINV comprises 10% of usage, PONV 2% of usage, and other diagnoses 22% of usage.

Provider Survey – Overall, providers preferred ondansetron, primarily due to more familiarity over the other 5-HT3 antagonists. Several providers commented that they preferred the newer antiemetics over the older antiemetics due to less sedation, which is particularly beneficial for active duty members or those with childcare responsibilities.

Conclusion for the newer antiemetics – The committee concluded that there is insufficient evidence to suggest that the antiemetic effects of the 5-HT3 antagonists differ significantly between drugs. Ondansetron, granisetron and dolasetron show efficacy for CINV, RINV, and PONV. Ondansetron shows efficacy for treating nausea and vomiting in pregnancy, but should be used third line. Aprepitant has shown efficacy in placebo controlled trials for CINV when used as an adjunct to 5-HT3 antagonists for patients undergoing highly emetogenic chemotherapy regimens. The adverse effect profiles of 5-HT3 antagonists and aprepitant are similar in nature. Ondansetron has the largest number of oral formulations, and is approved for use in pediatrics, along with dolasetron.

2) Older Antiemetics

A) Place in therapy and national guidelines – The older antiemetics are still widely used to treat nausea, vomiting and motion sickness. Many of the older antiemetics are mentioned in national guidelines for the treatment of CINV and PONV, and are commonly used in these

settings. Prochlorperazine is used for indications other than nausea and vomiting, including for anxiety and schizophrenia. Promethazine is a second-line therapy for treatment of nausea and vomiting in pregnancy, according to ACOG guidelines. Dronabinol is commonly employed in the treatment of glaucoma, AIDS, chemotherapy-related anorexia and spasticity associated with multiple sclerosis.

B) Adverse effects – All the older antiemetics are associated with drowsiness, dizziness and somnolence. The phenothiazines (prochlorperazine, thiethylperazine) and antihistamines (meclizine, promethazine) can cause rare but serious adverse events including neuroleptic malignant syndrome, reversible dystonic reactions, seizures, irreversible tardive dyskinesias, agranulocytosis and severe leukopenia. Common adverse effects of the anticholinergic agents (trimethobenzamide, scopolamine) include dry mouth and eyes, and urinary retention in elderly patients. Confusion, distorted perception, and rare hallucinations and severe paranoia have been linked to dronabinol.

C) Other factors – Four of the older antiemetics are available in generic formulations; meclizine, promethazine, prochlorperazine, and trimethobenzamide. The older antiemetics are available in various dosage forms that are advantageous for use as rescue therapy in nausea and vomiting when the oral route can not be used. Prochlorperazine, promethazine and trimethobenzamide are available in suppository form. Transdermal scopolamine patches offer a topical route, but should not be used for acute nausea and vomiting, due to delayed absorption. With the exception of meclizine, which has a pregnancy category B rating, all of the older agents are ranked pregnancy category C by the FDA. The older antiemetics are indicated for use in children, with the exception of thiethylperazine. The package insert for promethazine has a black box warning regarding use in children under the age of two due to respiratory depression. Dronabinol is a Drug Enforcement Administration (DEA) controlled schedule III substance. The most widely prescribed older antiemetic in the MHS is promethazine, with 40,000 prescriptions per month.

Conclusions for the older antiemetics – The older antiemetics are frequently used for nausea and vomiting, and several are used for indications other than emesis. The availability of non-oral dosage formulations is useful for rescue therapy of nausea and vomiting. Thiethylperazine is the only older antiemetic not approved for pediatric use, although promethazine should be used with caution in children due to possible respiratory depression. All the older agents can cause sedation and dizziness.

Overall clinical effectiveness conclusion – The Committee concluded: (1) the 5-HT3 antagonists ondansetron, granisetron and dolasetron have shown similar complete response rates in patients with CINV, RINV, and PONV; (2) the NK-1 receptor antagonist aprepitant serves a unique role in preventing CINV caused by highly emetogenic chemotherapy regimens and is required for clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as third-line therapy in pregnant women requiring IV hydration who have not responded to other therapies; (4) there is insufficient evidence to suggest that there are major differences in the adverse effect profiles of the 5-HT3 antagonists or aprepitant; headache and gastrointestinal effects are the most commonly reported adverse events; (5) aprepitant is the newer antiemetic that has the most clinically important drug interaction profile, due to its metabolism via the CYP3A4 enzyme system; (6) there are differences among the newer antiemetics in terms of availability of oral formulations, approval for use in children, and number of FDA-approved indications; (7) none of the newer antiemetics is sufficiently less clinically effective than the others to be classified as non-formulary, based on clinical issues

alone; and (8) none of the older antiemetics has a significant, clinically meaningful therapeutic disadvantage in terms of safety, effectiveness, or clinical outcome compared to the other agents to warrant classification as non-formulary, based on clinical issues alone.

COMMITTEE ACTION: The Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the clinical effectiveness conclusions stated above.

B. Antiemetic Relative Cost Effectiveness: In considering the relative cost-effectiveness of pharmaceutical agents in this class, the P&T Committee evaluated the costs of the agents in relation to the efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). Three separate pharmacoeconomic analyses were performed: a cost-minimization analysis (CMA) on the newer 5-HT3 antiemetics subclass, followed by a budget impact analysis (BIA); a cost-effectiveness analysis (CEA) of aprepitant to evaluate its place in therapy; and lastly a cost-analysis on the older antiemetic subclass.

Given the evidenced-based relative clinical effectiveness evaluation conclusion that there was insufficient evidence to suggest that the 5-HT3 antagonists differed in regards to efficacy, safety, tolerability, and clinical outcomes in the treatment of CINV, RINV, and PONV, a CMAwas performed to determine the relative cost-effectiveness of the agents within the 5-HT3 subclass. The cost examined was the total weighted average cost per treatment episode across all points of service. Results of the analysis for the newer antiemetic drugs (5HT-3s) showed granisetron was the most cost effective 5HT-3 antiemetic agent with the lowest average cost per treatment episode across the MHS.

The results of the above analysis were then incorporated into a BIA. A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of 5-HT3 antagonists best meet the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the results of the BIA and other clinical and cost considerations (ondansetron is projected to undergo generic competition in 2006), the Committee agreed that a group of 5-HT3 antagonists that included granisetron and ondansetron best achieved this goal when compared to other combination groups of 5-HT3 antagonists, and thus were determined to be more cost-effective relative to other combination groups.

A CEA was also conducted to evaluate the place in therapy for aprepitant, a NK-1 antagonist. Aprepitant is indicated for adjunctive therapy along with other antiemetics for delayed nausea and vomiting associated with chemotherapy. The results of the CEA showed that: 1) the blanket purchase agreement (BPA) offered price for aprepitant improved its cost-effectiveness over baseline, and 2) when total health care costs are considered, aprepitant is cost-effective as an adjunct in the treatment of chemotherapy induced nausea and vomiting.

