DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

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## IN THIS ISSUE



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# Hospital consortium standardizes prescription writing for members

*Protocols integrate Joint Commission goals*

A consortium of hospital systems in the Minneapolis-St. Paul area has implemented a program to standardize protocols for hand-written prescriptions. The effort integrates Joint Commission on Accreditation of Healthcare Organizations goals for 2004 targeting the elimination of dangerous abbreviations.

As of April 1, hospitals that are members of the Safest in America (SIA) consortium no longer accept medication orders that contain unsafe abbreviations **(see list on p. 43)**. SIA is composed of nine metropolitan hospitals in addition to the Mayo Clinic in Rochester.

SIA was formed several years ago because the hospitals had health care professionals, including physicians and pharmacists, who worked at more than one of the hospital systems, reports **Alison Page**, MHA, RN, vice president of patient safety at Fairview Health Services in Minneapolis. "[We said], let's improve processes together with an eye to standardize them so that doctors, nurses, and pharmacists experience the same thing from institution to institution."

The Institute Clinical Systems Improvement in Bloomington manages the collaborative. "They manage the infrastructure of our improvement work," she adds.

SIA introduced one of its patient safety initiatives last year. In September, it adopted a single, metrowide standard for surgical site marking in an effort to reduce incidences of wrong-site surgeries.

SIA then launched its medication error collaborative, led by **Mark Thomas**, MS, RPh, pharmacy director at Children's Hospital and Clinics. The collaborative included teams of clinicians and hospital staff who developed common outcome measures. At that time, Thomas said the group would work to standardize protocols and processes related to:

- the use of high-risk drugs (one or two would be selected to start);
- the use of medication-ordering abbreviations;
- the use of pediatric medications frequently associated with dosing errors.

In addition, the group planned to establish a mechanism to use local

expertise among participating hospitals to conduct a peer-reviewed assessment of an identified list of practice recommendations at participating hospitals.

Since that time, SIA implemented a standardized dosing concentration or protocol for certain medications used with children. The consortium also has recommended a standardized protocol for prescribing heparin. The next project in medication safety is insulin management, Page says. This project launched about a month ago.

## Meeting Joint Commission goals

When addressing safe prescribing practices, the collaborative wanted to standardize across the hospitals which abbreviations and practices would not be allowed, Page notes.

About halfway into the project, the Joint Commission published requirements regarding the elimination of unsafe abbreviations. For example, accredited organizations now must have a minimum list of five dangerous abbreviations, acronyms, and symbols (U for unit; IU for international unit; QD for daily and QOD for every other day; trailing zero; and MS, $MSO_4$, and $MgSO_4$ for morphine sulfate or magnesium sulfate). As of April 1, accredited organizations also must identify and apply at least another three "do not use" abbreviations, acronyms, or symbols. **(See box, p. 43.)**

The collaborative integrated the Joint Commission requirement with its list and standardized the items across the community, Page explains.

Currently, prescriptions that are not written appropriately are not filled, she reports. An exception is when the patient is put at risk if the medication order is not filled right away. As the Joint Commission says, the safety of the patient always comes first:

> "If, in the judgment of the people providing care to the patient (e.g., the registered nurse and pharmacist), the order is clear and complete and the delay to obtain confirmation from the prescriber prior to execution of the order would place the patient at greater risk, then the order should be carried out and the confirmation obtained as soon as possible thereafter."

With other prescriptions, the physician is called regarding the order, and a form correcting the order is filled out. The consortium initially saw "big numbers" of prescriptions that needed to be corrected, Page reports. These numbers, however, now are declining rapidly. The consortium makes a point of stating that it is looking for flaws in the system that create opportunities for error; it does not want to place blame on any one facility or individual.

The hardest abbreviation to make the change has been QD because physicians don't think the change is necessary, she says. "Getting them to change their habits around QD has been difficult."

Soon all the hospitals will be putting a "hard stop" on incorrect medication orders, not allowing them to be re-verified and changed verbally. "Eventually, [physicians] will have to fix it themselves."

SIA is in the midst of collecting data about the new protocols and hopes to continually measure their effectiveness throughout the year. The data collection will help in other ways as well. Minnesota passed a new system for mandatory reporting of medical errors during the 2003 legislative session. The new law will require public reporting of certain data related to errors within hospitals, including patient death or serious disability associated with a medication error. ■

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**Editorial Questions**

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.



Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@thomson.com).
Senior Production Editor: **Nancy McCreary**.

## List of Standardized Unsafe Practices and Abbreviations

Here are the unsafe abbreviations and practices that are now prohibited among member hospitals of the Safest in America consortium in the Minneapolis/St. Paul area:

| Unsafe practice | Practice prone to error | Safe prescribing protocol |
|---|---|---|
| ☐ U instead of Units | Regular Insulin 5 u SC now<br>"u" can be misinterpreted as cc, 4, 6, or 0. | Regular Insulin 5 units SC now |
| ☐ IU for International Units | Mistaken as IV (intravenous) or 10 (ten). | Write "International Unit." |
| ☐ Trailing zero (1.0) | Ativan 1.0 mg IV x1<br>Can be misinterpreted as 10 mg. | Ativan 1 mg IV x1 |
| ☐ Lack of leading zero (.5) | Hydromorphone .5 mg IV Q12H<br>This can result in an overdose of medication. | Hydromorphone 0.5 mg IV Q12H |
| ☐ Greek letter "μ" used to indicate "micro" | Digoxin 125 μg PO today<br>This can be misread as "mg" or "units." | Digoxin 125 mcg PO today |
| ☐ An abbreviation or symbol used instead of the drug name | $MSO_4$; $MgSO_4$; MS<br>These drugs can be confused with each other. | Magnesium Sulfate or Morphine |
| ☐ A problematic medical abbreviation was used | QD, QOD<br>These can be misread as "qid." | Q day, daily, every other day, q24h |
| ☐ Chemotherapy abbreviation used | MTX, CTX, VCR, VBL, DOX, AZT<br>These can be misinterpreted for other drugs including other chemotherapy. | Spell out all chemotherapy drug names. |
| ☐ Archaic abbreviations for ear and eye routes used | au, as, ad, od, os, ou<br>These designations are unfamiliar to many practitioners and lead to wildly incorrect administration errors. | Spell out the words "eye" and "ear." Spell out the words "left," "right," and "both." |

# Compendia disagree on drug-drug interactions

*Researchers develop their own list of serious DDIs*

Pharmacists may turn to drug interaction compendia for detailed information on serious drug-drug interactions (DDIs). New research, however, shows that the compendia seldom agree on which DDIs are considered to be of the highest clinical importance.

