



Volume 14 Issue 2
June 2003

Treatment Options for Primary Hypercholesterolemia Including the New Selective Cholesterol Absorption Inhibitor, Ezetimibe

Objectives:

1. Classify the type of patients that are the focus of NCEP's ATP III.
2. Discuss what constitutes metabolic syndrome.
3. Be familiar with the different LDL-C goals of the NCEP's ATP III and which patients fit into the different categories.
4. Describe the advantages and disadvantages of the different therapeutic options for hypercholesterolemia.
5. Summarize the advantages and disadvantages for the use of ezetimibe.

Coronary heart disease caused more than 20% of deaths in the United States in the year 2000. Indirect and direct costs of coronary heart disease in the United States are estimated to be 130 billion dollars.¹ The National Cholesterol Education Program (NCEP) was implemented as a joint effort between the National Institutes of Health and the National Heart Blood and Lung Institute with the goal of reducing the number of Americans with high blood cholesterol.



Krys Modrzejewski is currently the Drug Informatics Resident at the Iowa Drug Information Network. She graduated in 2002 with a Pharm.D. from the University of Iowa College of Pharmacy. She is taking a position with the American Society of Health-System Pharmacists after she completes her residency.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) is an updated clinical guideline from the NCEP for the levels of cholesterol and thresholds for therapy in adults.² Although these guidelines exist, it is reasonable to assume that they are not being followed as optimally as possible in North America or Europe, given the data on morbidity and mortality in recent years.^{3,4} The Lipid Treatment Assessment Project (L-TAP) assessed adult patients with dyslipidemia in the United States and reported that only 38% of patients achieved NCEP-specified low density lipoprotein (LDL-C) goals, and the subcategory that had the hardest time reaching their LDL-C goals were patients with coronary heart disease (CHD).⁴ Although the number of patients with CHD in Europe who are

being treated with lipid-lowering medications increased from 1996 to 2000, more than 50% did not have therapeutic control of their cholesterol levels.³

The recent NCEP guidelines call greater attention to specific groups of people, such as diabetics and others who have multiple risk factors that put them at high absolute risk (>20% in the next 10 years for having a coronary heart disease event). These patients are put into a LDL-C category recommending more aggressive therapy than has been recommended in the past.

LDL-C has always been the focus of treatment to prevent primary myocardial infarction (MI) and as secondary prevention in those with a history of MI. Although this still has not changed, there is a greater emphasis on people who have what is called the metabolic syndrome, a cluster of

IN THIS ISSUE

5 CE ASSESSMENT QUESTIONS

6 KEY REFERENCES FOR NEW DRUGS

7 NEW FDA APPROVALS

8 PERSPECTIVE FROM AN *IDIS* SUBSCRIBER: MEGESTROL (MEGASE): IN THE TREATMENT OF WASTING SYNDROME IN THE ELDERLY-SAFETY CONCERNS

11 INTRODUCING: PIVOTAL STUDIES

12 NEW DESCRIPTOR: 163 MODIFICATION OF EFFECT SEX/GENDER

lipid related risk factors and other risk factors that are metabolic in nature. Overweight, sedentary people with insulin resistance are prone to the development of metabolic syndrome and generally have high blood pressure, elevated triglycerides (>150 mg/dl), and abdominal obesity (men >40 inches and women >35 inches). This is addressed in ATP III as well.

There are three general categories of CHD risk: low, average, and high, and there is a corresponding LDL level for all of them. Patients at low risk have 0-1 risk factors (Table 1.) and a threshold LDL value of 160 mg/dl. Although less than 130 mg/dl is ideal, these patients have a very low risk of a CHD event, and unless the clinical situation is indicative of more serious risk than might be originally based on risk factors, they generally are not treated with drug therapy until they reach 190 mg/dl.

Patients with 2 or more risk factors and a 10-year risk of <10% have a LDL-C goal of <130 mg/dl. Drug therapy at this stage may not be cost-effective, but can reduce long-term risk.

Patients with 2 or more risk factors and a 10-year risk of 10-20% also have a goal of LDL-C of <130 mg/dl. Drug therapy at this stage is directed toward decreasing short- and long-term risk for CHD and is cost-effective to use.

Patients who have **coronary heart disease** or patients who have **diabetes** have the same level of risk — high. ATP III treats diabetes as a CHD risk equivalent because the absolute risk of developing CHD in these patients is equal to the risk of patients who have already had a coronary event. Other patients that have a CHD equivalent are patients with **peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease**. These are all forms of **atherosclerotic disease** that have a high level of risk. Also in this category are people with **multiple risk factors that confer a >20% risk of CHD in the next 10 years**.

Table 2.
Framingham Scoring

Point Total Men	Men 10-Year Risk, %	Point Total Women	Women 10-Year Risk, %
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	> or = 25	> or = 30
> or = 17	> or = 30		

Table 1.
Risk Factors used to Determine LDL Goals

Positive Risk Factors:

- Cigarette smoking
- Hypertension (blood pressure > 140/90 mmHg or on medication)
- Low HDL cholesterol (<40 mg/dl)
- Family history of premature CHD (in male first-degree relative less than 55 years old, in female first-degree relative less than 65 years old)
- Age (men > 45 years; women > 55 years)

Negative Risk Factor:

- HDL >60 mg/dl (counts as -1 when adding risk factors)

Risk Category	LDL Goal
CHD or CHD equivalent	<100 mg/dl
Multiple risk factors (2+)	<130 mg/dl
0-1 risk factors	<160 mg/dl

If a patient has CHD (or the equivalent) or 0-1 risk factors, then it is not necessary to calculate their 10-year risk. If, however, the patient has multiple risk factors, then 10-year risk is assessed with Framingham scoring (Table 2.). Framingham scoring divides risk into three categories, >20%, 10-20%, <10%. The Framingham score helps to determine the level of risk, which then determines LDL-C goals.