Finally, a cost analysis for the older antiemetics (promethazine, prochlorperazine, trimethobenzamide, thiethylperazine, meclizine, scopolamine, and dronabinol) was presented. The results of the cost-analysis showed that the cost associated with these agents is about 25% of the overall anti-emetic drug spend. However, 72% of the costs for these older anti-emetic

drugs were generated in the retail setting. Over half of this figure was for promethazine, which is available in generic form. The conclusion of the cost analysis was that no savings would be achieved by placing any of the older antiemetics in the non-formulary tier of the UF.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 2 absent) to accept the antiemetic pharmacoeconomic analyses presented by the PEC. The Committee concluded that granisetron and ondansetron are the more cost effective 5HT-3 antiemetic drugs; that dolasetron is not cost-effective relative to the other 5-HT3 antagonists, that it is cost-effective for aprepitant to be used as an adjunct for the treatment of CINV; and that the older antiemetics are all relatively cost-effective.

The P&T Committee also recommended that the current quantity limits for the newer antiemetics should remain unchanged. They agreed, however, that a more systematic set of criteria addressing severe nausea and vomiting associated with pregnancy should be developed. Such criteria would be particularly beneficial for MTFs.

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the anti-emetic drugs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 1 opposed, 1 abstained, 2 absent) to recommend that dolasetron be classified as non-formulary under the UF, with granisetron, ondansetron, aprepitant, dronabinol, meclizine, prochlorperazine, promethazine, scopolamine, thiethylperazine, and trimethobenzamide remaining on the UF.

C. Antiemetic Medical Necessity Criteria: Based on the clinical evaluation of the antiemetics, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for dolasetron.

1) Use of formulary antiemetics is contraindicated, and dolasetron is not contraindicated.
2) The patient has experienced significant adverse effects from the formulary antiemetics, or is likely to experience significant adverse effects from formulary antiemetics, and the patient is expected to tolerate dolasetron.
3) Treatment with formulary antiemetics has resulted in therapeutic failure, and the patient is expected to respond to dolasetron.

Because of the clinical differences between antiemetics, the Committee agreed that the most appropriate formulary alternatives for dolasetron are the other 5-HT3 antagonists.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to approve the anti-emetic medical necessity criteria.

D. Antiemetic UF Implementation Period: The P&T Committee recommended an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have dolasetron on their local formularies. MTFs will be able to fill non-formulary requests for dolasetron only if both of the following conditions are met: 1) the prescription is written by an MTF provider, and 2) medical necessity is established. MTFs

may (but are not required to) fill a prescription for dolasetron written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee voted (14 for, 1 opposed, 1 abstained, 2 absent) for an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

E. Antiemetics BCF Review and Recommendations: The P&T Committee had previously determined that zero to one newer antiemetics and at least one older antiemetic should be added to the BCF, based on clinical and cost effectiveness review. As a result of the clinical and economic evaluations presented, the P&T Committee recommended that promethazine be maintained on the BCF.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 1 abstained, 2 absent) to maintain oral and rectal promethazine on the BCF.

8. CONTRACEPTIVE AGENTS DRUG CLASS REVIEW

A. Contraceptive Relative Clinical Effectiveness Review: The P&T Committee evaluated the relative clinical effectiveness of the oral, transdermal, injectable, and vaginal ring contraceptives available in the U.S. Contraceptive products were divided into the subgroups outlined in Table 1, based on estrogen content, phasic formulation, and route of administration.

Table 1: Oral, Transdermal Patch, Vaginal Ring, and Injectable Contraceptive Products Available in the U.S.
(Source of Prescription Data: Pharmacy Data Transaction Service)

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
Monophasic OCs with 20 mcg EE	EE 20 mcg; 0.1 mg levonorgestrel	Alesse	Wyeth	86,569
		Aviane	Duramed	
		Lutera	Watson	
		Lessina	Barr	
		Levlite	Berlex	
	EE 20 mcg; 1.0 mg norethindrone	Junel 1/20	Barr	2,038
		Loestrin-21 1/20	Warner Chilcott	
		Microgestin 1/20	Watson	
	EE 20 mcg; 1.0 mg norethindrone; ferrous fumarate	Junel Fe 1/20	Barr	18,356
		Loestrin Fe 1/20	Warner Chilcott	
		Microgestin Fe 1/20	Watson	
	EE 20 mcg; 3 mg drospirenone	Yaz	Berlex	Approved March 2006
Monophasic OCs with 30 mcg EE	EE 30 mcg; 0.15 mg levonorgestrel	Levlen 28	Berlex	25,092
		Levora 0.15/30-28	Watson	
		Nordette-28	Duramed/Barr	
		Portia-28	Barr	
	EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	Duramed/Barr	20,153
	EE 30 mcg; 0.3 mg norgestrel	Cryselle	Barr	123,501
		Lo/Ovral	Wyeth	
		Low-Ogestrel	Watson	
	EE 30 mcg; 0.15 mg desogestrel	Apri	Barr	59,086
		Desogen	Organon	
		Ortho-Cept	Ortho	
		Reclipsen	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
		Solia	Prasco	
	EE 30 mcg; 1.5 mg norethindrone acetate	Junel 1.5/30	Barr	1,048
		Loestrin 1.5/30	Duramed/Barr	
		Microgestin 1.5/30	Watson	
	EE 30 mcg; 1.5 mg norethindrone; ferrous fumarate	Junel Fe 1/5/30	Barr	19,472
		Loestrin-FE 1.5/30	Duramed/Barr	
		Microgestin Fe 1.5/30	Watson	
	EE 30 mcg; 3 mg drospirenone	Yasmin	Berlex	125,965
Monophasic OCs with 35 mcg EE	EE 35 mcg; 0.5 mg norethindrone	Brevicon	Watson	144
		Modicon	Ortho	628
		Necon	Watson	
		Nortrel 0.5/35	Barr	
	EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	Warner-Chilcott	6,681
		Ovcon-35 chewable		
	EE 35 mcg; 0.25 mg norgestimate	Mononessa	Watson	46,123
		Ortho-Cyclen	Ortho	
		Previfem	Teva	
		Sprintec	Barr	
	EE 35 mcg; 1.0 mg norethindrone	Necon	Watson	92,114
		Norinyl 1+35	Watson	
		Nortrel	Barr	
		Ortho-Novum 1/35	Ortho	
	EE 35 mcg; 1.0 mg ethynodiol diacetate	Demulen 1/35	Pharmacia/Upjohn	17,171
		Kelnor	Barr	
		Zovia 1/35E	Watson	
Monophasic OCs with 50 mcg EE or mestranol	Mestranol 50 mcg; 1 mg norethindrone	Necon	Watson	3,979
		Norinyl 1+50	Watson	
		Ortho-Novum 1/50	Ortho	
	EE 50 mcg; 1 mg norethindrone	Ovcon-50	Warner Chilcott	2,061
	EE 50 mcg; 1 mg ethynodiol diacetate	Demulen 1/50	Pharmacia/Upjohn	1,368
		Zovia 1/50E	Watson	
	EE 50 mcg; 0.5 mg norgestrel	Ogestrel	Watson	2,938
		Ovral-28	Wyeth	
Biphasic OCPs	EE 35 mcg; 0.5/1.0 mg norethindrone	Necon	Watson	168
		Ortho-Novum 10/11	Ortho	
	EE 20/10 mcg; 0.15 mg desogestrel	Kariva	Barr	22,731
		Mircette	Duramed/Barr	
Triphasic OCPs	EE 25 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen Lo	Ortho	101,349
	EE 35 mcg; 0.18/0.215/0.25 mg norgestimate	Ortho Tri-Cyclen	Ortho	331,429
		Trinessa	Watson	
		Tri-Previfem	Teva	
		Tri-Sprintec	Barr	
	EE 30/40/30 mcg; 0.05/0.075/0.125 mg levonorgestrel	Enpresse	Barr	76,559
		Tri-levlen	Berlex	
		Triphasil	Wyeth	
		Trivora	Watson	
	EE 35 mcg; 0.5/1/0.5 mg norethindrone	Aranelle	Barr	1,516
		Leena	Watson	
		Tri-Norinyl	Watson	

