DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

Under 10 U.S.C. § 1074g, as implemented by 32 C.F.R. 199.21, the DoD P&T Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to non-formulary status receive comments from Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. Antiemetic Drug Class Review

P&T Comments

A. 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 Uniform Formulary Rule. The newer and older antiemetics together account for approximately $37.4 million dollars annually, and are ranked 48th in 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 vs. 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 PONV: The majority of studies evaluating prevention of PONV used IV therapies and rarely continued oral medication after hospital discharge. There are 7 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 3 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 Obstetrics and Gynecology (ACOG) relegate IV ondansetron for use as 3rd line therapy only 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 adjustment is 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 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 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 and 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 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 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 desired for improved clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as 3rd-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 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 are sufficiently less clinically effective than the others to be classified as non-formulary, based on clinical issues alone.

COMMITTEE ACTION: The Committee voted to accept the clinical effectiveness conclusions stated above

B. 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 on the newer 5-HT3 antiemetics subclass, followed by a budget impact analysis; a cost-effectiveness analysis 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 cost-minimization analysis was 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 Budget Impact Analysis (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 groups 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 cost-effectiveness analysis (CEA) was also conducted to evaluate the place in therapy for aprepitant (Emend), 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 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.

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 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 UF.

C. Implementation Plan: See below.

COMMITTEE ACTION: The P&T Committee voted 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.

III. Antiemetic Drug Class Review (cont.)

BAP Comments

A. Relative Clinical Effectiveness*:* The Committee concluded (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 desired for improved clinical coverage; (3) for nausea and vomiting in pregnancy, ondansetron should be reserved for use as 3rd-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 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 are sufficiently less clinically effective than the others to be classified as non-formulary, based on clinical issues alone.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted to accept the antiemetic pharmacoeconomic analyses presented by the PEC. The Committee concluded that dolasetron was not cost-effective relative to the other 5-HT3 antagonists, and that it is also cost-effective to add aprepitant as an adjunct for the treatment of chemotherapy induced nausea and vomiting. The cost-effectiveness of the older antiemetics was also considered, and it was determined that nothing would be gained clinically or economically by making any of the older antiemetics non-formulary.

C. Uniform Formulary Recommendation 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 UF.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

D. Implementation Plan: The Committee voted to recommend an implementation period of 60 days.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

IV. Contraceptive Agents Drug Class Review

P&T Comments

***A.* Relative Clinical Effectiveness:** 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 Military Health System (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).

2) Potential Differences Among 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 6 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 (94 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. This product 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 depot medroxyprogesterone acetate (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 UK 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 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; major surgery with prolonged immobilization, 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; 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., ≤ 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 [AUC] 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 (BMD), 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 2 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 1-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, 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 Committee voted to accept the clinical effectiveness conclusion as stated above

B. 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 TRICARE Mail Order Pharmacy (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) other medications which must be used acutely are available through mail order (e.g., antibiotics), and 2) availability of Plan B through mail order may ameliorate access problems. The P&T Committee also supported a quantity limit that would provide 1 Plan B package per copay, to reduce the potential for diversion or stockpiling.

A cost-minimization analysis (CMA) and budget impact analysis (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

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted to recommend Seasonale, Ovcon-35, Ovcon-50 and Estrostep Fe be classified as non-formulary pharmaceutical agents, 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.

C.* 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, 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.

COMMITTEE ACTION: See Above

V. Contraceptive Agents Drug Class Review (cont.)

BAP Comments

A.* Relative Clinical Effectiveness:*** 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, 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.

B. Relative Cost Effectiveness: The P&T Committee, based upon its collective professional judgment, voted 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.)

C. Uniform Formulary Recommendation: 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 OCs be retained on the UF.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions:

D. Implementation Plan: The Committee voted to recommend an implementation period of 180 days.

BAP Comment:	☐ Concur ☐ Non-concur Additional Comments and Dissentions: