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Tekturna Approved as Novel Antihypertensive by Diana Nguyen

In March 2007, Tekturna (aliskiren) received FDA approval for treatment of hypertension. Briefly, Tekturna is an orally active, direct renin inhibitor and may be used alone or in combination with hydrochlorothiazide, ACE inhibitors or Angiotensin Receptor Blockers (ARBs). In addition to preventing the formation of Angiotensin II, a potent vasoconstrictor, the drug also reduces the amount of plasma renin activity as a result of using ACE-inhibitors or ARBs. Tekturna is poorly absorbed and when taken with a high-fat meal, the amount of drug decreases by 75% to 80%.¹ It is excreted in the urine and metabolized, to an unknown extent, by the liver through the CYP450 pathway. Although Tekturna is excreted in the urine unchanged and metabolized in the liver, the use of this drug is not contraindicated in patients with renal or hepatic impairment.¹ Tekturna is associated with dose related GI adverse effects such as diarrhea, abdominal pain, dyspepsia and gastroesophageal reflux.¹ Tekturna is anticipated to be on the market in Spring 2007. The product will be available as a once daily formulation in strengths of 150 mg and 300

mg. Doses of greater than 300 mg offer only minimal decreases in blood pressure³ and increase the risk of GI side effects. The maximum effect (~80-90%) of Tekturna is obtained within two weeks of starting the medication.

There are several advantages to Tekturna since it is a direct renin inhibitor and blocks the production of renin at the rate limiting step further up in the renin-angiotensin-aldosterone system cascade. Tekturna can be useful in blocking the overproduction of renin as a result of positive feedback from the use of ARBs or ACE-inhibitors. This makes Tekturna a good adjunct to other therapies, such as diuretics, ARBs, ACE inhibitors or calcium channel blockers, if the patient is not responding to monotherapy.³ Pool et al concluded that Tekturna 150 and 300 mg can lower the mean diastolic blood pressure by ~10.3 mmHG and the same doses can lower the mean systolic blood pressure by ~12.1 mmHG.² In addition, the study concluded that there is an additive blood pressure lowering effect when combined with valsartan. The combination of the two has been shown to be safe and most commonly causes headache, fatigue, back pain and diarrhea.²

Although Tekturna has been shown to be efficacious in treating hypertension, there are several disadvantages that may impact the use of Tekturna. It has been theorized that a drug which inhibited the renin-angiotensin-aldosterone system further up in the cascade it could dramatically help control blood pressure. However, an 8 week randomized, placebo-controlled trial enrolling 1123 patients looked at the antihypertensive effects of aliskiren and valsartan alone or in combination. As a result, the study concluded that patients had modest and similar decrease in systolic and diastolic blood pressure, respectively, than compared to valsartan. Therefore, aliskiren

appears to have no greater benefit than valsartan, which has been on the market for a longer time and has been studied more.

Another concern with Tekturna is its association with drug-drug interactions. The product is a substrate for the Cytochrome P450 enzyme, so may interact with other drugs which impact this system. It has been reported that Tekturna increases the AUC and C_{max} of atorvastatin by 50%.¹ In addition, it can decrease the AUC and C_{max} of irbesartan by 50%.¹ Tekturna has also been shown to reduce the effects of furosemide when given concomitantly.¹ Tekturna has a very similar side effect profile to that of ACE inhibitors because of the potential to cause angioedema and an increase in potassium levels,, especially if combined with an ACE inhibitor used in diabetics.¹ Occasional monitoring of potassium levels should be implemented with use of this product.

It is unclear what effect Tekturna will have on the treatment of hypertension. Based on the clinical trials, Tekturna is another choice for the treatment of hypertension, but currently doesn't appear to provide any significant benefit over ACE inhibitors or ARBs. Information on the benefit in comorbidities such as diabetes or heart failure is limited at this time. Further research on this group of medications is warranted.

References

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3. Gradman AH, Schmieder RL, Lins RL et al. Aliskiren, novel orally effective renin inhibitor, provides dose dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation.* 2005;111(8):1012-8.