Subgroup	Generic Product Description (Ethinyl estradiol = EE; progestogen)	Brand Name	Manufacturer	Total MHS Rxs Jan-Dec 05
	EE 35 mcg; 0.5/0.75/1 mg norethindrone	Necon 7/7/7	Watson	59,536
		Nortrel 7/7/7	Barr	
		Ortho-Novum 7/7/7	Ortho	
	EE 25 mcg; 0.1/0.125/0.15 mg desogestrel	Cesia	Prasco	5,648
		Cyclessa	Organon	
		Velivet	Barr	
	EE 20/30/35 mcg; 1.0 mg norethindrone	Estrostep Fe	Warner-Chilcott	9,916
Progestogen-Only OCPs	0.35 mg norethindrone	Errin	Barr	71,003
		Ortho Micronor	Ortho	
		Jolivette	Watson	
		Camila	Barr	
		Nora-BE	Watson	
		Nor-QD	Watson	
Contraceptive patch	EE/Norelgestromin ~ 60% higher exposure than oral contraceptive with 35 mcg EE (= >50 mcg EE), but lower peak concentrations	Ortho Evra	Ortho	268,223
Contraceptive vaginal ring	Daily dose: ~ EE 15 mcg; ~0.12 mg etonogestrel	Nuvaring	Organon	55,415
Injectable Contraceptives	104 mg/ 0.65mL depot medroxyprogesterone acetate	Depo-subqProvera104	Pfizer	39
	150 mg/mL depot medroxyprogesterone acetate	Depo-provera (disp syr)	Pharmacia/Upjohn	10,912
		Medroxyprogesterone acetate (disp syr)	Sicor	
		Depo-provera (vial)	Pharmacia/Upjohn	59,931
		Medroxyprogesterone acetate (vial)	Greenstone	
			Sicor	
Emergency Contraceptives	0.75 mg levonorgestrel	Plan B	Duramed/Barr	4,049

Oral contraceptives (OCs) differ from most other drug classes in two regards: 1) unique combinations of varying strengths of specific estrogen and progestogen components are considered to be separate products (e.g., Ortho-Novum 1/35 and Ortho-Novum 1/50) rather than different strengths of the same product; and 2) generic versions of branded contraceptive products typically have brand names of their own. Other factors (such as FDA-approved special packaging/labeling or the content of "placebo" tablets) may also affect generic equivalency. For the purpose of making formulary recommendations, the P&T Committee made its selections at the "generic product" level as outlined in Table 1, consistent with its actions in other drug classes. For example, ethinyl estradiol 35 mcg; 1.0 mg norethindrone constituted a single line item to be considered for placement on the UF. Specific originator products (e.g., Ortho-Novum 1/35) and generic equivalents (Necon, Norinyl, and Nortrel) were not considered individually.

The clinical review included consideration of pertinent information from a variety of sources determined by the P&T Committee to be relevant and reliable, including but not limited to sources of information listed in 32 CFR 199.21(e)(1). The P&T Committee was advised that there is a statutory presumption that pharmaceutical agents in a therapeutic class are clinically effective and should be included on the UF, unless the P&T Committee finds by a majority vote that a pharmaceutical agent does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome over the other pharmaceutical agents included on the UF in that therapeutic class.

During a twelve-month period ending 31 Jan 2006, 552,272 MHS beneficiaries received one or more contraceptive prescriptions, accounting for about $80 million in annual expenditures across the MHS.

1) DoD Provider Input

A total of 79 survey responses were received from providers in time to be tabulated for P&T Committee review. Responders were family practice physicians (26), women's health nurse practitioners (21), obstetricians /gynecologists (18), family nurse practitioners (6), certified nurse-midwives (4), or other providers (4). A number of responses, including some from internal medicine physicians, were received too late for tabulation, but were not qualitatively different from other providers' responses.

2) Potential Differences between Contraceptive Products

There are a wide variety of contraceptive products. Points of difference include estrogen content; progestogen content; regimen (e.g., extended use, 24-day cycle products); phasic formulation; proven or potential usefulness for other conditions in addition to contraception (e.g., acne); and route of administration. Most OCs contain both an estrogen and a progestogen component. Progestogen-only OCs are used much less commonly than combined OCs, but fill a distinct clinical niche for women who should not receive estrogen.

Estrogen content – The estrogen component in almost all combined contraceptives is ethinyl estradiol; mestranol (a prodrug of ethinyl estradiol) is used in a few older products. The amount of ethinyl estradiol included in specific products varies from as little as 15-20 mcg per day to as much as 50 mcg per day in older products. Low-estrogen products (20-30 mcg of ethinyl estradiol) are most commonly used. The availability of a wide array of contraceptive products with differing ethinyl estradiol levels is necessary because of the need to maintain contraceptive effectiveness and control irregular bleeding (cycle control) while minimizing common adverse effects and thromboembolic risk. Considerable intra- and inter-patient variability in estrogen metabolism contributes to the need for multiple products. Another contributing factor may be the fact that adverse effects and cycle control problems with all contraceptive products tend to occur more frequently in the first few cycles after initiation of treatment; switching products prematurely may lead women to falsely believe that they cannot tolerate specific products.

Progestogen content – Contraceptive products available in the U.S. include a variety of progestogens. Based on chemical structure, a recent Cochrane review (Maitra et al, 2005) classified progestogens (not including non-U.S. products) as follows:

- First generation: norethindrone, ethynodiol diacetate
- Second generation: levonorgestrel, norgestrel
- Third generation: desogestrel, norgestimate (some authors classify norgestimate as second generation, since it is partially metabolized to levonorgestrel)
- Unclassified: drospirenone

The injectable contraceptives (Depo-Provera and generics, Depo-subq Provera 104) contain depot medroxyprogesterone acetate (DMPA), a derivative of progesterone.

Regimen – While most combined contraceptives—including the transdermal patch and vaginal ring—are based on a 21-day "on", 7-day "off" cycle, this regimen is often modified in clinical practice by either extending the active treatment period and/or shortening the medication-free period. Extended treatment cycles or continuous (daily) use of combined OCs have been used

clinically for many years to treat menstrual migraines, dysmenorrhea, endometriosis, and other conditions associated with menses. Over time, extended or continuous use of OCs for practical or convenience reasons (reducing or eliminating menstrual periods) has come into more common use. A Cochrane review [Edelman et al, 2005] concluded that extended or continuous use of contraceptives was reasonable for women without contraindications, based on the results of six trials. A single contraceptive product, Seasonale, is labeled and specially packaged for extended cycle use (84 days on, 7 days off), although any monophasic OC could be used for extended or continuous treatment by eliminating unneeded placebo tablets.