In the study, researchers found that of the 406 DDIs identified in one or more of the references as having the greatest clinical severity or importance, only nine were identified as major in all four compendia.

This study was the first part of a partnership devised to reduce clinically important DDIs. The partners include the Centers for Disease Control and Prevention in Atlanta, which provided financial support; the AdvancePCS Center for Healthier Aging in Hunt Valley, MD; the University of Arizona in Tucson, the University of Washington in Seattle, and the Albert Einstein College of Medicine in New York City. Their findings were published in the March/April 2004 issue of the *Journal of the American Pharmacists Association*.

To evaluate which DDIs are considered to be of the highest clinical importance, the researchers selected four compendia during the fall of 2001 that they thought health care professionals used the most to find out more about drug interactions. These were *Evaluations of Drug Interactions* (EDI), *Drug Interaction Facts* (DIF), *Drug Interactions: Analysis and Management* (DIAM), and MicroMedex (Drug-REAX) computer program. The researchers used specific criteria for each compendium to develop the clinically important drug interactions since the compendia used slightly different rating systems to classify the drug interactions.

The researchers also focused on the DDIs likely

to be captured by computerized prospective drug utilization review systems in community and ambulatory pharmacies. Even so, health system or hospital pharmacists will see these combinations as well, says **Daniel C. Malone**, PhD, RPh, associate professor at the University of Arizona Colleges of Pharmacy and Public Health, and director of the Division of Pharmaceutical Policy within the Center for Health Outcomes and PharmacoEconomic Research.

Malone and the other researchers identified a total of 406 DDIs — listed as being at the highest level of severity in at least one of the four compendia. Thirty-five of these DDIs were listed in three compendia, 71 in two compendia, and 291 in only one compendium. Only nine of the DDIs were listed as being the most severe in all four compendia.

The researchers hypothesized several reasons for the lack of consistency across the compendia, Malone says. First, the different rating systems used in the compendia guarantee some variation. For example, EDI rated drug interactions using a four-item summary measure, such as Code 1: highly clinically significant. MicroMedex, on the other hand, used a five-item rating scale (major, moderate, minor, none, and not specified)."We tried to minimize [the discrepancy] by trying to be more inclusive, if possible."

An editor or a reviewer also rates the drug interactions, so they are somewhat subjective, Malone says. "There is no gold standard for comparison."

In addition, the evidence for most of these interactions is usually circumstantial, he says. The circumstantial evidence might include a few occasional cases reports, a pharmacodynamic study done in an animal model, or possibly a pharmacokinetic study done in an animal or human model.

"Usually, the amount of evidence to support the interaction is quite limited. Therefore, people are trying to make judgments about the seriousness of these interactions based upon little or sometimes no information. It is a theoretical basis for the interaction," Malone says.

In the study, the researchers included a table of the unique DDIs with the highest severity rating in three or four drug interaction compendia. However, an outside reviewer says he found a "disconnect from clinical reality" in the table.

"Where are the DDIs that experience tells us bring so many patients [those lucky enough not to die suddenly] to medical attention? Sulfonylureas and CYP 2C9 inhibitors, digoxin and P-glycoprotein inhibitors, angiotensin-converting enzyme inhibitors and potassium-sparing diuretics — the severity of these DDIs is undisputable, and countless patients are exposed to them each year," says **David N. Juurlink**, BPhm, MD, PhD, FRCPC, attending physician for the Divisions of General Internal Medicine, Clinical Pharmacology and Toxicology, and the Clinical Epidemiology Unit at Sunnybrook and Women's College Health Sciences Centre in Toronto. He also is an assistant professor in the Departments of Medicine and Health Policy, Management, and Evaluation at the University of Toronto.

## *Identifying their own serious DDIs*

After evaluating the compendia, the researchers then went on to develop their own list of clinically important DDIs, which they defined as those interactions most likely to cause harm if not detected. The list also was published in the same issue of the journal.

They used a three-step process to devise their list. First, they selected drug interactions from a review of drug interaction compendia followed by a systematic literature review. The researchers also developed an evidence report for each candidate DDI. These evidence reports then were evaluated and rated by an expert panel using a modified Delphi process.

For each DDI, the researchers tried to define the object and precipitant drug. The precipitant drug is the medication that affects the pharmacologic actions of pharmacokinetics of the object drug.

They identified a total of 25 clinically important DDIs after excluding products no longer available in the United States, products not likely to be used in an outpatient setting, and combinations that can be used for therapeutic benefit.

The panel did a better job of choosing interactions that occur in clinical reality, Malone reports.

"The paradox of these sort of ratings systems is that the interaction may exist in a theoretical sense, but when it is translated into day-to-day patient care, it means a lot less," he explains.

The researchers would have included other interactions had the focus been on the hospital setting, Malone notes. "Those interactions are certainly important, but all of the ones that we have identified here can and probably do occur in the hospital setting," he says. "Pharmacists in the hospital setting need to be aware of them, too."

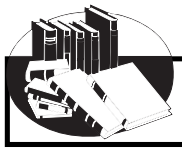
The list may contain 25 interactions, but they can be logically grouped into several categories. "If you think of it in terms of three major groups:

anticoagulants, monoamine oxidase inhibitors, and anti-infectives, you have captured 20 or 21 of the interactions identified. Then there is a small number of other interactions that fall outside that realm. It's an easy way of putting the list into one's memory," he says.

The downside to making such a list is that other interactions are important, too. "This is a first cut," Malone says. "I don't want people to stop thinking about interactions after they have learned the 25. There are certainly other ones that are important."

The original goal was to identify 10-15 clinically important DDIs. That was expanded to 25, and Malone says that number could have been higher. "Phil Hansten [PharmD, a professor at the School of Pharmacy at the University of Washington], one of our expert panel members, constantly reminds me and everyone else that these are important interactions and ones that we should be aware of. There are others that are important, too, and the list is dynamic. It will change as new product and information comes out. It's not something that one can learn and think [he or she] has a handle on it.

"You have to stay up on it. I think most pharmacists and physicians realize that." ■



## JOURNAL REVIEW

# Gene mutation patients respond to gefitinib

*Screening may identify those who would benefit*

New research shows that mutations in the epidermal growth factor receptor *(EGFR)* gene correlate with clinical responsiveness in patients with non-small-cell lung cancer to the tyrosine kinase inhibitor gefitinib (Iressa). The study was published in the May 20 issue of The *New England Journal of Medicine* (*NEJM*), but was posted in early release on the *NEJM* web site on April 29.