Non-pharmacologic interventions are available. Dietary therapy can be followed to decrease cholesterol levels. Exercise, in addition to the benefits that it provides for weight loss or maintenance, can also help modify lipid profiles (raises HDL and decreases very low density lipoproteins (VLDL) concentrations); however, if both of these strategies are unsuccessful, there is pharmacologic therapy.⁵

The hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or the “statins” are generally the first choice for drug therapy to reduce LDL-C. On the US market right now there are five statins: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Rosuvastatin is currently in phase III clinical trials. These agents work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme involved in de novo cholesterol synthesis. Biosynthesis in the liver accounts for 60-70% of total cholesterol pool, so it does not completely inhibit cholesterol synthesis.⁶ The decrease in the amount of cholesterol in the liver causes the LDL receptors to upregulate. This results in 19-51% lower LDL-C levels.⁷ Statins also decrease the synthesis and secretion of VLDL and intermediate-density lipoprotein.⁸ Triglycerides (TG) have been lowered with statin monotherapy proportional to the LDL-lowering capabilities of the individual statin and to the patient’s baseline TG level. They also can raise HDL-C, although not as effectively as they lower LDL-C.⁹ Pravastatin is the only statin not metabolized by the P450 system and is useful in patients who might need to avoid drug interactions.⁶

Liver enzymes need to be monitored with statins as they are known to elevate liver enzymes and cause myopathy. Myopathy occurs in 0.1% of patients. Elevated liver enzymes greater than 3 times the upper limit of normal occur in 1% of patients. If elevated liver enzymes occur, the liver enzymes do generally return to normal 2-3 months after discontinuation of drug therapy.⁹

Colestipol, colestevlam, and cholestyramine are the bile acid sequestrants currently available in the US. They decrease LDL-C by 11-30% and increase HDL.¹⁰ Triglycerides can be increased with resins. They bind bile acids in the intestine so they form a complex that can be excreted in the feces. Bile acid sequestrants are used as an alternative to statins in managing dyslipidemias. They can also be used in combination with another therapy when lipid goals are not met. Sequestrants should not be used in patients with elevated TG. The most common adverse effects are GI, including constipation which can be controlled with a high fiber diet, increased fluids, and possibly a stool softener. Less common adverse effects include, nausea, vomiting and diarrhea, and general abdominal discomfort.¹¹

Niacin is available as an immediate release and an extended release product. At normal daily doses, it can be used to reduce LDL and VLDL. It can decrease total cholesterol, LDL, VLDL, and TG concentrations and increase HDL levels. Niacin can be used in primary hypercholesterolemia and mixed dyslipidemia. It can be used as adjunct or single agent pharmacologic therapy in patients with hypertriglyceridemia.² The extended release formulation is thought to be better tolerated than the immediate release because of decreased incidence of flushing, GI upset, and pruritus.¹² Administration of aspirin 325 mg 30 minutes before taking niacin may help to reduce flushing. Most of the side effects appear to lessen within 2-6 weeks of chronic therapy. Liver functions need to be monitored.⁷

The fibric acid derivatives, gemfibrozil, fenofibrate, and clofibrate, are considered possible therapy in patients with highly elevated triglycerides (>500 mg/dl).^{2,13} In general, the fibric acid derivatives decrease triglycerides, increase HDL,

and may either increase or decrease LDL-C. Their mechanism of action has yet to be fully elucidated. Clinical trials have shown that the fibric acid derivatives are useful in patients with hypertriglyceridemia and low high-density lipoproteins.¹³

Ezetimibe, Zetia™, is a relatively new agent on the US market, approved by the FDA on October 25, 2002, for the treatment of hypercholesterolemia. It inhibits dietary and biliary cholesterol absorption at the brush border of the intestine.¹⁴ Ezetimibe has been shown to reduce the intestinal absorption of cholesterol in humans by 54% relative to placebo, which, after a compensatory increase in cholesterol synthesis, resulted in a 22.3% reduction in plasma LDL concentrations.¹⁵ The increase in hepatic synthesis of cholesterol by ezetimibe and statins administered together may produce the favorable effect on LDL-C. Ezetimibe is glucuronidated in the intestine, and both ezetimibe and the glucuronidated metabolite are recycled, returning to the intestine to then be active again.¹⁶ The glucuronidated metabolite is thought to be more active than the parent molecule.^{17,18} Ezetimibe has a long half-life that allows for once-daily administration.¹⁶ Ezetimibe is not metabolized by the cytochrome P450 enzymes, so it does not appear to have clinically important interactions with other drugs.¹⁹ Many of the studies published have evaluated its efficacy and safety in treating primary hypercholesterolemia and homozygous familial hypercholesterolemia.^{14,20-24} Patients using ezetimibe 5mg or 10mg as monotherapy saw LDL-C decrease from 15.7%-18.5%, and HDL-C increases of 2.9-3.5%, compared to placebo in one trial.²¹ Another monotherapy trial conducted with ezetimibe 10 mg noted a 16.9% drop in LDL-C versus a 0.4% increase in the placebo group and 1.3% increase in HDL-C, versus a 1.6% drop in the placebo group.²² Studies have also investigated ezetimibe as adjunct therapy with a statin.^{14,20,23,24} In one study the LDL-C levels decreased by 9.9-18.7% and in another by 13.8%-18.2% following 12 weeks of ezetimibe therapy compared with placebo therapy (both p<0.01).²¹ Other cholesterol lowering medications, such as bile acid resins and pancreatic lipase inhibitors, unfavorably alter triglyceride profiles and can also inhibit the absorption of fat-soluble vitamins, which ezetimibe does not do.^{17,25}