A majority of DoD providers surveyed indicated that extended or continuous cycle offered advantages over conventional dosing, with 29 citing convenience/lifestyle advantages, and 36 citing advantages in treating menstrual-related problems. A total of 43 providers (out of 62 commenting) did not agree that Seasonale provided a benefit relative to another OC given on the same dosing schedule (84 days on, 7 days off); 19 commented on the greater convenience of packaging. Many providers without experience with Seasonale reported using other OCs on an extended-cycle basis.

Two newly approved low-estrogen contraceptive products, Loestrin 24 Fe and Yaz, are labeled for use as a 24-day on, 4-day off regimen. The shortened "off" cycle is intended to decrease adverse effects associated with hormone withdrawal. It may also provide a greater safety margin for contraceptive effectiveness by decreasing the likelihood of follicle development during the "off" cycle.

Phasic formulations – Biphasic and triphasic oral contraceptives attempt to "mimic" changes in levels of estrogen and progesterone seen during the normal menstrual cycle, in an attempt to decrease adverse effects by decreasing hormonal steroid exposure. The introduction of these products was probably primarily a reaction to the controversy about the relationship between thromboembolic events and progestogen content, since lower total amounts of progestogens can be achieved by providing a varying amount throughout the cycle. The biphasic OCs initially introduced to the market were rapidly superseded by triphasic OCs, resulting in infrequent use of the older biphasic products. Triphasic products, which vary doses of progestogen and/or estrogen three times during the treatment period, remain popular.

Although classified as a biphasic product, Mircette and its generic equivalents (21 days of EE 20 mcg/desogestrel 150 mcg followed by 2 days of placebo and 5 days of 10 mcg EE) are more similar to a low-estrogen monophasic product plus supplemental estrogen than to the older biphasic products. Mircette may be useful in perimenopausal women due to the more constant estrogen levels.

Usefulness for other conditions – Most if not all combined contraceptives offer non-contraceptive benefits, including control of heavy menstrual bleeding or irregular cycles, reduction of acne and dysmenorrhea, and favorable effects on other conditions, such as endometriosis pain and menstrual migraines. Relatively few contraceptive products have FDA-approved indications in addition to prevention of pregnancy. However, given the lack of substantial differences between products with regard to contraceptive effectiveness, the choice of a specific contraceptive product may depend on its proven or potential usefulness for another condition.

Alternative routes of administration – Contraceptive products offering alternative routes of administration include DMPA injections, a transdermal patch (Ortho Evra), and a vaginal ring (Nuvaring). Two DMPA formulations are available: 150 mcg, given by deep intramuscular (IM) injection (Depo-Provera, generics), and 104 mcg (Depo-subq Provera 104), given by

subcutaneous (SC) injection (less painful and may allow patient self-administration). DMPA injections are given every 11 to 13 weeks. In addition to prevention of pregnancy, the 104 mcg formulation is also approved by the FDA for endometriosis pain. The transdermal patch is applied weekly for three weeks, followed by a patch-free week, while the vaginal ring is inserted on a monthly basis and then removed after 3 weeks, followed by a 7-day ring-free period.

Emergency contraception – The only product currently labeled as emergency contraception is levonorgestrel 0.75 mg (Plan B), which is given as one dose (1 tablet) within 72 hours after unprotected intercourse and a second dose 12 hours later. A combination emergency contraception product (Preven) was discontinued in 2004. In addition to Plan B, the FDA has declared several brands of combined OCs to be safe and effective for emergency contraception, including Ovral, Alesse, Nordette or Levlen, Lo/Ovral, Triphasil or Tri-Levlen. Progestogen-only regimens such as Plan B have been shown to be more effective and better tolerated for emergency contraception than combination OCs.

3) Efficacy / Effectiveness

Contraceptive effectiveness – All of the reviewed contraceptives are highly effective at preventing pregnancy when used correctly. Progestogen-only OCs may be slightly less effective than combined OCs and for that reason have stricter use requirements (i.e., they must be taken at the same time each day, without an "off" period). There is some question as to whether the lowering of estrogen content in combined OCs over time has resulted in a decrease in contraceptive effectiveness, although data are lacking. Methods that reduce the potential for user error (e.g., injectable contraceptives) are known to decrease "actual use" failure rates. Whether or not potentially improved compliance related to less-frequent dosing of the transdermal patch and vaginal ring results in decreases in "actual use" failure rates remains to be seen; contraceptive effectiveness so far appears similar to combined OCs. Drug interactions and patient weight may also affect contraceptive effectiveness.

Overall, the differences in contraceptive effectiveness among the reviewed contraceptive products appear minor, with no reliable evidence to suggest substantial differences in contraceptive effectiveness based on progestogen content, phasic formulation, or regimen.

Efficacy in treating other conditions

Acne – All combined contraceptives are likely to have beneficial effects on acne, based on several potential mechanisms, including decreased production and increased binding of free testosterone, blocking androgen receptors, and inhibiting conversion of testosterone to dihydrotestosterone in the hair follicles and skin. Clinically, progestogens with relatively low binding to androgen receptors have been preferred for patients with androgenic adverse effects (such as acne or hirsutism), although actual differences between products are unclear. A 2005 Cochrane review [Arowojolu et al] reviewed 14 head-to-head contraceptive trials (9 different comparisons) focusing on acne; unfortunately, most products included in the review are not currently available in the U.S. The three trials remaining either reported no difference between products or inconclusive results.

Contraceptive products with an additional FDA approved indication for acne include Ortho Tri-Cyclen (a triphasic product containing 35 mcg EE and varying amounts of norgestimate, which is now generically available) and Estrostep Fe (a triphasic product containing varying amounts of estrogen and 1 mg norethindrone). Trials with products containing drosperinone, which has anti-androgen properties, have reported comparable to somewhat superior results

compared to a product containing cyproterone (a progestogen traditionally favored in the United Kingdom for acne treatment, but not available in the U.S.) [Van Vloten et al, 2002] and Ortho Tri-Cyclen [Thorneycroft et al, 2004].

The vast majority of DoD providers surveyed (76/79) agree that other OCs work as well for acne as Ortho Tri-Cyclen, despite its FDA indication.

Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD) – Continuous use of OCs may decrease premenstrual symptoms. Several clinical trials with drospirenone-containing OCs have reported favorable effects on PMDD, a severe form of PMS, especially with regard to fluid retention and weight fluctuations ("bloating").

Endometriosis pain – OCs with higher progestational activity and/or continuous use of contraceptives may be preferred in patients with endometriosis pain, which is related to the menstrual cycle. Progestogen-only DMPA injections are associated with improvements in endometriosis; the subcutaneous administered 104 mg strength (Depo-subq Provera 104) has an FDA-approved indication for endometriosis pain.

Heavy menstrual bleeding and dysmenorrhea (menstrual pain) – Combined OCs have been used to treat dysmenorrhea (by decreasing prostaglandins and thus uterine motility/cramping) and heavy menstrual bleeding (by promoting regular shedding of a thinner endometrial lining) since their introduction in 1960. While clinical evidence supports efficacy, most of the literature addresses the older products (≥ 50 mcg EE) and does not support conclusions about the efficacy or comparative efficacy of currently used low estrogen products.