The work of Lynch, et al, if borne out by additional studies, will fundamentally change targeted therapy for solid tumors, says **Mark R. Green**, MD, professor of medicine and Gilbreth Professor of Clinical Oncology at the Medical University of South Carolina in Charleston. He commented on the research in the *NEJM*.

"For patients with lung cancer, mutational analysis of *EGFR* by experienced laboratories should provide guidance about treatment. More generally, this work suggests the relevance of a two-step evaluation of targeted therapy."

The researchers wanted to look closer at gefitinib, which targets *EGFR,* to see why some patients show a "remarkably rapid and often profound response" to the drug, while others showed no clinically significant response. The researchers searched for mutations in the *EGFR* gene in primary tumors in patients who had a response to gefitinib, those who did not have a response, and those who had not been exposed to the drug.

They found somatic mutations within the tyrosine kinase domain of *EGFR* in eight of nine patients who had exhibited a response to gefitinib. The researchers believe that the ninth patient may have had an undetected mutation or a mutation in a heterodimerization partner of *EGFR*. "These results, together with the finding of *EGFR* mutations in tumors from two of 25 patients with non-small-cell lung cancer who had not received gefitinib (8%), suggest that such mutations account for the majority of responses to gefitinib reported in clinical studies," the researchers say.

Understanding the molecular basis of responsiveness to gefitinib has immediate clinical implications for patients with this disease, they continue. Diagnostic testing can help guide the clinical use of gefitinib, and patients may benefit if they receive an earlier course of treatment.

"Prospective validation of *EGFR* tyrosine kinase mutations as predictors of the responsiveness to gefitinib is warranted, and genotype-directed clinical trials of this tyrosine kinase inhibitor in the initial treatment of advanced non-small-cell lung cancer — and even in the adjuvant setting after surgical resection — should now be considered." ■

## NEWS BRIEFS

### Few new antibiotics are in the pipeline

Despite a critical need for new antibiotics to treat drug-resistant infections and other infectious diseases, very few new antibiotics are being developed, according to a study published in the May 1 issue of *Clinical Infectious Diseases*.

To document trends, researchers evaluated U.S. Food and Drug Administration (FDA) databases of approved drugs and the research and development (R&D) programs of the world's largest pharmaceutical and biotechnology companies, by looking at the companies' web sites and 2002 annual reports. They found that the FDA approvals of new antibiotics declined 56% during the past 20 years (1998-2002 vs. 1983-1987). Looking to the future, the researchers found only six new antibiotics in the R&D pipeline out of 506 drugs being developed. The FDA recently approved one of those drugs, telithromycin.

Bacteria, which are treated with antibiotics, are by far the most common cause of infection-related deaths in the United States. Because of the emergence of drug-resistant bacteria, the researchers note that there are few or no treatment options for many infections.

Although the need for new antibiotics is increasing, a number of factors make these drugs less economically attractive than drugs that treat chronic diseases. For instance, antibiotics usually are prescribed for one or two weeks at most while some drugs are taken for life. In addition, the researchers note that in order to prevent the evolution of resistant strains of bacteria, infectious disease physicians try very hard to limit the overuse of newer antibiotics. One of the researchers, however, believes that the lack of new antibiotics in development is caused by a complicated "systems problem," and not by irresponsibility on the part of the pharmaceutical companies, the FDA, or physicians. ▼

## Pharmacy groups establish compounding accreditation board

A coalition of pharmacy-related professional and regulatory organizations has announced the creation of a voluntary accreditation program for pharmacy compounding.

The Pharmacy Compounding Accreditation Board was established to help improve the quality and raise awareness of compounding. The governing board is expected to consist of the following organizations: the American College of Apothecaries, the American Pharmacists Association, the International Academy of Compounding Pharmacists, the National Association of Boards of Pharmacy, the National Community Pharmacists Association, the National Council of State Pharmacy Association Executives, the National Home Infusion Association, and the United States Pharmacopeia. Stakeholder organizations invited to provide input include the American Association of Colleges of Pharmacy, the American Society of Consultant Pharmacists, the American Society of Health-System Pharmacists, and the National Association of Chain Drug Stores.

The program should be developed within the following months with the first pharmacy site accredited by the end of the year. ▼

## Be aware of possible drug mix-ups for obstetrical patients

Pharmacists are being warned again of possible dangerous mix-ups between the pharmacological opposites methylergonovine maleate (Methergine) and terbutaline sulfate (Brethine).

Numerous reports of injuries have been related to lookalike packaging of these products, and two alerts have been previously published warning health care providers about the risk of mix-ups. Both agents frequently are stored and used in labor and delivery settings, but for different clinical reasons. Terbutaline is used to treat pre-term labor, and methylergonovine primarily is used after delivery of the placenta to treat uterine atony, subinvolution, or hemorrhage. Since methylergonovine has abortifacient properties, it is contraindicated in pregnancy and would be especially dangerous to a patient in pre-term labor. Both of these products are packaged as 1 mL ampules within an amber plastic tub covered by a foil label with the product name in tiny print, making them difficult to tell apart. Both ampules also have similar colored "rings" around the ampule necks that can be seen through the amber plastic, which further adds to their similarity. With so many risk factors, these medications are prone to being interchanged.

Interchanging these two drugs could result in serious adverse outcomes for the mother and baby. In one reported case, four doses of methylergonovine were administered to a patient in preterm labor, which was believed to contribute to fetal demise. In another recently reported case, a 35-year-old female was experiencing significant preterm uterine contractions. Her physician diagnosed fetal distress and asked a nurse to administer terbutaline IV push. Instead, the nurse accidentally administered Methergine. The mother experienced significant contractions requiring an emergency

cesarean. Fortunately, the patient and newborn were discharged two days later unharmed. ▼

## Pancreatic extract makers to submit marketing applications

The U.S. Food and Drug Administration (FDA) has notified manufacturers of pancreatic insufficiency products that these drugs must get approval by the agency within the next four years to remain on the market. The FDA decided to require approval of new drug applications for all pancreatic extract drug products after reviewing data that showed substantial variations among currently marketed products.

Specifically, the FDA review found that variations in the formulation, dosage, and manufacturing processes affected the potency — in terms of both the products' activity and release rate — of the enzymes after patients take them. The resulting variations in drug potency could significantly affect the safety and effectiveness of the drugs.

The FDA does not expect prices to change as a result of this notice. The FDA's economic analysis of this action found that although some firms may choose to discontinue marketing, enough manufacturers would continue producing pancreatic enzyme products to keep the market competitive. ▼

## Concurrent oxandrolone, warfarin use may have adverse effect

Savient Pharmaceuticals is updating health care professionals about the use of its product oxandrolone (Oxandrin) when used in patients concurrently treated with the oral anticoagulant warfarin for systemic anticoagulation.