There are no recommendations in the prescribing information about monitoring for adverse effects of ezetimibe therapy; however, in the clinical trials, laboratory tests performed included liver enzymes (AST and ALT), creatine phosphokinase, routine chemistries, urinalyses, tests of renal function, hematologic parameters, and electrocardiographic changes.^{14,20-24,26} Ezetimibe is primarily viewed as adjunct therapy with statins, and therefore, when part of that regimen, all the monitoring parameters are similar to that of statins. It remains to be seen whether these lab tests will be recommended when using ezetimibe as monotherapy.

Although combination therapy with statins and fibrates has been successful for treating combined hyperlipidemia, using fibric acid derivatives with statins increases the risk of myopathy and fatal rhabdomyolysis. A recent review determined an incidence of 0.12% for myopathy associated with the combination, which is relatively rare.²⁶ Ezetimibe offers another combination option for patients and prescribers.

In the future, we will probably see further research with ezetimibe and other lipid-modifying drugs. As research continues to show the value of lowering LDL-C levels and other lipid parameters, it appears that ezetimibe is one of the safer and better tolerated drugs in the cholesterol fighting armamentarium.

Reference List

1. American Heart Association. Heart disease and stroke statistics-2003 update. www.americanheart.org (accessed 2003 May 8).
2. Cleeman JJ, Grundy SM, Becker D et al. Executive summary of the third report of the national cholesterol education program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). *JAMA* 2001; 285(19):2486-2497. (IDIS Article 464555)
3. Kotseva K, Wood D, De Backer G et al. Clinical reality of coronary prevention guidelines: A comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001; 357(9261):995-1001. (IDIS Article 461848)
4. Pearson TA, Laurora I, Chu H et al. The lipid treatment assessment project (L-TAP). A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; 160(4):459-467. (IDIS Article 443635)
5. Rosengren A, Wilhelmsen L. Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Goteborg. *Ann Epidemiol* 1997; 7(1):69-75.
6. Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? *Pharmacol Ther* 1998; 80(1): 1-34.
7. Cardiovascular Drugs: HMG CoA Reductase Inhibitors. AHFS Drug Information McEvoy GK, ed. Bethesda: STAT!Ref, 2003.
8. Chong PH. Lack of therapeutic interchangeability of HMG-CoA reductase inhibitors. *Ann Pharmacother* 2002; 36(12):1907-1917. (IDIS Article 490160)
9. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000; 101(2):207-213. (IDIS Article 442050)
10. Schechtman G, Hiatt J. Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996; 125(12):990-1000. (IDIS Article 378007)
11. Steinmetz KL. Colesevelam hydrochloride. *Am J Health-Syst Pharm* 2002; 59(10):932-939. (IDIS Article 481202)
12. Cardiovascular Drugs: Miscellaneous Antilipemic Agents. AHFS Drug Information McEvoy GK, ed. Bethesda: STAT!Ref, 2003.
13. Rader DJ, Haffner SM. Role of fibrates in the management of hypertriglyceridemia. *Am J Cardiol* 1999; 83(S9B):30F-35F. (IDIS Article 429827)
14. Gagne C, Gaudet D, Bruckert E et al. Efficacy and safety of ezetimibe coadministered with atorvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002; 105(21):2469-2475. (IDIS Article 482036)
15. Sudhop T, Lutjohann D, Kodal A et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; 106(15):1943-1948. (IDIS Article 490884)
16. Ezzet F, Krishna G, Wexler DB et al. A population pharmacokinetic model that describes multiple peaks due to enterohepatic recirculation of ezetimibe. *Clin Ther* 2001; 23(6):871-885. (IDIS Article 467647)
17. van Heek M, Farley C, Compton D et al. The potent cholesterol absorption inhibitor, ezetimibe, is glucuronidated in the intestine, localizes to the intestine, and circulates enterohepatically. *Atherosclerosis* 2000; 151(1):155.
18. Zhu Y, Statkevich P, Kosoglou T et al. Effect of SCH 58235 on the activity of drug metabolizing enzymes in vivo (abst). *Clin Pharmacol Ther* 2000; 67:152.
19. Davidson MH, McGarry T, Bettis R et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002; 40(12):2125-2134. (IDIS Article 491163)
20. Dujovne CA, Ettinger MP, Mcneer JF et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002; 90(10):1092-1097. (IDIS Article 490188)
21. Bays HE, Moore PB, Drehobl MA et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin Ther* 2001; 23(8):1209-1230. (IDIS Article 469323)
22. Gagne C, Bays HE, Weiss SR et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002; 90(10):1084-1091. (IDIS Article 490187)
23. Kerzner B, Corbelli J, Sharp S et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol* 2003; 91(4):418-424. (IDIS Article 495185)
24. Knopp RH, Bays H, Manion CV et al. Effect of ezetimibe on serum concentrations of lipid-soluble vitamins. *Atherosclerosis Supplements* 2001; 2(2):90.
25. Kosoglou T, Meyer I, Veltri EP et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. *Br J Clin Pharmacol* 2002; 54(3):309-319. (IDIS Article 489553)
26. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; 35(8):908-917. (IDIS Article 467909)



Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-03-019-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation, and return to Division of Drug Information Service with a \$5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists must complete this program by December 1, 2004 to receive credit.