4) Safety and Tolerability

Serious adverse events/contraindications – Use of combined OCs is associated with increased risk of several serious conditions, including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the absolute risk of these events is very low in women without additional risk factors. Much of the available epidemiological data was obtained from studies using higher estrogen and progestogen doses than those currently in use; the effect of long-term, low-estrogen OC use has yet to be determined. Risks associated with the patch and vaginal ring are largely unknown, although they are presumed to be similar to those of combined OCs.

Use of combined OCs is associated with an increased risk of venous thromboembolism (VTE) (e.g., deep vein thrombosis, pulmonary embolism). Most data relate to products with higher doses of estrogen than are currently used; low estrogen products may be associated with a lower risk. The issue of whether third-generation progestogens (e.g., desogestrel) are associated with an increased thromboembolic risk compared to second-generation progestogens has been controversial; however, many sources now appear to agree that there is a modestly increased risk with products containing desogestrel, compared to those containing levonorgestrel. The risk of VTE with norgestimate appears similar to levonorgestrel and lower than desogestrel, based on limited data [Gomes et al, 2004]. Epidemiological data for drospirenone is not yet available. A 2004 safety review reporting 3-year interim results from a large, controlled, postmarketing surveillance study [Heinemann & Dinger, 2004] did not suggest an excess risk with drospirenone-containing products compared to those containing levonorgestrel or other progestogens.

An increased risk of myocardial infarction (MI) and stroke has been associated with OC use, primarily in smokers or women with underlying risk factors for coronary artery disease. Most data relate to products with higher doses of estrogen than are currently used; low estrogen

products may be associated with lower risk. Whether progestogen content affects the risk of MI or stroke is unclear.

Absolute contraindications to the use of combined contraceptives include: previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, or valvular heart disease with complications; severe hypertension; headaches with focal neurologic symptoms; known or suspected estrogen-dependent tumor (e.g., endometrial, breast cancer); liver disease; cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use; major surgery with prolonged immobilization; pregnancy; undiagnosed abnormal uterine bleeding; and women over age 35 years who smoke.

Common adverse effects – In general, adverse effects of oral, transdermal, or vaginal ring contraceptives may include: breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, fluid retention, tiredness, decline of libido, and increased blood pressure.

Estrogen content and adverse effects – Logically, lower estrogen products (e.g., $\leq$ 20 mcg EE) are associated with a lower risk of estrogen-related adverse effects and a lower risk of thromboembolic events (although data are limited). However, this must be balanced against a greater vulnerability to compromises in contraceptive effectiveness due to missed doses or drug interactions, a potential decrease in non-contraceptive benefits (e.g., reduction in risk of ovarian cancer or protection against functional ovarian cysts), and a higher incidence of cycle control problems (e.g., breakthrough bleeding and spotting). Determination of the "best" estrogen dose – reliable pregnancy prevention with acceptable cycle control and minimal adverse effects – is complicated by wide inter-patient variability in hormonal blood levels.

Progestogen content and adverse effects – There is considerable difference of opinion among providers concerning the extent to which the choice of progestogen affects tolerability. Products containing third-generation progestogens appear to have fewer androgenic effects than the first- and second-generation products, and may be favored in patients with androgenic adverse effects such as acne or hirsutism (although all combined OCs reduce free testosterone levels and therefore tend to have favorable effects on acne). According to a Cochrane review last updated in 2005 (Maitra et al), second- and third-generation products may offer some advantage over first generation products with respect to cycle control (e.g., minimizing spotting or breakthrough bleeding). The magnitude of the difference is unclear.

Drospirenone is a derivative of spironolactone with anti-mineralocorticoid and anti-androgenic properties similar to progesterone. In addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney; the effect is similar to 25 mg of spironolactone. As a consequence, drospirenone reduces fluid retention and weight fluctuations ("bloating"). It may cause concerns about hyperkalemia in patients with a predisposing condition or on other medications that increase potassium levels (women receiving daily, long-term treatment with medications that can increase potassium should have their serum potassium levels checked during the first treatment cycle). While precautions are indicated, there appears to be little evidence to cause serious concern. About 14 million women worldwide have received drospirenone-containing products, according to the manufacturer.

Adverse effects with the transdermal patch – Based on a comparative trial, adverse effects of the transdermal patch appear similar to a combined OC comparator, with the exception of a higher incidence of site reactions, breast symptoms (e.g., breast tenderness), and dysmenorrhea. Another obvious concern with the patch is adhesion; about 5% of patches used during clinical trials had to be replaced, because they fell off or partially detached. A small study cited in

labeling showed a relatively small percentage of patches falling off under conditions of heat, humidity, or exercise; anecdotal reports and survey results from deployment sites suggest a much larger percentage. Site reactions, reported in about 17% of patients, were mostly mild to moderate (92%). Skin pigmentation changes were rarely reported (overall in <1% of patients), with one severe case reported in labeling.

Based on pooled data from North American pivotal trials (Archer et al, 2002), the patch may have compliance advantages compared to combined OCs, with perfect compliance (21 days of drug-taking followed by 7 drug-free days) in 79% of cycles for patients receiving comparator OCs vs. 98% receiving the patch.

DoD providers surveyed cited advantages of the transdermal patch as being improved compliance with infrequent dosing and availability of a different dosing option; disadvantages included the patch coming off, the uncertainty regarding estrogen exposure and VTE risk, the incidence of skin reactions, and weight limitations.

A recent pharmacokinetic study noted that systemic exposure (area under the curve and steady state concentrations) with the patch was about 60% higher than a combined OC with 35 mcg ethinyl estradiol and 0.25 norgestimate, although peak concentrations are about 25% lower. This information, which has been added to product labeling, has caused uncertainty regarding safety of the patch with respect to estrogen content and associated thromboembolic risk. Epidemiological data is limited to one published and one unpublished study, with conflicting results.

Adverse effects with the vaginal ring – Adverse effects with the vaginal ring appear low compared to rates typically reported with combined OCs. Overall, 5-14% of women reported the most common adverse effects (vaginitis, headache, vaginal secretion, weight gain, and nausea). A cross-over study focusing on genital symptoms (Veres et al, 2004) showed a higher percentage of women reporting vaginal wetness during ring use compared to a combined OC (63% vs. 43%), but did not find evidence of any pathological conditions associated with ring use. Specific to the vaginal ring are issues such as interference with intercourse (about 85% of women and 71% of partners say they cannot feel the device during intercourse), premature expulsion (occurring in about 0.5% of cycles), and lack of comfort with inserting and removing the vaginal ring (which does not require exact positioning). After insertion, the product remains effective for about 35 days, providing a safety margin if the patient fails to remove the ring on schedule and making extended or continuous use feasible.

DoD providers surveyed cited advantages of the vaginal ring as being improved compliance with infrequent dosing and a good adverse effect profile; disadvantages included a substantial number of patients who are not comfortable with the method and deployment limitations related to storage requirements.

Adverse effects with DMPA injections – Women receiving injectable DMPA may lose significant bone mineral density, an effect which may not be completely reversible. It is unclear whether use during adolescence or early adulthood reduces peak bone mass and increases the risk of osteoporotic fracture in the future. Injectable DMPA products carry a black box warning advising that it be used as a long-term birth control method (e.g., longer than two years) only if other birth control methods are inadequate.