Oxandrin, a synthetic derivative of testosterone, is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma; in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, or to offset the protein catabolism associated with prolonged administration of corticosteroids; and for the relief of the bone pain frequently accompanying osteoporosis.

A recent clinical study conducted by Savient demonstrated a significant decrease (80%-85%) in the warfarin dose needed to achieve therapeutic effect in subjects also treated with oxandrolone. The study results were significant, and the U.S. Food and Drug Administration approved a change to the oxandrolone labeling as a result. The recommendations are specific to oxandrolone and cannot be presumed to be applicable for other anabolic androgenic steroids.

For complete label information, see www.fda.gov/medwatch/SAFETY/2004/safety04.htm#oxandrin. ■

## *New FDA Approvals*

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• ***Apomorphine (Apokyn), manufactured for Bertek Pharmaceuticals by Draxis Pharma.*** The FDA has approved apomorphine (Apokyn) as an injectable drug for treating Parkinson's patients during episodes of hypomobility. Apomorphine was given priority review because injectable apomorphine is the first therapy approved to treat these episodes acutely. Apomorphine also was designated as an orphan product.

Apomorphine must be taken with an antiemetic drug because, when taken alone, it causes severe nausea and vomiting. It must not be taken with 5-$HT_3$ antagonists because the combination of these drugs can lead to very low blood pressure and loss of consciousness.

Apomorphine is intended for subcutaneous

### COMING IN FUTURE MONTHS

- Iron complex evaluation
- The link between working memory and medication errors
- A look at food and drug allergies
- The effect of rosuvastatin calcium (Crestor) on the HMG market
- Confusion about USP Chapter 797 Sterile Compounding provisions

injection only. Apomorphine's labeling also includes specific warnings about low blood pressure, fainting, hallucinations, and excessive sleepiness.

The most common adverse events seen in controlled trials were yawning, dyskinesias (abnormal movements), nausea and vomiting, sedation or sleepiness, dizziness, runny nose, hallucinations, edema, chest pain, increased sweating, flushing, and pallor.

• ***Hyaluronidase for injection (Vitrase) by Ista Pharmaceuticals back on market***. The FDA has approved hyaluronidase for injection (Vitrase) as an adjunct to other injected drugs to increase their absorption and dispersion.

Hyaluronidase has been used most commonly in combination with local anesthetics in the setting of ophthalmic surgery. Hyaluronidase increases tissue permeability and promotes the spread or dispersion of other drugs. Hyaluronidase also is approved for use as an adjunct to rehydrating agents, and for use with certain imaging agents. Vitrase is a sheep-source (ovine) form of hyaluronidase.

Hyaluronidase has not been available in the United States for the past three years due to the previous manufacturer's business decision no longer to market the product. This approval was based on product specific manufacturing information together with published literature on hyaluronidase, and other available public information. The manufacturer also conducted a clinical safety study.

Hyaluronidase should not be used to reduce the swelling of bites, stings, and infected or inflamed areas because of the possibility of spreading a localized infection.

• ***Insulin glulisine [rDNA origin] injection (Apidra) by Aventis***. The FDA has approved insulin glulisine [rDNA origin] injection (Apidra) for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. The drug is a recombinant DNA human insulin analogue that has a more rapid onset and a shorter duration of action than regular human insulin after subcutaneous administration.

Insulin glulisine [rDNA origin] injection has been studied in clinical trials in adult patients with Type 1 and Type 2 diabetes. The drug should be injected within 15 minutes before a meal or within 20 minutes after starting a meal and given by subcutaneous injection, or by continuous subcutaneous pump infusion. It has been used in combination with insulin glargine [rDNA origin] injection (Lantus), a 24-hour basal insulin also made by Aventis.

Adverse events commonly associated with human insulin therapy include allergic reactions, injection site reaction, lipodystrophy, pruritus, and rash.

• ***New indication for doxercalciferol (Hectorol) capsules by Bone Care International***. The FDA has approved a new indication and strength for doxercalciferol (Hectorol) capsules. Doxercalciferol, a prohormone vitamin $D_2$ analog, is now approved for the treatment of secondary hyperparathyroidism (SHPT) that develops in the earlier stages (Stages 3 and 4) of chronic kidney disease prior to dialysis. It also is approved for the treatment of SHPT in dialysis patients in the United States. ■

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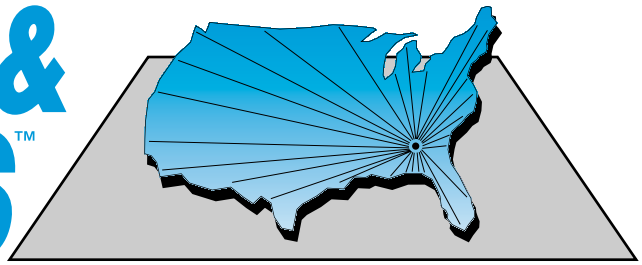

# Aprepitant (Emend) Formulary Evaluation

*Part 2: Clinical Trials Summary, Recommendations, and Criteria for Use*

By **Omar Dudar**, PharmD Candidate
Harrison School of Pharmacy
Auburn (AL) University
Written while on clinical rotation at Huntsville (AL) Hospital

## Clinical trial summary

*Phase IIa studies*

Four Phase IIa studies have been conducted with aprepitant to establish a time period for therapy, dose, and a regimen of combination therapy with aprepitant for the Phase IIb trial.

Cocquyt, et al conducted the first randomized, double-blind, clinical trial to evaluate the efficacy of the $NK_1$ antagonist (aprepitant) **(see Table 4)**. The purpose of the trial was to evaluate the prevention of emesis during the acute and delayed phases of chemotherapy with cisplatin-naïve patients. In this earlier trial the pro-drug of aprepitant "L-758,298" was given intravenously to 30 patients at doses of 60 mg or 100 mg daily for seven days. The standard group of 23 patients received only ondansetron 32 mg intravenously for the course of seven days and was compared with the L-758,298 group (designated aprepitant IV group). Both treatment groups were evaluated for efficacy of "no emesis" through the seven days of therapy. Nausea was assessed as a secondary endpoint with the use of a four-point scale.

*Summary:* During the delayed phase, the aprepitant IV group's prevention of emesis was significantly improved compared to the ondansetron group, P = 0.005.

*Other results*

- Average nausea score distribution for the delayed phase was lower in the aprepitant IV group compared to the ondansetron group (P = 0.15).
- There were no serious side effects in the aprepitant IV group.