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Erythropoiesis Stimulating Agents by Rachel Mostek

The FDA issued an alert on March 9, 2007, based off of multiple studies regarding Erythropoiesis Stimulating Agents (ESA). The ESA included are Aranesp® (Darbepoetin), Epogen® (Epoetin Alfa), and Procrit® (Epoetin Alfa). The FDA and the manufacturers have included a new Boxed Warning for the ESA (Figure 1). The FDA also recommends to monitor hemoglobin twice a week for 2-6 weeks after any dosage change and to withhold ESA if the hemoglobin increases above 12 g/dL or rises by 1 g/dL in any 2 week period. For patients with chronic renal failure who are receiving an ESA, monitor hemoglobin twice a week after initiating treatment until hemoglobin has stabilized. Cancer patients and HIV patients receiving zidovudine should have their hemoglobin monitored once a week after start of ESA until hemoglobin has stabilized.¹

Four recent studies evaluated ESA in cancer patients. A Danish Head and Neck Cancer Study Group trial comparing radiation therapy to radiation therapy plus Aranesp® in the treatment of advanced head and neck cancer, found worsening of patients receiving Aranesp® with target hemoglobin 14 to 15.5 g/dL resulting in the termination of the study. Another trial looking at the use of Aranesp® in anemic cancer patients not currently receiving chemotherapy, found that the Aranesp® group had an increase in mortality (Hgb target 12 g/dL). In February, the final results of a study looking at the use of epoetin alpha in anemic non-small cell lung cancer patients currently not on chemotherapy saw a higher incidence of mortality in patients receiving epoetin alpha (Hgb target 12-14 g/dL). Also, in February, a study involving an investigational ESA (pegylated epoetin beta) in patients with Stage IIIB or IV non-small cell lung cancer receiving chemotherapy was suspended due to safety concerns.¹

One study looking at the use of Procrit® in patients undergoing elective spinal surgery, found an increased occurrence of deep venous thrombosis in the Procrit® group.¹

Two recent studies published in the *New England Journal of Medicine* focused on treatment with ESA in chronic renal failure patients (CHOIR and CREATE study). The CHOIR study had target hemoglobin of 13.5 g/dL or 11.3 g/dL. This study showed an increase in serious and potentially life threatening cardiovascular events with the higher target hemoglobin levels. The CREATE study showed cardiovascular events similar to that in the CHOIR study using epoetin beta (not approved in USA).¹

Procrit® and Epogen® are approved for the use in anemia in patients with non-myeloid malignancies due to antineoplastic adverse reactions, in anemia due to chronic renal failure, and in anemia due to a Zidovudine adverse reaction. Both Epogen® and Procrit® are also approved for prophylaxis use in surgical procedures to reduce the need for allogeneic blood transfusion. Aranesp®, on the other hand, is approved for use in anemia due to chronic renal failure and in anemia in neoplastic disease due to chemotherapy.^{3,4,5} Caution should be used when using these agents for non-approved indications.

Figure 1

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of [Aranesp®/EPOGEN®/PROCIT®] that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

[Aranesp®/EPOGEN®/PROCIT®] and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;
- increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when EPOGEN®/PROCIT® is used to reduce allogeneic red blood cell transfusions. Aranesp® is not approved for this indication (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

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FDA Orders Warnings for Sleep Medications by Amy Hupp-Torgusen

The Food and Drug Administration (FDA) has requested that all manufacturers of sedative-hypnotic drug products strengthen their product labeling to include stronger language concerning potential risks. Specifically, these risks are to include severe allergic reactions and sleep-driving caused by somnambulism (sleep walking).

In December of 2006, the FDA requested that the manufacturers of sleep aid products revise their product labeling to specifically include the following two adverse events labeling¹:

- Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling), which can occur as early as the first time the product is taken.
- Complex sleep-related behaviors which may include sleep-driving, making phone calls, and preparing and eating food (while sleeping).

In addition to the updated labeling, the FDA has now requested that manufacturers send letters to health care providers to notify them about the new warning, as well as develop *Patient Medication Guides* given to patients receiving the drugs to advise them of risks and precautions. The letters to the providers started immediately; while the *Patient Medication Guides*, as requested by the FDA, must contain FDA-approved information on the “proper use and recommendation to avoid ingesting alcohol and/or other central nervous system depressants” while taking sedative hypnotic drugs.¹

Somnambulism (sleepwalking) incidents involve complex tasks like driving, preparing and eating food, and having sexual intercourse while asleep, with no memory of the tasks when awakened. Somnambulism does occur on its own, most commonly in childhood because children spend more time in deep sleep stages, whereas older people spend more time in light sleep.² Upon review of the literature, medication-induced sleepwalking is not rare and usually related to fatigue, prior sleep loss, anxiety and reactions to drugs interacting with other drugs or alcohol. Sleepwalking has been reported with lithium, neuroleptics, benzodiazepines, and other sedatives.³ Sleepwalking is a rare side effect of zolpidem and upon review of the literature found only two reported cases⁴