Of the contraceptives reviewed, only injectable DMPA appears to be associated with progressive (and substantial) weight gain, with labeling for the 150 mg IM strength reporting an average weight gain of 5.4 lb in women completing 1 year of treatment, 8.1 lb after 2 years,

13.8 lb after 4 years, and 16.5 lb after 6 years. Labeling for the 104 mg SQ strength provides one-year results from three large clinical trials (average weight gain 3.5 lbs in the first year of use) and 2-year results from a small study comparing the two strengths (average weight gain of about 7.5 lbs with either strength).

Other issues with DMPA injections include amenorrhea in a high percentage of users (may be an advantage or disadvantage); irregular menses and unpredictable spotting/bleeding in the first several months of use; and lack of immediate reversibility (10 months to return to baseline fertility).

Drug interactions – A large number of medications may interact with hormonal contraceptives. Oral contraceptives may also affect levels of other medications. Data do not suggest a higher incidence of clinically significant drug interactions based on differences in progestogen content, phasic formulation, regimen, or route of administration.

Use in special populations – There are multiple considerations which may affect the choice of contraceptives in women with concomitant conditions (e.g., endometriosis). Progestogen-only OCs may be preferred in women who are breastfeeding, due to concerns about estrogen effects on the content and quality of breast milk, and the potential for infant exposure.

5) Other Factors – One practical concern with the vaginal ring is storage. Refrigeration is required prior to dispensing. After dispensing, the product may remain at controlled room temperature for up to 4 months, but should not be exposed to excessive heat. Heat, humidity, and exercise may also affect adhesion of the transdermal patch.

6) Overall Clinical Effectiveness Conclusion – The P&T Committee concluded that: 1) contraceptives vary in estrogen and progestogen content, regimen (e.g., extended use), phasic formulation, desirability for non-contraceptive uses, and routes of administration; 2) there is wide intra- and inter-patient variability in pharmacokinetics; 3) differences may affect safety, adverse effects/tolerability, convenience/compliance, or effectiveness for non-contraceptive uses; 4) there do not appear to be substantial differences in contraceptive effectiveness across products; 5) providers desire a wide variety of choices based on estrogen and progestogen content consistent with variable patient response and the clinical niches for which multiple are required; 6) the alternative formulations (vaginal ring, patch, IM and SQ injection) are required for adequate clinical coverage; and 7) none of the reviewed contraceptives are sufficiently less clinically effective than the others to be classified as non-formulary based on clinical issues alone.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the clinical conclusion as stated above.

B. Contraceptive UF Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the contraceptive agents in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

The clinical review identified 35 unique contraceptive entities, the majority of which are available generically. For clinical comparison, these agents were classified into one of 11 categories based upon their estrogen content, phasic formulation, or route of administration. This classification system was also used in the economic review. However, for the initial cost assessment, the contraceptives were stratified into three broad groups: 1) OCs available only as brand-name products; 2) OCs available generically; and 3) non-oral contraceptives.

Respectively, these groups represented 20%, 53%, and 27% of the total annual contraceptive drug spend.

The initial cost assessment was based on average weighted cost per cycle across the MHS. This assessment found generically available oral contraceptives to be, in general, more cost-effective than brand name oral contraceptives and non-orally administered contraceptives. Additionally, it was determined that further opportunity exists to obtain lower prices for generic agents through national pharmaceutical contracts. For these reasons, the P&T Committee concluded that all generically available contraceptives should be maintained on the UF.

The P&T Committee also concluded that despite a somewhat higher average weighted cost per cycle for non-orally administered contraceptives (Nuvaring, Ortho Evra, Depo-Provera and equivalents, Depo-subq Provera 104) compared to generically available OCs, these agents should remain on the UF to ensure clinical coverage for patients who need these methods of administration. Likewise, the P&T Committee concluded that Plan B should remain on the UF, because of the clinical advantages of this progestogen-only product over other OCs for emergency contraception. The P&T Committee also discussed availability of Plan B from the TMOP, which currently does not fill prescriptions for Plan B. Although Plan B must be used within 72 hours of unprotected intercourse to be effective, which is not possible via mail order, the P&T Committee agreed that: (1) Under 32 CFR 199.21(h)(2)(i), formulary pharmaceutical agents are required to be available under the Pharmacy Benefits Program from all four points of service identified in paragraph 199.21(h)(1), except for military treatment facilities which are required only to have available BCF agents, with other formulary agents based upon their scope of practice; (2) consistent with this requirement, other medications which must be used acutely are available through mail order (e.g., antibiotics); and (3) this requirement of availability through mail order can ameliorate access problems.

A CMA and BIA were performed to determine the relative cost-effectiveness of the brand name oral contraceptives. The comparators for these analyses were the OCs within the same subgroup (as defined by the clinical review) as the brand name agent being analyzed. The brand name contraceptives considered in these analyses were: Estrostep Fe, Ovcon-35, Ovcon-50, Yasmin, Yaz, Ortho Tri-Cyclen Lo, and Seasonale.

The results of each category-specific CMA were incorporated into a BIA to account for other factors and costs associated with a potential decision to recommend non-formulary status for one or more brand-name contraceptive agents. The BIA accounted for market share migration, cost reductions associated with non-formulary cost shares, and medical necessity processing fee. Based on the CMA and BIA results of the combined category-specific analyses, the P&T Committee agreed that Yasmin, Yaz, and Ortho Tri-Cyclen Lo offered clinical and/or economic value for retention on the UF. The P&T Committee agreed that Seasonale, Ovcon-35, Ovcon-50, and Estrostep Fe should be non-formulary, because the category-specific cost-minimization analyses showed clinically similar alternatives were available at a significantly lower cost.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 3 absent) to accept the UF cost analysis presented by the PEC. The P&T Committee concluded that Seasonale (EE 30 mcg; levonorgestrel 0.15 mg in special packaging for extended use); Ovcon 35 (EE 35 mcg; 0.4 mg norethindrone); Ovcon 50 (EE 50 mcg; norethindrone 1 mg), and Estrostep Fe (EE 20/30/35 mcg; norethindrone 1 mg) were not cost-effective relative to other contraceptive agents with similar clinical attributes. Taking into consideration the conclusions from the relative clinical effectiveness and relative

cost-effectiveness determinations of the contraceptive agents, and other relevant factors, the P&T Committee recommended that Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary under the UF, and that Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, Plan B, and all generically available OCs be retained on the UF (See Table 1 on Pages 19-20 for a complete list of generically available OCs).

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified non-formulary under the UF, with Yasmin, Yaz, Ortho Tri-Cyclen Lo, Ortho Evra patches, Nuvaring, Depo-Provera, Depo-subq Provera 104, and all generically available contraceptives (and equivalents) being added to the UF. In a separate vote, the P&T Committee recommended (12 for, 1 opposed, 3 abstained, 2 absent) that Plan B should continue to be classified as formulary on the UF.

The P&T Committee also voted (11 for, 2 opposed, 3 abstained, 2 absent) to recommend that Plan B be available from the TMOP; with a quantity limit of one Plan B package per copay applying to prescriptions filled by TMOP and retail network pharmacies.