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

ACPE # 020-000-03-019-H01

TREATMENT OPTIONS FOR PRIMARY HYPERCHOLESTEROLEMIA INCLUDING THE NEW SELECTIVE CHOLESTEROL ABSORPTION INHIBITOR, EZETIMIBE

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date _____

(circle the correct answer)

1. The new National Cholesterol Education Program guidelines calls greater attention to all groups listed below EXCEPT?
 - a. diabetics
 - b. patients who are at high absolute risk (>20% risk of having a coronary heart event in the next 10 years)
 - c. patients who have a LDL-C level of 100-130
 - d. patients with multiple risk factors (>2 risk factors)
2. All of the following are positive risk factors for CHD EXCEPT?
 - a. HDL level > 60 mg/dl
 - b. Age of > 55 for women and >45 for men
 - c. Cigarette smoking
 - d. Hypertension (> 140/90 mmHg or medicated for hypertension)
3. Statins affect VLDL by
 - a. decreasing the synthesis and secretion of VLDL
 - b. decreasing LDL concentrations, which increases VLDL production
 - c. increasing the amount of receptors on the liver cell to decrease VLDL concentrations
 - d. lowering HDL production which increases VLDL production
4. Biosynthesis in the liver accounts for how much of the production of the total cholesterol pool?
 - a. 3-5%
 - b. 15-20%
 - c. 60-70%
 - d. 90-100%
5. Myopathy with statins occurs in what % of patients?
 - a. 0.1%
 - b. 1%
 - c. 5%
 - d. 7%
6. What antilipidemic should not be used to lower triglycerides?
 - a. atorvastatin
 - b. cholestyramine
 - c. niacin
 - d. ezetimibe
7. What is generally considered the first-choice pharmacologic therapy in patients with elevated LDL-C levels?
 - a. statins
 - b. niacin
 - c. gemfibrozil
 - d. cholestyramine
8. Ezetimibe works to decrease LDL-C levels by
 - a. inhibiting dietary and biliary cholesterol absorption at the brush border of the intestine
 - b. forming a non-absorbable complex with cholesterol
 - c. increasing the LDL-receptors on the liver cell
 - d. None of the above
9. Metabolic Syndrome is a constellation of all of the following factors EXCEPT:
 - a. elevated triglycerides (> 150 mg/dl)
 - b. abdominal obesity (men >40 inches; women >35 inches)
 - c. hypertension (>140/90 or on medication)
 - d. family history of CHD
10. Ezetimibe inhibits absorption of fat soluble vitamins.
 - a. true
 - b. false

PROGRAM EVALUATION

	Excellent				Poor	
Overall quality	5	4	3	2	1	
Relevance to practice	5	4	3	2	1	
Value of content	5	4	3	2	1	
Important to pharmacists	Agree				Disagree	
	5	4	3	2	1	
Increased my knowledge	5	4	3	2	1	
Achieved stated objectives	5	4	3	2	1	
Was educational and not promotional	5	4	3	2	1	

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Drugs: Key References

This new drug bibliography provides a selection of key critical studies and reviews of new drugs approved by the FDA March 2003 through May 2003. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses.

Aprepitant

Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001;19:1759-1767.

(*IDIS* Article Number 462128)

A multicenter, double-blind, parallel-group study of 351 patients found MK-869 (aprepitant), at oral doses of 300 mg and 400 mg, to be effective in reducing cisplatin-induced delayed nausea and emesis.

Enfuvirtide

Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J* 2002;21:653-659. (*IDIS* Article Number 487366)

This pediatric cohort study compared subcutaneous doses of 30 mg or 60 mg of T-20 (enfuvirtide) in HIV-1 infected children 4-12 years of age.

Zhang X, Nieforth K, Lang J-M, et al. Pharmacokinetics of plasma enfuvirtide after subcutaneous administration to patients with human immunodeficiency virus: Inverse Gaussian density absorption and 2-compartment disposition. *Clin Pharmacol Ther* 2002; 72:10-19. (*IDIS* Article Number 484779)

Twelve HIV-infected patients participated in this randomized, 4-way cross-over study of the pharmacokinetics of 90 mg intravenous doses and 45 mg, 90 mg and 180 mg subcutaneous doses of enfuvirtide.

Gemifloxacin mesylate

Lode L, File, Jr, TM, Mandell L, et al. Oral gemifloxacin versus sequential therapy with intravenous ceftriaxone/oral cefuroxime with or without a macrolide in the treatment of patients hospitalized with community-acquired pneumonia: a randomized, open-label, multicenter study of clinical efficacy and tolerability. *Clin Ther* 2002;24:1915-1936. (*IDIS* Article Number 490967)

This multicenter, open-label study randomized 345 patients to either gemifloxacin 320 mg orally once a day for 7-14 days, or ceftriaxone 2 g intravenously once a day for 1-7 days then cefuroxime 500 mg orally twice a day for 1-13 days for a total of 14 days or less and found comparable clinical efficacy between the two regimens.

