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