C. Contraceptive Agents UF Medical Necessity Criteria: Based on the clinical evaluation of contraceptive agents, and the conditions for establishing medical necessity for a non-formulary medication provided for in the UF rule, the P&T Committee recommended the following medical necessity criteria for the combined OCs that were recommended for non-formulary status:

1) Use of formulary combined OCs is contraindicated.
2) The patient has experienced significant adverse effects from formulary combined OCs, or is likely to experience significant adverse effects from formulary combined OCs, and is expected to tolerate a non-formulary contraceptive agent.
3) Use of formulary combined OCs has resulted in therapeutic failure.

The P&T Committee agreed that it was extremely unlikely that a non-formulary contraceptive agent would truly be medically necessary, given the number and variety of contraceptive agents recommended for formulary status and the inclusion of contraceptives that are very similar to the recommended non-formulary agents.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to approve the medical necessity criteria.

D. Contraceptive Agents UF Implementation Plan: Because a high proportion of beneficiaries who would be affected by this formulary action are receiving Seasonale, which necessarily requires a 90-day prescription (about 11,000 DoD beneficiaries receive one or more prescriptions for Seasonale annually, out of about 23,000 patients with one or more prescriptions annually for Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe), the P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have Seasonale, Ovcon-35, Ovcon-50, or Estrostep Fe on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both

of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for non-formulary contraceptives written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 3 absent) an effective date no later than the first Wednesday following a 180-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

E. Contraceptive Agents BCF Review and Recommendations

The P&T Committee had previously determined that at least one but no more than two contraceptive products would be added to the BCF in each of the following subgroups. The P&T Committee could also consider addition of contraceptives in other subgroups, if needed. Based on the relative clinical effectiveness and cost effectiveness of the agents within each subgroup recommended for UF addition and taking into account the desire to maximize clinical coverage by providing a wide array of products within the most commonly used subgroups, the P&T Committee recommended the following OCs for BCF status.

- *Monophasic OCs with 20 mcg EE*
  - EE 20 mcg; 3 mg drospirenone (Yaz)
  - EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- *Monophasic OCs with 30 mcg EE*
  - EE 30 mcg; 3 mg drospirenone (Yasmin)
  - EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- *Monophasic OCs with 35 mcg EE*
  - EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
  - EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- *Triphasic OCs*
  - 25 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
  - 35 mcg EE; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- *Progestogen-only OCs*
  - 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

The P&T Committee extensively discussed addition of the vaginal ring product (Nuvaring) to the BCF. Factors supporting addition included potential compliance advantages with once monthly dosing, a low adverse effect profile, and positive provider comments. The major factor opposing addition was the P&T Committee's uncertainty as to whether the clinical advantages outweighed the substantially higher cost per cycle compared to the OCs recommended for the BCF. The P&T Committee ultimately voted not to recommend Nuvaring for the BCF (6 for, 7 opposed, 2 abstained, 3 absent).

The P&T Committee noted that BPA prices submitted by manufacturers contingent upon UF and BCF status had a substantial impact on cost-effectiveness, particularly for some of the brand-name products (e.g., Yasmin, Yaz, and Ortho Tri-Cyclen Lo), which resulted in BCF recommendations that should broaden clinical coverage and reduce the unit cost of these widely used contraceptive products at MTFs. MTFs considering formulary status for products previously on the BCF should take into consideration local needs, as well as the potential that further cost reductions for generically available products may result from national contracting initiatives.

COMMITTEE ACTION: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 3 absent) to recommend the following contraceptive agents for the BCF:

- EE 20 mcg; 3 mg drospirenone (Yaz)
- EE 20 mcg; 0.1 mg levonorgestrel (Alesse, Levlite, or equivalent)
- EE 30 mcg; 3 mg drospirenone (Yasmin)
- EE 30 mcg; levonorgestrel 0.15 mg (Nordette or equivalent; excludes Seasonale)
- EE 35 mcg; 1 mg norethindrone (Ortho-Novum 1/35 or equivalent)
- EE 35 mcg; 0.25 mg norgestimate (Ortho-Cyclen or equivalent)
- EE 25 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen Lo)
- EE 35 mcg; 0.18/0.215/0.25 mg norgestimate (Ortho Tri-Cyclen or equivalent)
- 0.35 mg norethindrone (Nor-QD, Ortho Micronor, or equivalent)

9. ABBREVIATED CLASS REVIEWS: HISTAMINE-2 (H2) BLOCKERS; HMG-Co A REDUCTASE INHIBITORS (STATINS), COMBINATION PRODUCTS, AND ADD-ON THERAPIES OF EZETIMIBE AND NIACIN; AND NEWER SEDATIVE HYPNOTIC AGENTS

Portions of the clinical reviews for each class were presented to the Committee. The Committee provided expert opinion regarding those clinical outcomes considered most important for the PEC to use in completing the clinical effectiveness review, and for developing the appropriate cost effectiveness models. Both the clinical and economic analyses of these three classes will be completed during the August 2006 meeting; no action necessary.

10. ADJOURNMENT

The second day of the meeting adjourned at 1600 hours on May 10, 2006. The dates of the next meeting are August 15-17, 2006.

Patricia Buss

Patricia L. Buss, M.D., M.B.A.
Captain, Medical Corps, U.S. Navy
Chairperson

List of Appendices

Appendix A – Table 1. Implementation Status of UF Decisions

Appendix B – Table 2. Newly Approved Drugs

Appendix C – Table 3. Abbreviations

Appendix A – Table 1. Implementation Status of UF Class Review Recommendations/Decisions

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Feb 06	OABs	tolterodine IR (Detrol) oxybutynin patch (Oxytrol) trospium (Sanctura)	BCF	oxybutynin IR (Ditropan tabs/soln) tolterodine SR (Detrol LA)	26 Apr 06	26 July (90 day implementation period)	
Feb 06	Misc Antihypertensive Agents	felodipine/enalapril (Lexxel) verapamil/trandolapril (Tarka)	BCF	amlodipine/benazepril (Lotrel) hydralazine clonidine tablets	26 Apr 06	26 July (90 day implementation period)	
Feb 06	GABA-analogs	pregabalin (Lyrica)	BCF	gabapentin (Neurontin)	26 Apr 06	28 Jun (60 day implementation period)	
Nov 05	Alzheimer's Drugs	tacrine (Cognex)	ECF	donepezil (Aricept)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Nasal Corticosteroids	beclomethasone dipropionate (Beconase AQ, Vancenase AQ) budesonide (Rhinocort AQ) triamcinolone (Nasacort AQ)	BCF	fluticasone (Flonase)	19 Jan 06	19 April (90 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Macrolide/ Ketolide Antibiotics	azithromycin 2gm (Zmax) telithromycin (Ketek)	BCF	azithromycin (Z-Pak) erythromycin salts and bases	19 Jan 06	22 March 2006 (60 day implementation period)	BCF selections effective 19 Jan 06
Nov 05	Antidepressants (excluding MAOIs and TCAs)	paroxetine HCL CR (Paxil) fluoxetine 90mg (weekly regimen – Prozac Weekly) fluoxetine (special packaging for PMDD – Sarafem) escitalopram (Lexapro) duloxetine (Cymbalta) buproprion extended release (Wellbutrin XL)	BCF	citalopram fluoxetine (excluding weekly regimen and special packaging for PMDD) sertraline (Zoloft) trazadone buproprion sustained release	19 Jan 06	19 July 2006 (180 day implementation period)	BCF selections effective 19 Jan 06