File, Jr, TM, Schlemmer B, Garau J, et al. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: a randomized, double-blind comparison with trovafloxacin. *J Antimicrob Chemother* 2001;48:67-74. (*IDIS* Article Number 467735)

Gemifloxacin was found to be well tolerated and effective in this multicenter, randomized, double-blind, parallel group study of 571 patients with community-acquired pneumonia comparing 7-14 days of 320 mg gemifloxacin or 200 mg trovafloxacin orally once a day.

Pegvisomant

Sesnilo G, Fairfield WP, Katznelson L, et al. Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. *J Clin Endocrinol Metab* 2002;87:1692-1699. (*IDIS* Article Number 481970)

In a 3-part, placebo-controlled study, 48 patients with acromegaly were randomized to 12 weeks of once daily subcutaneous injections of 10, 15 or 20 mgs pegvisomant or placebo. In the longitudinal study, 83% of patients randomized to pegvisomant 20 mg per day achieved normal IGF-1 (insulin-like growth factor 1) levels.

Trainer PJ, Drake WM, Katznelson L, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 2000;342:1171-1177. (*IDIS* Article Number 444363)

Use of the study drug, pegvisomant, was found to result in clinical improvement in this 12-week, randomized, double-blind study that investigated three different doses of pegvisomant, 10 mg, 15 mg or 20 mg, or placebo, given subcutaneously in 112 patients with acromegaly.



Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a Pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug and Descriptor vocabulary and contributing articles for the *World of Drug Information* newsletter.

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	Valid IDIS Disease Term Modified ICD-9-CM Number
Aprepitant (1P)***** <i>Emend</i>	Merck (Mar. 26)	APREPITANT 28160445 (11 citations)	Prevention of acute and delayed nausea and vomiting associated with emetogenic chemotherapy.	Nausea and Vomiting 787.0
Bortezomib + <i>Velcade</i>	Millennium Pharmaceuticals, Inc. (May 13)	BORTEZOMIB 10120216 (3 citations)	Multiple myeloma.	Myeloma, Multiple 203.
Enfuvirtide (1P)**** <i>Fuzeon</i>	Roche (Mar. 13)	ENFUVIRTIDE 8180807 (6 citations)	Treatment of HIV-1 infection.	Syn-Acq Immune Deficiency 042.
Gefitinib + <i>Iressa</i>	Astra Zeneca (May 5)	GEFITINIB 10120192 (19 citations)	Non-small cell lung cancer.	NEOP, MGN-Bronchus/Lung 162.
Gemifloxacin Mesylate (1S)*** <i>Factive</i>	LG Life Sci (Apr. 4)	GEMIFLOXACIN 8122032 (25 citations)	Treatment of acute bacterial exacerbation of chronic bronchitis and community-acquired pneumonia caused by susceptible microorganisms.	Bronchitis, Acute 466.0 Pneumonia, Bacterial NEC 482.
Laronidase (BIOL) <i>Aldurazyme</i>	Biomarin Pharmaceutical Inc. (Apr. 30)	ALRONIDASE 44000002 (1 citation)	Hurler and Hurler-Scheie forms of mucopolysaccharidosis I and moderate to severe symptoms of the Scheie form.	Mucopolysaccharidosis 277.5
Pegvisomant (1PV)**** <i>Somervert</i>	Pharmacia and Upjohn (Mar. 25)	PEGVISOMANT 68280202 (19 citations)	Treatment of acromegaly.	Acromegaly and Gigantism 253.0

* Through May 2003 Update. Complete bibliographic citations will be provided upon request.

** Not applicable.

*** New molecular entity given standard review by FDA.

**** Designated orphan drug.

***** New molecular entity given priority review.

+ Accelerated Approval.

Additional information on these newly approved drugs will be available in the FDA Approval Package [an official United States Food and Drug Administration (FDA) document] that is compiled for new drugs following approval. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are indexed and included as part of the *IDIS* database. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

Megestrol (Megace): In the treatment of wasting syndrome in the elderly – safety concerns

Perspective from an



IDIS Subscriber

Megestrol is a synthetic progesterone analog, originally developed for use in hormone sensitive carcinomas of the breast or endometrium. It is now also indicated for the palliative treatment of cachexia associated with AIDS and malignancy. Because of its ability to improve appetite, caloric intake, and nutritional status in cancer and AIDS patients, megestrol is now commonly used in hospitalized and nursing home dwelling elderly patients in the United States with unintentional weight loss. It is generally considered to be well tolerated in the short term, with some excess edema and the risk of thromboembolic events as potential complications. Because megestrol has not demonstrated any effect on survival or provided a “substantial” benefit to the quality of life in patients with cancer or AIDS, in the opinion of some groups, its high cost has made its use controversial. Recent reports of serious adverse outcomes possibly associated with megestrol have renewed interest in its risk-benefit ratio.