*Authors' conclusions*: Single daily doses of IV aprepitant were sufficient to suppress delayed nausea and vomiting associated with cisplatin treatment and also to decrease the rate of vomiting during the acute phase. The data collected seem to concur with the assumption that there is a different mechanism for the acute vs. delayed phases of vomiting.

Campos, et al organized a randomized, multicenter, double-blind, parallel-group, controlled clinical trial to evaluate the prevention of acute and delayed emesis after cisplatin 70 mg/m$^2$ or more for each of the groups listed in **Table 5**.

**Table 4: Cocquyt et al prevention of emesis between groups**

| Phase | Aprepitant IV | Ondansetron 32 mg IV | P value |
|---|---|---|---|
| Acute phase | | | |
| Patients with no emesis | 37% | 52% | No significant difference between groups |
| Delayed phase | | | |
| Patients with no emesis | 72% | 30% | P = 0.005 |

**Table 5: Campos et al groups for comparison**

| Group, and n = number of patients | Treatment plan |
|---|---|
| I—(standard therapy) n = 90 | Granisetron 10 µg/kg IV and 20 mg PO dexamethasone (day 1); placebo (days 2-5) |
| II—(main experimental comparison group) n = 86 | Granisetron and 400 mg MK-869 PO and 20 mg PO dexamethasone (day 1); 300 mg MK-869 PO (days 2-5) |
| III—(n = 89) | 400 mg MK-869 PO (in the evening before cisplatin therapy) and 20 mg PO dexamethasone (day 1); 300 mg MK-869 PO (days 2-5) |
| IV—(n = 86) | 400 mg MK-869 PO one hour before cisplatin and 20 mg PO dexamethasone (day 1); 300 mg MK-869 PO (days 2-5) |

Note: MK-869 was the former name given to the first oral dosage form of aprepitant in **Table 5, above**.
*Rescue therapy*: Metoclopramide 20-30 mg PO four times a day (qid) or 1-2 mg/kg metoclopramide IV qid for the first day, and dexamethasone 8 mg PO twice a day (bid) (days 2-5) as needed (PRN) vomiting.

*Inclusion criteria*:
- 16 years or older.
- Negative assay for serum B human chorionic-gonadotropin (for safety of the fetus).

*Exclusion criteria*:
- Karnofsky scale score of less than 60; allergy to metoclopramide, dexamethasone, or granisetron; emesis before cisplatin (24 hours before day 1); seizure treatment in the past two months, severe illness other than neoplasm; or lab criteria for hemoglobin, WBC, platelets, AST, ALT, alkaline phosphatase, bilirubin, and Scr.

*Summary of results*
Acute phase (no emesis)
- Group II vs. Group I (80% vs. 57%), $P < 0.01$, 90% confidence interval (8-38%).
- Group III (46%), no P value given.
- Group IV (43%), no P value given.

Acute phase (no emesis and no rescue therapy)
- Group II vs. Group I (75% vs. 51%), $P < 0.01$.
- Group III (44%), no stated P value.
- Group IV (41%), no stated P value.

Delayed Phase (no emesis)
- Group I (29%).
- Group II (63%).
- Group III (51%).
- Group IV (57%).

($P < 0.01$ for groups II, III, and IV vs. group I)

*Summary of results*
- Quality of life (QOL) measure of nausea reviewed from nausea diary as secondary endpoint.
  - Diary with visual analog scale (0-100 mm).
    - No nausea = 0; 100 = nausea as bad as it can get.
- Distribution of scores in delayed period was lower in comparison with Group II vs. Group I ($P < 0.05$ for days 1-5 and days 2-5) **(see Table 6)**.
- During the first 24 hours, the difference between Group II vs. Group I was statistically significant for fewer nausea episodes, $P < 0.05$.
- Delayed phase: Group II was associated with a lower frequency of nausea than Group I, $P < 0.05$.
  - The difference between Group III vs. Group I was statistically significant, $P < 0.05$.
- Delayed (day 2): Frequency of nausea for Groups II, III, and IV was lower than Group I. (The difference of Group IV vs. Group I was statistically significant, $P < 0.05$; other P values were not stated.)

*Global satisfaction (for treatment with cisplatin documented on day 2 and day 6)*
- QOL measure of satisfaction of anti-emetic treatment on a visual analog scale (0-100 mm).
  - 0 = not at all satisfied; 100 = completely satisfied.
- Results for groups I, II, III, and IV on day 2 were 94, 98, 96, and 96, and day 6 were 92, 95,

**Table 6: Campos et al nausea scores**

| Group | Acute and delayed (days 1-5) | Delayed (days 2-5) | Delayed (day 2 alone) |
|---|---|---|---|
| I | 7.5 | 7 | 12 |
| II | 1 | 2 | 4 |
| III | 8.5 | 3 | 5 |
| IV | 9.5 | 3 | 3 |

**Table 7: Strengths and weaknesses of Campos et al trial**

| *Strengths:* | *Weaknesses:* |
|---|---|
| • Multicenter, double-blind, randomized controlled trial.<br>• QOL analysis included.<br>• Intent-to-treat analysis.<br>• Power study to avoid Type II error. | • Parallel group.<br>• No alpha value stated.<br>• No specification as to which labs were evaluated for change. |

96, and 98, respectively.
- There was no statistically significant difference in scores on the scale from 0-100 mm for satisfaction.

*Authors' conclusions*
- Experimental therapy with aprepitant (Group II) displayed decreased incidence of acute and delayed phase emesis as compared to Group I.
- In the acute period, the proportion of patients without emesis was increased by 23% in Group II compared to Group I.
- During the acute phase of emesis, Group II results showed no further benefit vs. Groups III and IV.
- Treatment for Group II showed benefit in the delayed phase to decrease emesis rates.
- Once-daily dosing of aprepitant and standard therapy is sufficient to reduce emesis significantly vs. the standard therapy (Group I).

*Strengths and weaknesses:* Strengths and weaknesses of the Campos et al trial are summarized in **Table 7.**

The two other Phase IIa trials assessed aprepitant in combination with dexamethasone (Van Belle et al) and dexamethasone together with a 5-$HT_3$-RA (Navari et al). These two trials had similar endpoints and design as the Campos trial and are not addressed in detail.

## Summary of important findings of the trials

• During acute and delayed phases, aprepitant as monotherapy or coadministered with corticosteroids shows less efficacy in CINV compared to 5-$HT_3$-RA.

• Once-a-day dosing of aprepitant demonstrated efficacy in CINV.