The following is a list of sedative-hypnotic drugs subject to new labeling language:⁵

- Ambien
- Ambien CR (zolpidem tartrate)
- Butisol sodium
- Carbrital (pentobarbital and carbromal)
- Dalmane (flurazepam hydrochloride)
- Doral (quazepam)
- Halcion (triazolam)
- Lunesta (eszopiclone)
- Placidyl (ethchlorvynol)
- Prosom (estazolam)
- Restoril (temazepam)
- Rozerem (ramelteon)
- Seconal (secobarbital sodium)
- Sonata (zaleplon)



Dr. Michael Siber of the Mayo Clinic in Rochester, Minnesota, who first described the effects of sleep-eating and driving in the *Journal of Sleep Medicine* stated, “It’s certainly a minority of Ambien[™] patients who develop problems with either sleep-eating or driving and it generally disappears after the patients stop taking Ambien[™].”⁶ However, like many other doctors, Siber believes all sleeping pills are overprescribed.

References:

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Oral phenylephrine: safe and effective? by Susan Draftz

Concerns about methamphetamine addiction and production in the United States has led to the passing of the Combat Methamphetamine Epidemic Act which requires the “behind the counter” placement of products containing pseudoephedrine.¹ These limitations, which are intended to curb methamphetamine production, have the secondary effect of prompting manufacturers to formulate and market decongestant products that are pseudoephedrine-free. Pseudoephedrine-alternative products have the advantage of being more available to the consumer. Many of these alternative products contain phenylephrine; however, the safety and efficacy of oral phenylephrine is questionable. This substitution was made possible without additional safety and efficacy studies due to a 1976 Food and Drug Administration (FDA) panel which found oral phenylephrine and pseudoephedrine safe and effective for over-the-counter (OTC) use for nasal congestion. Though additional studies are not required, questions have been raised regarding the efficacy of the 10 mg maximum FDA-approved decongestant dose. The *Annals of Pharmacotherapy* recently published a report on the efficacy and safety of oral phenylephrine as a decongestant.²

This investigation involved a thorough literature search for studies (published or unpublished) regarding the effects of oral phenylephrine on nasal airway resistance (NAR) in patients experiencing nasal congestion. This search yielded two groups of studies, those examining the effects of 10 mg phenylephrine and those examining the effects of 25 mg phenylephrine. Studies found were completed between 1959 and 1975. Of the eight studies which reported findings for a total of 138 patients receiving 10 mg phenylephrine, four reported an improvement in NAR with phenylephrine, while the other four found no significant difference from placebo. The results of patient-reported decongestant effects also showed four studies with significant improvement compared to placebo and four studies with no benefit. No significant outcomes on blood pressure or heart rate were observed. The investigators expanded their examination of studies evaluating phenylephrine 10 mg by analyzing an additional eight studies which assessed the effects of 25 mg phenylephrine. These eight studies included 93 patients, and all eight found a positive effect for phenylephrine compared with placebo (random effects estimate 27.6%).²

This meta-analysis did not find 10 mg

oral phenylephrine efficacious for nasal congestion. There is evidence to suggest that higher doses may be effective, which is logical given the poor bioavailability of oral phenylephrine (38%). Overall, the investigators conclude by suggesting a change from “generally recognized as safe and effective” to “requires further testing of efficacy and safety” for oral phenylephrine as a nasal decongestant.²

The findings indicate that patients may not experience adequate relief from phenylephrine-formulated products at the indicated doses. Until more information is available, or the FDA reconsiders the maximum oral dose of phenylephrine, patients may find that purchasing a pseudoephedrine product from the pharmacist behind the counter is a better course of action.

References:

¹Combat Methamphetamine Epidemic Act of 2005 (H.R. 3889, Title VII). <http://www.deadiversion.usdoj.gov/meth/index.html> (accessed 2007 March 26).

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Ibuprofen most effective analgesic in children by Vy Do



A common question that arises in pediatric care is “What analgesic is most effective for a child?” Although studies comparing pain-relievers in children are limited, a new study was recently published in the March issue of *Pediatrics*, revealing that ibuprofen may be the preferred agent.