The possible relationship of megestrol to weight gain began with the clinical observation that approximately 30% of patients who received megestrol, in conventional doses of 160 mg daily, for advanced breast cancer experienced weight gain as a side effect of therapy.^{1,2}

Early Trials

Aisner and colleagues³ conducted a phase I-II trial of escalating doses of megestrol to evaluate the dose response relationship in the treatment of breast cancer. The first evaluations of this trial demonstrated considerable weight gain in patients receiving higher doses of megestrol regardless of response to therapy or disease severity. The median weight gain for 28 patients treated for at least seven weeks was 5.1 kg (range 0.9-20.1 kg). The evaluators believed the weight gain was caused by tissue mass rather than edema. No patient developed cushingoid features. Weight gain was present in five of six patients with no antitumor response and was considered not to be dependent on antitumor activity.

The same group conducted a phase III trial of megestrol in patients with advanced incurable cancer other than breast or endometrial cancer.⁴ Patients were randomly assigned to receive 160 mg, 480 mg, 800 mg, or 1280 mg of megestrol daily. Patient perceived fluid retention related to megestrol was a common finding in 19 of 88 in the 160 mg group, 33 of 86 in the 480 mg group, 31 of 85 in the 800 mg group, and 19 of 83 in the 1280 mg group. The

investigators believed that the fluid retention could have been related to the patients' disease or other drugs. In the remaining patients, without clinical evidence of edema or ascites, the weight gain associated with increased appetite appeared to be due to increases in body mass, not excess fluid accumulation. They did not find any dose response effect for edema. They concluded that 160 mg of megestrol daily was a reasonable dose for use in the treatment of cancer anorexia/cachexia. The small incremental benefit in appetite stimulation of higher daily doses did not justify the cost of the higher doses in routine clinical practice. There was a trend for more thromboembolic events in patients randomized to higher doses. Similar trends were reported in two previous dose-response trials in women with breast cancer.^{5,6}

AIDS Trials

Two randomized placebo controlled clinical trials were completed in which high doses of megestrol were given to AIDS patients. Both trials chose weight gain as the primary objective end point of treatment. Both trials also included a questionnaire to assess the patients' perception of well being. One trial⁷ compared three different

megestrol dose levels with placebo and the other⁸ compared the highest dose level in the first trial, 800 mg per day, with placebo. The treatment period in both trials was 12 weeks. Both trials reported almost identical weight gain of 3.63 kg at the 800 mg dose level. Both studies reported an increase in daily caloric intake of greater than 600 calories per day. Body composition measurements indicated the weight gain was not related to water retention but primarily related to increased levels of stored fat. In both trials the nine-question scale used to assess patient perception of well being consistently favored megestrol to placebo, with the most favorable response at the highest daily dose. Although one of the investigators recommended treatment of all AIDS patients with persistent weight loss of 5% or more of ideal body weight with megestrol, the issue of which AIDS patients to treat and the effects, if any, of treatment on functionality or survival remained unanswered.

Glucocorticoid like activity of Megestrol

Mann and colleagues⁹ reviewed adverse drug experience reports submitted to the FDA from 1984-1996 for cases of Cushing's syndrome, diabetes mellitus, and adrenal

insufficiency associated with megestrol. Five cases of Cushing's syndrome were reported in association with megestrol use, one was taking 160 mg daily, one 160-320 mg daily and three 800 mg or more daily. All cases were reported in women, four of whom had cancer. All five patients had taken megestrol for at least nine months. Two patients improved clinically after megestrol dosage was reduced or its use discontinued. One patient did not improve despite stopping megestrol use and no information was available for the fifth patient. In two cases the response to corticotropin was consistent with adrenal insufficiency.

Twelve cases of new onset diabetes mellitus were reported in association with megestrol use. Seven patients were men with AIDS, four were women with cancer and one was a man with prostate cancer. In patients for whom data was available, megestrol daily dose ranged from 80 to 800 mg and the duration of therapy ranged from three weeks to five months. Two patients had diabetic ketoacidosis. Four patients required hospitalization and discontinuation of megestrol. The diabetes resolved in three patients who discontinued megestrol treatment. Follow up

information was unavailable for the remaining five patients. Twelve cases of exacerbation of preexisting diabetes in association with megestrol use were reported. In one case the presentation was diabetic coma.

Sixteen cases of adrenal insufficiency in association with megestrol were reported. Four in AIDS patients, eight in men with prostate cancer, and four in women with breast cancer. The duration of megestrol therapy ranged from six weeks in one patient to four months or more in six patients, and nine patients had an unknown duration of therapy. Megestrol doses ranged from 60 to 320 mg daily for nine patients and from 800 to 1600 mg daily in three patients. All patients had symptoms consistent with adrenal suppression, including nausea, vomiting, dizziness or hypotension, weight loss or profound fatigue. All patients had some laboratory data consistent with adrenal suppression. Five patients experienced symptoms within days or weeks of reducing or discontinuing megestrol use and eleven experienced symptoms while continuing megestrol use. All patients required treatment with replacement doses of steroids and improved while receiving steroid therapy. An additional seventeen cases were suggestive of adrenal insufficiency, most had no symptoms or vague dizziness or weakness. All patients had low serum cortisol levels. Although some of the reported cases had missing confirmatory data, the authors believed the evidence supporting glucocorticoidlike activity for megestrol was compelling.