• Activity of aprepitant in the delayed phase compared to 5-$HT_3$-RA in the acute phase demonstrates distinct mechanisms of emesis during these times.

• Triple therapy of aprepitant, dexamethasone, and 5-$HT_3$-RA on day 1 and aprepitant on subsequent days is more efficacious than the standard therapy without aprepitant (dexamethasone and 5-$HT_3$-RA day 1, and dexamethasone on subsequent days).

## Other trials

Poli-Bigelli et al organized a multicenter, randomized, double-blind, placebo-controlled trial to compare aprepitant in combination therapy with ondansetron and dexamethasone to the standard therapy. In this study, 283 patients were randomized to the aprepitant group, leaving 286 for standard therapy treatment **(see Table 8)**.

Patients reported the frequency of their CINV in a diary over the five-day period for assessment of outcomes: date and time for emesis, and retching. Nausea was evaluated with a visual analogue scale (VAS), and a Functional Living Index-Emesis (FLIE) questionnaire was completed on day 6 for final evaluation. The study ended between day 19 and 29 when the patients returned.

*Result summary for emetic prevention*: The results for complete response, which focused on the four-day duration, was characterized by no emesis and no use of rescue therapy for the overall study time. During the acute phase, the difference between Group 1 and Group 2 was statistically significant for preventing vomiting. During the delayed phase, Group 1 results also showed a statistically significant improvement from Group 2 **(see Table 9)**.

**Table 8: Poli-Bigelli et al — Aprepitant vs. standard therapy**

| Group | Day 1 | Day 2-4 |
|---|---|---|
| Group 1<br>Aprepitant (n = 283) | Oral aprepitant 125 mg, ondansetron 32 mg IV, and oral dexamethasone 12 mg | Oral aprepitant 80 mg and oral dexamethasone 8 mg on days 2-3, and dexamethasone 8 mg on day 4 |
| Group 2<br>Standard therapy (n = 286) | Oral placebo, ondansetron 32 mg IV, and oral dexamethasone 20 mg | Oral dexamethasone 8 mg tablets bid |

**Table 9: Poli-Bigelli et al results for prevention of emesis during specific time periods**

| Endpoint (phase of emesis) | Group 1 | Group 2 | P value |
|---|---|---|---|
| Complete response (days 1-4) | 62.7% | 43.3% | < 0.001 |
| Acute phase (0-24 hours) | 82.8% | 68.4% | < 0.001 |
| Delayed phase (days 2-4) | 67.7% | 46.8% | < 0.001 |

*QOL measure*: The FLIE questionnaire showed more patients in the aprepitant group (74.7%) compared with 63.5% in the standard therapy group having minimal or no impact of CINV on their daily lives.
*Safety*: The most common adverse drug reactions of the aprepitant group compared to standard group were neutropenia (1.8% vs. 2.1%), dehydration (1.6% vs. 0.7%), septic shock (1.1% vs. 0.7%), dyspnea (1.1% vs. 0.7%), and respiratory insufficiency (1.8% vs. 0.45).

*Authors' conclusions*: Poli-Bigelli et al concluded that aprepitant can help in the delayed phase of nausea and vomiting associated with highly emetogenic chemotherapy, such as cisplatin > 70 mg/m$^2$. A more frequent use of rescue medication was observed in the standard group vs. the aprepitant group. Overall side effects were similar in occurrence between the two groups; however, the aprepitant group exhibited a greater incidence of neutropenia, dehydration, septic shock, dyspnea, and respiratory insufficiency.

*Strengths and weaknesses:* Strengths and weaknesses of the Poli-Bigelli et al trial are summarized in **Table 10.**

Chawla et al conducted a multicenter, randomized, double-blind, placebo-controlled study of cisplatin-naïve cancer patients to find an appropriate dose of aprepitant to use with standard CINV prevention therapy. The study group included patients 18 years or older with solid tumors and a Karnofsky score of 60 or more, who would be started on a cisplatin regimen ≥ 70 mg/m$^2$. Patients were excluded if they had other treatment with nonapproved drugs within four weeks of study, or abnormal lab values: WBC < 3,000/mm$^3$, ANF < 1,500/mm$^3$, platelet count < 100,000/mm$^3$, LFTs > 2.5 times upper limit, bilirubin > 1.5 times upper limit, or creatinine > 1.5 times upper limit. Patients

**Table 10: Strengths and limitations of the Poli-Bigelli et al trial**

*Strengths*
- Power study 90% for difference of 15 points between groups.
- Alpha value stated a priori ($\alpha = 0.05$).
- Multicenter, randomized, double-blind, placebo-controlled trial.
- Samples to include cross-continental sites.

*Limitations*
- Reporting bias of nausea and vomiting diary (unblinding with translation).
- Sample exclusion limits aprepitant to narrow population for use.
- Possible confounding use of unclassified emetogenic therapy between groups.

**Table 11: Randomized groups for the Chawla et al study**

| Group | Day 1 | Day 2 | Days 3-5 |
|---|---|---|---|
| 1—Standard therapy (n = 120) | IV ondansetron 32 mg and oral dexamethasone 20 mg | Oral dexamethasone 8 mg | Oral dexamethasone 8 mg |
| 2—Aprepitant 375/250 | Oral aprepitant 375 mg, IV ondansetron 32 mg, and oral dexamethasone 20 mg | Oral aprepitant 250 mg and oral dexamethasone 8 mg | Oral aprepitant 250 mg and oral dexamethasone 8 mg |
| 3—Aprepitant 125/80 (n = 127) | Oral aprepitant 125 mg, IV ondansetron 32 mg, and oral dexamethasone 20 mg | Oral aprepitant 80 mg and oral dexamethasone 8 mg | Oral aprepitant 80 mg and oral dexamethasone 8 mg |
| 2[1]-Aprepitant 40/25 (assessed for study instead of aprepitant 375/250) | Oral aprepitant 40 mg, IV ondansetron 32 mg, and oral dexamethasone 20 mg | Oral aprepitant 25 mg and oral dexamethasone 8 mg | Oral aprepitant 25 mg and oral dexamethasone 8 mg |

Note: The aprepitant 375/250 (Group 2) was canceled for further study and replaced with aprepitant 40/25 (Group 2[1]), due to aprepitant's inhibition of CYP3A4 enzyme and subsequent increase in serum concentration of dexamethasone. $NK_1$ receptor saturation was achieved below 375/250 mg dosing level, and no greater efficacy was documented during an earlier attempt in the study.