A randomized, controlled trial enrolled 336 children ages 6-17 yrs who presented to the emergency department with a musculoskeletal injury (to the extremities, neck, or back) that occurred within 48 hours before any analgesic was given. Patients were randomized to receive either 15 mg/kg of acetaminophen, 10 mg/kg of ibuprofen, or 1mg/kg of codeine by mouth.

A visual analog scale, a 100-mm hatched line with “no pain” labeled at one end and “worst pain” at the other end, was used to measure pain. Pain scores were taken before drug administration and every 30 minutes afterwards for 120 minutes. Additional medication was withheld for 60 minutes before another dose could be given since the primary outcome was to measure the effect on a single dose of the analgesic after 60 minutes.

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Ibuprofen, cont. from page 4 Results showed that at 60 minutes, ibuprofen had significantly greater improvement in pain scores (Table 1) and had more patients achieve adequate pain relief (defined as pain score <30 mm) compared to acetaminophen or codeine (Table 2). There was no significant difference between the acetaminophen or codeine group.¹

Table 1: Change of Pain Score from Baseline Table 2: Adequate analgesia (below)

Time (min)	Codeine		Acetaminophen		Ibuprofen		P
	N	Mean Pain Score	N	Mean Pain Score	N	Mean Pain Score	
30	105	-10	103	-7	103	-12	0.230
60	100	-11	100	-12	100	-24	<0.001
90	85	-13	88	-17	90	-29	0.001
120	75	-17	79	-20	83	-31	0.004

*# pts at each time decreased because patients were discharged home and did not f/u

Time	Codeine N (%)	Acetaminophen N (%)	Ibuprofen N (%)	P - Value
60 min	40(40%)	36 (36%)	52 (52%)	<0.001
120 min	39 (52%)	27(47%)	51 (61%)	0.170

In summary, ibuprofen was shown to be superior to acetaminophen or codeine for musculoskeletal pain within an hour for the pediatric patient. No significant adverse effects were reported during the study.¹ However, since the study was conducted for a brief period of time, there is not enough evidence to conclude that ibuprofen will continue to improve pain relief for extended periods of therapy or if risks in adverse effects of longer therapy may potentially outweigh the benefits of using ibuprofen compared to other analgesics.

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FDA Warning on Zyvox (linezolid) by Jennifer Meyer

In March 2007, the FDA issued an alert advising healthcare professionals of new safety concerns regarding the antibiotic Zyvox (linezolid). An open-label, randomized trial compared linezolid, vancomycin, oxacillin, and dicloxacillin for the treatment of seriously ill patients with intravenous catheter-related bloodstream infections including catheter-site infections. The study found that certain patients treated with linezolid had an increased risk of death over those treated with the other antibiotics. Mortality was only higher in linezolid patients who were infected with gram negative organisms alone or both gram positive and gram negative organisms, or were not infected. Linezolid patients with only gram positive infections did NOT have an increased mortality risk. Linezolid is not approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or gram negative infections. The approved indications include vancomycin resistant enterococci (VRE) infections, nosocomial pneumonia and community acquired pneumonia caused by *S. aureus* and *S. pneumoniae*, complicated and uncomplicated skin/skin structure infections including diabetic foot infections without concomitant osteomyelitis caused by *S. aureus*, *S. pyogenes*, or *S. agalactiae*².

The study was designed to compare IV or oral linezolid 600mg every 12 hours to vancomycin IV every 12 hours for 7-28 days. Vancomycin patients could have therapy switched to oxacillin or dicloxacillin if the organism was found to be methicillin-sensitive. Seven hundred twenty-six patients 13 years and up were included, with 363 in each arm. There were an increased number of deaths up to 84 days after the first dose of linezolid compared to the other drugs (21.5% versus 16%). The table below summarizes the deaths by drug and organism.

bloodstream infections, catheter site infections, or gram negative infections. If a gram negative infection is suspected appropriate therapy should be started immediately.

References:

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2. Zyvox [package insert]. New York, NY: Pfizer Inc.; March 2007.

In conclusion, the FDA does NOT recommend the use of linezolid for

	Linezolid (n=363)	Other antibiotic (n=363)
Total deaths	78	58
Gram + only	16.7%	17.2%
Gram – only	26.7%	9.1%
Gram + and Gram -	34.8%	17.9%
No organism	26.3%	13%
Other	25%	16.7%

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Creighton University Drug Information Center
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Editor:

Amy Friedman Wilson, PharmD.
Director of Drug Information Services