In 1982 it was reported that megestrol had greater affinity for the glucocorticoid receptor on human mononuclear leukocytes than the naturally occurring ligand cortisol, 46% relative binding affinity versus 25%.¹⁰ Preclinical studies in the cat confirmed the glucocorticoidlike activity of megestrol. Loprinzi and colleagues¹¹ subsequently studied pituitary adrenal axis function in patients on megestrol 160 or 800 mg daily. They found that serum cortisol concentrations were consistently depressed in patients on 800 mg

of megestrol daily and were often reduced in patients on 160 mg daily when treated for more than six weeks. Eleven of 122 patients on megestrol plus chemotherapy for late stage small cell lung cancer versus 5 of 121 patients who did not receive megestrol died of sepsis. The authors hypothesized that inadequate adrenal function related to megestrol use might have been responsible.¹²

Subramanian and colleagues¹³ described a breast cancer patient who reported extreme fatigue after several months of improvement while on megestrol for treatment of bone metastasis. There was no indication of disease progression. She described her fatigue as so severe that she could not walk or perform any activities of daily living other than sitting on a sofa. She was noted to have a reduced blood pressure and her plasma cortisol level was low. She discontinued the megestrol therapy and reported improvement in her ability to perform her activities of daily living and in her feeling of fatigue. A repeat cortisol level obtained several months later was normal. Her experience prompted them to look at other patients receiving megestrol for metastatic breast cancer. Initially they obtained cortisol levels only when patients complained of fatigue or had hypotension. Of thirty-nine patients in the original group, sixteen had normal cortisol levels, thirteen had low levels and ten were not tested. If the cortisol level was low, a rapid corticotropin stimulation test was performed. All thirteen patients with low cortisol levels had normal activity levels when megestrol therapy was begun. All patients received the usual dose or oral megestrol 40 mg four times daily. Clinical manifestations of adrenal insufficiency were observed in all patients, except two long-term survivors, within a few months (range 2-72 months). The presentation was of profound fatigue and weakness in all thirteen patients. Hypotension defined as a drop in systolic pressure of 30 mm Hg compared with baseline systolic blood pressure or mean arterial pressure of less than 60 mm Hg was present in 8 of the

13 patients. Adrenal metastases were excluded by computed tomography. Adrenal insufficiency secondary to megestrol was diagnosed and 11 patients were treated with prednisone 5 to 12.5 mg daily. All improved clinically in two to three months. Two months after megestrol was withdrawn, corticotropin stimulation test results indicated normal adrenal function in two patients. They recommend screening for adrenal insufficiency whenever profound fatigue occurs on a patient receiving megestrol therapy and gradual withdrawal of megestrol therapy to avoid acute adrenal insufficiency.

Thrombotic Events Associated with Megestrol

The FDA had received ninety-two reports on 90 patients who had venous thrombotic events while on megestrol from January 1970 through October 1977.¹⁴ Thirty-eight patients were considered to have deep vein thrombosis, 45 pulmonary emboli, and seven various other vascular occlusions. Most of the thrombotic events occurred within three months of initiation of megestrol therapy. The mean daily megestrol doses in AIDS patients with thrombosis was 571 mg daily and in non-AIDS patients was 950 mg daily. When three outliers given high experimental doses were excluded, the mean daily doses for the patient groups were similar, 571 mg in the AIDS group and 514 mg in the non-AIDS group.

In the period from 1984 through early 1998, 1538 HIV (human immunodeficiency virus) infected patients received care at the Veterans Administration hospital in Washington DC representing over 7000 patient-years. Megestrol was prescribed to 129 cachectic AIDS patients for approximately 98 patient-years. Deep vein thrombosis was not described in any of the AIDS patients who did not receive megestrol. Among the 129 patients on megestrol, 11 developed venous thrombi. The retrospective nature of the review and voluntary nature of case reporting preclude any comment relating to direct causation.

There was only one case of deep venous thrombosis among 371 patients, randomized to megestrol in three major randomized trials, who were followed for 12 weeks.¹⁵ There have been fewer thromboembolic events reported in patients using megestrol for AIDS wasting than for malignancy. The majority of cases occurred within three months of megestrol initiation. A few cases occurred within two weeks of beginning therapy.

Recently Bennett¹⁶ reported deep venous thrombosis in 6 of 19 nursing home patients using megestrol for periods exceeding 50 days. He believes the issue of megestrol's safety in long term use is unresolved.

Thrombotic Events Associated with Other Progestins

The recently completed HERS II study of 2763 postmenopausal women with established coronary disease found that treatment with estrogen plus progestin did not reduce the rate of coronary heart disease events.¹⁷ HERS II also found a two to three fold increase in incidence of both deep venous thrombosis and pulmonary embolism in the hormone treated group. Venous thromboembolic events occurred at a rate of 5.9 per thousand patient-years in the hormone group and 2.8 per thousand person-years in the placebo group.¹⁸ Before the mid 1990's the progestin component of oral contraceptives was not believed to contribute to the risk of thrombosis. More recent data indicating a higher risk of venous thrombosis with third-generation progestins than with second-generation progestins has modified previously held beliefs. The relative risk of venous thrombosis in users of third generation oral contraceptives was 6 to 9 times higher than in non-users.¹⁹

Discussion

In the past there had been concerns about the efficacy and/or cost of megestrol in the treatment of wasting syndromes, but little concern about safety. It would seem prudent to reconsider the safety of megestrol in the treatment of wasting syndromes in cancer patients, AIDS patients, and the elderly. Recent reports of

clinically significant and relatively frequent glucocorticoid like effects and the possibility of increased thromboembolic events associated with progestin use suggest the need for much closer monitoring for the signs and symptoms of adrenal suppression and thromboembolic events.