**Table 12: Results of the Chawla et al study for prevention of emesis during pre-set phases**

| Endpoint (emesis phase) | Group 1 | Group 2[1] | Group 3 | P value (comparison of Group 3 vs. Group 1) |
|---|---|---|---|---|
| Complete response (days 1-5) | 43.7% | 58.0% | 71.0% | (reported significant difference only) |
| Acute phase (0-24 hours) | 71.4% | 75.6% | 83.2% | P = 0.014 |
| Delayed phase (days 2-5) | 45.2% | 63.9% | 72.7% | < 0.001 (P = 0.02 for Group 2[1] vs. Group 1) |

with CNS malignancy or those who were actively infected were excluded for safety reasons. The primary endpoint was complete response: no emesis and no rescue therapy. Patients were randomized and stratified by gender to either of three groups, with those in Group 1 receiving placebo instead of aprepitant **(see Table 11)**.

*QOL assessment*: Patients kept a diary and assessed their nausea with a visual analog scale for a secondary endpoint.

*Comments*: For each endpoint examined, prevention of emesis in Group 3 was statistically significant compared to Group 1 **(see Table 12)**. Group 2[1] was statistically significant vs. standard therapy (Group 1) for the delayed and complete response, when considering reported P values alone.

*Safety*: Tolerability was assessed for 214 patients receiving aprepitant 125/80 mg dose, 120 patients taking the aprepitant 40/25 mg doses, and 212 patients on standard therapy. The aprepitant 125/80 mg Group 3 had the highest rate of adverse events with a 1.06 relative risk (P = 0.448), and the relative risk of discontinuation due to adverse events was 1.32 (P = 0.804). Incidence of serious clinical adverse events was higher in the aprepitant groups than in the standard therapy: 21.5 % in the aprepitant 125/80 mg (Group 3), 16.7% in the 40/25 mg group (Group 2[1]), and 12.3% in the standard therapy (Group 1). Adverse events common in 10% or more of the patients were fatigue, constipation, diarrhea, nausea, neutropenia, anorexia, headache, and hiccups. Out of 580 patients on study therapy, 131 (22.6%) had one or more laboratory adverse event (specific laboratory values and tests were not stated in the study). Standard therapy had the highest incidence at 8.5%. There was an increased rate of infections, including febrile neutropenia in the aprepitant group at 13% compared to the standard therapy group at 4.2%.

*Authors' conclusions*: Authors concluded aprepitant at either dose level (40/25 mg or 125/80 mg) reduced the rate of emesis at the overall, acute, and delayed phases more frequently than standard therapy. Follow-up on the aprepitant 375/250 mg group showed efficacy similar to the 125/80 mg group, and there were no differences in the occurrence of clinically significant drug interactions between groups. The 125/80 mg aprepitant group displayed improved results for endpoints vs. the 40/25 mg aprepitant group. Tolerability from pooled data indicates the adverse effects reported were similar to population standards for those with cancer. Aprepitant's effect on increasing dexamethasone levels may be linked to greater efficacy and increased incidence of febrile neutropenia.

*Strengths and weaknesses:* Strengths and weaknesses of the Chawla et al trial are summarized in **Table 13**.

Two other Phase III multicenter, randomized, parallel, double-blind, controlled trials (Warr D, et al) evaluated 1,105 patients randomized to aprepitant therapy or standard therapy, and involved six cycles of chemotherapy **(see Table 14)**.

Endpoints of the study were evaluated at the acute phase (0-24 hours), delayed phase (25-120 hours) after cisplatin therapy, and overall (0-120 hours) post-cisplatin therapy for complete response (no emetic episodes and no rescue therapy.) **(See Table 15.)**

**Table 13: Strengths and weaknesses of the Chawla et al trial**

| *Strengths* | *Limitations* |
|---|---|
| • Multicenter, randomized, double-blind, placebo-controlled trial.<br>• Intent-to-treat design.<br>• Power study for 79% (100 patients per group) and $\alpha$ values stated. | • Unblinding due to changing the strengths of aprepitant.<br>• Reporting bias with diary.<br>• Possible confounding due to not knowing the individual effects of drugs used in combination.<br>• Unknown values of labs taken in study for difference between groups. |

**Table 14: Drug regimen for the Warr D et al studies**

| Treatment group | Day 1 | Days 2-4 |
|---|---|---|
| Standard therapy | Dexamethasone 20 mg PO<br>Ondansetron 32 mg IV | Dexamethasone 8 mg PO daily (morning)<br>Dexamethasone 8 mg PO daily (evening) |
| Aprepitant 125/80 mg | Aprepitant 125 mg PO<br>Dexamethasone 12 mg PO<br>Ondansetron 32 mg IV | Aprepitant 80 mg PO daily (days 2 and 3 only)<br>Dexamethasone 8 mg PO daily (morning) |

*Secondary endpoints*: Other endpoints were based on the visual analog scale (0-100 mm) ratings for: complete protection (VAS score < 25 mm), no emetic episodes, no rescue therapy; no emesis (no emetic episodes even with rescue therapy); no nausea, VAS score < 5 mm maximum; and no significant nausea (VAS < 25 mm maximum).

*QOL endpoints*: Quality of life was assessed using the FLIE questionnaire. The primary endpoint on this scale was from 0 to 126 with > 108 defined as minimal or no impact of nausea and vomiting on daily life. Patients had a diary in which to record nausea, vomiting, and use of rescue medication to be evaluated with the FLIE on day 6 of therapy. In this study, more than 108 on the FLIE was achieved by 74% vs. 64% of the aprepitant and standard therapy groups, respectively, P < 0.05. Therapy with cisplatin was repeated for six cycles and evaluated for the frequency of complete response, and achievement of this primary endpoint was found to be significantly higher (P ≤ 0.006) in the group receiving aprepitant, with rates for aprepitant of 61% (n = 516) in cycle 1 and 59% (n = 89) by cycle 6 vs. rates for standard therapy of 46% (n = 522) in cycle 1 and 40% (n = 78) by cycle 6. Adverse events were mild to moderate in intensity for the standard therapy group

**Table 15: Results of the Warr D et al studies**

| Endpoint | Aprepitant group (n = 260) | Standard Therapy (n = 261) | P value (significance) |
|---|---|---|---|
| **Complete response** (no emesis and no use of rescue therapy for overall four-day period) — primary endpoint | 73% | 52% | < 0.001 |
| **Secondary** | | | |
| *Complete response* | | | |
| Acute phase | 89% | 78% | < 0.001 |
| Delayed phase | 75% | 56% | < 0.001 |
| **Complete protection** (no emesis, no rescue, and no nausea, VAS < 25 mm) | | | |
| Overall | 63% | 49% | 0.001 |
| Acute phase | 85% | 75% | 0.005 |
| Delayed phase | 66% | 52% | < 0.001 |
| **No Emesis** (no emetic episodes regardless of rescue therapy) | | | |
| Overall | 78% | 55% | < 0.001 |
| Acute phase | 90% | 79% | 0.001 |
| Delayed phase | 81% | 59% | < 0.001 |
| **No Nausea** (VAS = 0 mm) | | | |
| Overall | 48% | 44% | > 0.050 |
| Delayed phase | 51% | 48% | > 0.050 |
| **No Significant Nausea** (VAS < 25 mm) | 73% | 66% | > 0.050 |
| Overall | 75% | 69% | > 0.050 |

and aprepitant groups, and were pooled from both Phase III studies.