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Aug 05	Alpha Blockers for BPH	tamsulosin (Flomax)	BCF	terazosin alfuzosin (Uroxatral)	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
Aug 05	CCBs	amlodipine (Norvasc) isradipine IR (Dynacirc) isradipine ER (Dynacirc CR) nicardipine IR (Cardene, generics) nicardipine SR (Cardene SR) verapamil ER (Verelan) verapamil ER for bedtime dosing (Verelan PM, Covera HS) diltiazem ER for bedtime dosing (Cardizem LA)	BCF	nifedipine ER (Adalat CC) verapamil SR diltiazem ER (Tiazac)	13 Oct 05	15 Mar 06 (150-day implementation period)	BCF selections effective 13 Oct 05
Aug 05	ACE Inhibitors & ACE Inhibitor / HCTZ Combinations	moexipril (Univasc), moexipril / HCTZ (Uniretic) perindopril (Aceon) quinapril (Accupril) quinapril / HCTZ (Accuretic) ramipril (Altace)	BCF	captopril lisinopril lisinopril / HCTZ	13 Oct 05	15 Feb 06 (120-day implementation period)	BCF selection effective 13 Oct 05
May 05	PDE-5 Inhibitors	sildenafil (Viagra) tadalafil (Cialis)	ECF	vardenafil (Levitra)	14 Jul 05	12 Oct 05 (90-day implementation period)	ECF selection effective 14 Jul 05
May 05	Topical Antifungals*	econazole ciclopirox oxiconazole (Oxistat) sertaconazole (Ertaczo) sulconazole (Exelderm)	BCF	nystatin clotrimazole	14 Jul 05	17 Aug 05 (30-day implementation period)	BCF selection effective 14 Jul 05
May 05	MS-DMDs	-	ECF	interferon beta-1a intramuscular injection (Avonex)	14 Jul 05	-	ECF selection effective 14 Jul 05
Feb 05	ARBs	eprosartan (Teveten) eprosartan/HCTZ (Teveten HCT)	BCF	telmisartan (Micardis) telmisartan/HCTZ (Micardis HCT)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

Meeting	Drug Class	Non-Formulary Medications	BCF/ ECF	BCF/ECF Medications	Status		
					Decision Date (DoD P&T Minutes signed)	Effective Date of Decision	Comments
Feb 05	PPIs	esomeprazole (Nexium)	BCF	omeprazole rabeprazole (Aciphex)	18 Apr 05	17 Jul 05 (90-day implementation period)	BCF selection effective 18 Apr 05

BCF = Basic Core Formulary; ECF = Extended Core Formulary; ESI = Express-Scripts, Inc; MN = Medical Necessity; TMOP = TRICARE Mail Order Pharmacy; TRRx = TRICARE Retail Pharmacy program; UF = UF
ER = extended release; IR = immediate release; SR = sustained release
ARBs = Angiotensin Receptor Blockers; ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors; BPH = Benign Prostatic Hypertrophy; CCBs = Calcium Channel Blockers; HCTZ = hydrochlorothiazide; MS-DMDs = Multiple Sclerosis Disease-Modifying Drugs; PDE-5 Inhibitors = Phosphodiesterase-5 inhibitors; PPIs = Proton Pump Inhibitors
*The topical antifungal drug class excludes vaginal products and products for onychomycosis (e.g., ciclopirox topical solution [Penlac])

Appendix B – Table 2. Newly Approved Drugs May 2006 DoD P&T Committee Meeting

Medication & Mechanism of Action	FDA approval date; FDA-approved indications	Committee Recommendation
Insulin detemir Injection (Levemir); Novo Nordisk; long-acting insulin	Jun 05: Treatment of insulin dependent diabetes mellitus in adults requiring long acting insulin for control of hyperglycemia. Oct 05: Treatment of pediatric Type I DM	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Insulin glulisine injection (Apidra); Sanofi-Aventis; ultra short acting insulin analogue	Apr 04: Treatment of insulin dependent diabetes mellitus in adults requiring ultra short acting insulin for control of hyperglycemia	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the injectable medications for diabetes drug class is reviewed.
Ranolazine tablets (Ranexa); CV Therapeutics; partial fatty oxidase inhibitor	Jan 06: Treatment of chronic angina when used in combination with amlodipine, beta blockers or nitrates	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until the miscellaneous cardiovascular drug class is reviewed.
Sunitinib capsules (Sutent); Pfizer; multi-kinase inhibitor	Dec 05 (priority review); Treatment of gastrointestinal stromal tumor after disease progression on, or intolerance to, imatinib (Gleevec). Treatment of advanced renal cell carcinoma	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed. Quantity limits recommended: TMOP: 50 mg: #60 caps/84 days, 25 mg: #120 caps/84 days, 12.5 mg: #180 caps/84 days. Retail Network: 50 mg: #30 caps/30 days, 25 mg:#60 caps/30 days, 12.5 mg: #120 caps/30 days
Lenalidomide capsules (Revlimid); Celgene; immunomodulatory drug (thalidomide analogue)	Dec 05: Treatment of myelodsyplastic syndromes in transfusion dependent patients with del 5q cytogenetic abnormality	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until oral cancer drug class is reviewed.
Mecasermin rinfabate injection (Iplex); Insmed Pharmaceuticals; recombinant human insulin-I-like growth factor-1 (IGF-1)	Aug 05: Long-term treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone	No Uniform Formulary recommendation at this meeting. Consideration of Uniform Formulary status deferred until growth hormone / IGF-1 drug class is reviewed. Added to existing PA criteria and forms for mecasermin (Increlex).

Appendix C – Table 3. Table of Abbreviations

5-HT3	type 5 serotonin antagonists
ACOG	American College of Obstetricians and Gynecologists
BAP	Beneficiary Advisory Panel
BCF	Basic Core Formulary
BIA	budget impact analysis
BPA	blanket purchase agreement
CEA	cost-effectiveness analysis
CFR	Code of Federal Regulations
CINV	chemotherapy-induced nausea and vomiting
CMA	cost minimization analysis
CYP450	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DEA	Drug Enforcement Administration
DMPA	depot medroxyprogesterone acetate
DoD	Department of Defense
EE	ethinyl estradiol
ESI	Express Scripts, Inc.
FDA	Food and Drug Administration
GIST	gastrointestinal stromal tumor
H2	histamine-2
IV	intravenous
MHS	Military Health System
MTF	military treatment facility
NK-1	neurokinin-1
NNT	number needed to treat
OCs	oral contraceptives
ODT	orally dissolving tablet
PA	prior authorization
P&T	Pharmacy and Therapeutics
PEC	Pharmacoeconomic Center
PONV	post-operative nausea and vomiting
RINV	radiation-induced nausea and vomiting
TMA	TRICARE Management Activity
TMOP	TRICARE Mail Order Pharmacy
TRRx	TRICARE Retail Network
TZDs	thiazolidinediones
UF	Uniform Formulary
VTE	venous thromboembolism