*Authors' conclusions*: The authors conclude that the primary endpoint for complete response was greater in the aprepitant group than the standard therapy for acute and delayed phases, with a $P < 0.001$. First emesis occurred at longer time after cisplatin administration in the aprepitant group than for standard therapy. These studies defined the dosing regimen, combination drugs, optimal time phase effects of aprepitant with combination drugs, and length of treatment. Some weaknesses of the study include reporting bias with the FLIE scale, and use of undefined emetogenic chemotherapy between groups. Strengths include large sample population, multi-regional study, double-blinding, stated alpha value and power, and ability to show difference in groups with a large study population.

## Cost

A complete three-day dose of aprepitant costs approximately $240 using Tri-fold pack units, compared to ondansetron's 32 mg IV one-time dose of approximately $200. A combination therapy with single-dose ondansetron 32 mg IV and three-day aprepitant regimen would cost approximately $440. A dexamethasone oral regimen for four days costs approximately $5-$10.

## Recommendations

Nausea and vomiting are two of the most feared and devastating consequences of chemotherapy, considering the possibility of broken bones, torn esophagus, surgical sutures tears, and overall intolerance of chemotherapy. Patients undergoing highly emetogenic chemotherapy may experience emesis, despite standard antiemetic therapy in 50% of cases. Acute-phase prevention of emesis with standard therapy fails in 25% of patients, and for 50% during the delayed phase, indicating a clear need for CINV standard therapy improvement.

The benefit aprepitant offers is an increase in emesis prevention rate for the acute and delayed phases compared to standard therapy. Studies indicate a different mechanism of action esxists between the acute and delayed phases that could have a link to substance P-$NK_1$ receptor antagonism. Clinical trials tested cisplatin-naïve patients at a highly emetogenic dose of 70mg/$m^2$. Trial data also demonstrate that aprepitant improves secondary measures for nausea prevention and positive outcomes for the effect of CINV on quality of life. As other highly emetogenic drugs were allowed for clinical trial patients, a broad use of aprepitant for CINV might be explored.

Some of the limitations to aprepitant include the potential for drug interactions and adverse events. As a mild inhibitor of CYP3A4, aprepitant has a higher chance of drug interactions than standard therapy alone, so dose reduction of corticosteroids has been suggested as an example intervention. Adverse events were similar between aprepitant and standard therapy with exception of fatigue, constipation, diarrhea, neutropenia, headache, and hiccups. Despite propensity for these adverse events, patients in Phase III trials were able to tolerate aprepitant therapy, and criteria can restrict the use of aprepitant when benefit outweighs the risk.

Another concern is the added aprepitant cost to standard therapy, as three days of aprepitant therapy is approximately $240 compared to about $200 for ondansetron infusion. Even though aprepitant adjunct therapy is more expensive, criteria for judicious use of aprepitant from trial results will help to contain costs and allow benefit for those who meet the need for inclusion. The addition of aprepitant to the formulary for patients who meet the criteria listed below is therefore recommended.

## List of highly emetogenic drugs

*Severe*

- Cisplatin (Platinol), carboplatin (Paraplatin), carmustine (BICNU) — ≤ 250 mg/$m^2$; dactinomycin (Cosmegen), daunorubicin (Cerubidine), doxorubicin (Adriamycin) — > 60 mg/$m^2$, irinotecan (Camptosar), methotrexate (Folex PFS) — > 1 g/$m^2$; procarbazine (Matulane) — PO doses, cyclophosphamide (Cytoxan), cytarabine (Cytosar), dacarbazine (DTIC-Dome), mechlorethamine (Mustargen), and streptozocin (Zanosar).

## Criteria for use

- Start aprepitant even in patients who have not tolerated highly emetogenic therapy in the past.
- Do not use aprepitant for nonchemotherapy-related emesis, such as postoperative, rescue emetic therapy, or radiation-induced emesis.
- Use aprepitant in adults older than 18 years, due to trial exclusion of younger patients.
- Monitor for side effects when aprepitant is co-administered with drugs metabolized by CYP 450 enzymes.
- Do not use aprepitant PRN or as monotherapy.

- Use only in combination with a $5HT_3$-RA ± a corticosteroid, e.g., dexamethasone.

## Resources


- Aprepitant (Emend) for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drugs Ther* 2003;45:62-63.
- Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokini-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001;19:1759-1767.
- Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003;97:2290-2300.
- Cocquyt V, Van Belle S, Reinhardt RR, et al. Comparison of L-758,298, a pro-drug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur J Cancer* 2001;37:823-825.
- GlaxoSmithKline. *Zofran Injection Product Information*. Research Triangle Park, NC; 2001.
- Granisetron (drug evaluation in electronic form). MICROMEDEX Healthcare Series. Englewood, CO: MICROMEDEX; 2003.
- Hansten P, Horn J. *Drug Interactions — Hansten & Horn's Analysis & Management: A Clinical Perspective and Analysis of Current Development*. St. Louis: Wolters Kluwer Health; 2003:347, 878.
- Merck & Co. Emend formulary information request. West Point, PA; 2003.
- Merck & Co. Emend product information. Whitehouse Station, NJ; 2003.
- Ondansetron (drug evaluation in electronic form). MICROMEDEX Healthcare Series. Englewood, CO: MICROMEDEX; 2003.
- Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin-1 receptor antagonist aprepitant to standard anti-emetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090-3098.
- Thomas T. Nausea and Vomiting. In: Dipiro JT, et al. *Pharmacotherapy: A Pathophysiologic Approach.* 5th ed. New York: McGraw-Hill; 2003:247-249.
- Warr D, Gralla RJ, Hesketh, PJ, et al. The oral NK1 antagonist aprepitant for the prevention of chemotherapy induced nausea and vomiting: Two randomized, double-blind, placebo controlled trials. *Proc Am Soc Clin Oncol* 2003;22:726 (abstr 2919). ■