In my experience, I have seen many geriatric patients with wasting syndromes treated with megestrol 400-800 mg daily for weeks or months who had exacerbations of their stable diabetes mellitus, complained of nausea, anorexia, worsened fatigue and/or weakness, or vague unexplained dizziness. It was not uncommon for them to have acute septic episodes that could induce steroid resistance. Many of them had congestive heart failure, chronic renal disease, or chronic obstructive pulmonary disease, all of which are now known to be associated with cachexia.²⁰ Even short-term high dose glucocorticoid therapy commonly causes adrenal suppression.²¹ In hindsight, who knows how many of them could have had "functional adrenal insufficiency" or actually were unable to mount any cortisol response to the increased stress of exacerbations of chronic diseases or acute infections? No specific monitoring was done when megestrol was abruptly discontinued. In any event, the vast majority of them did not experience increases in weight, strength, or function which might be expected with increased body cell mass.

Three recent articles by Oelkers²², Cooper and Stewart²³, and Krasner²⁴ describe the causes, clinical presentation, laboratory evaluation, and treatment of adrenal insufficiency. The Cooper article discusses the corticosteroid response to acute illness.

It is possible that in the future the treatment of the various wasting syndromes will increasingly involve human growth hormone and androgens which have been shown to increase body cell mass and increase function. Steroids and progestins may be relegated to use in the pre-terminal period.

References

- Alexieva-Figusch J, et al. Progestin therapy in advanced breast cancer. Megestrol acetate: an evaluation of 160 treated cases. *Cancer* 1980;46:2369-2372. (IDIS Article Number 131984)
- Haller DG, et al. Progestational agents in advanced breast cancer: an overview. *Semin Oncol.* 1986;13:2-8.
- Tchekmedyan NS, Tait N, Moody M et al. High-dose megestrol acetate. A possible treatment for cachexia. *JAMA.* 1987;257:1195-1198. (IDIS Article Number 225863)
- Loprinzi CL, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol.* 1993; 11:762-767.
- Cruz JM, et al. Weight changes in women with metastatic breast cancer treated with megestrol acetate: a comparison of standard versus high-dose therapy. *Semin Oncol* 1990;17:63-67. [*did not review original]
- Abrams JS, et al. A phase III dose response trial for megestrol acetate (MA) in metastatic breast cancer. *Proc Am Soc Clin Oncol.* 1992 (absts);11:56.[* did not review original]
- Von Roenn JH, Armstrong D, Kotler DP et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med.* 1994;121:393-399. (IDIS Article Number 335038)
- Oster MH, Enders SR, Samuels SJ et al. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med.* 1994;121:400-408. (IDIS Article Number 335039)
- Mann M, Koller E, Murgu A et al. Glucocorticoidlike activity of megestrol: a Summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med.* 1997;157:1651-1656. (IDIS Article Number 391075)
- Kontula K, et al. Binding of progestins to the glucocorticoid receptor. *Biochem Pharmacol.* 1983;32:1511-1518. [* did not review original]
- Loprinzi CL, et al. Effect of megestrol on the human pituitary adrenal axis. *Mayo Clin Proc.* 1992;67:1160-1162.
- Rowland KM, et al. Phase III randomized double blind placebo controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive stage small cell lung cancer: a North Central Cancer Treatment Group study. *Proc Annu Meet Am Soc Clin Oncol.* 1994;13:330. (abstract) [*did not review original]
- Subramanian S, Goker H, Kanji A et al. Clinical adrenal insufficiency in patients receiving megestrol therapy. *Arch Intern Med.* 1997;157:1008-1011. (IDIS Article Number 388179)
- Koller E, et al. Thrombotic events associated with megestrol acetate in patients with AIDS cachexia. *Nutrition.* 1999;15:294-298.
- Von-Roenn JH. Randomized trials of megestrol for AIDS-associated anorexia and cachexia. *Oncology.* 1994;51(suppl 1)19. [*did not review original]
- Bennett RG. Megestrol complications. *Chest.* 2003;123:309-310. (IDIS Article Number 492082)
- Grady D, Herrington D, Bittner V et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS-II) *JAMA.* 2002; 288:49-57. (IDIS Article Number 483612)
- Hulley S, Furbert C, Barrett-Connor E et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS-II) *JAMA.* 2002;288:58-66. (IDIS Article Number 483613)
- Vandenbroucke JP, Rosing J, Bloemenkamp KWM et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med.* 2001;344:1527-1535. (IDIS Article Number 463775)
- Kolter DP. Cachexia. *Ann Intern Med.* 2000;133:622-634. (IDIS Article Number 454779)
- Henzen C, Suter A, Lerch E et al. Suppression and recovery of adrenal response after short-term high-dose glucocorticoid treatment. *Lancet.* 2000;355:542-545. (IDIS Article Number 440259)
- Oelkers W. Adrenal Insufficiency. *N Engl J Med.* 1996;335:1206-1212. (IDIS Article Number 373550)
- Cooper MS and Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med.* 2003;348:727-734. (IDIS Article Number 493136)
- Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA.* 1999;282: 671-676. (IDIS Article Number 430445)

EDITORS NOTE:

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS CONSULT ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE CONSULT DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL AND WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

About the Author:

Dave Mace, R.Ph., Drug Information Specialist, wrote the article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

Introducing . . . Pivotal Studies

As the term implies, pivotal studies are the most important studies conducted while investigating the safety and efficacy of a new drug. Pivotal studies are trials that are well-controlled and generally show the most rigorous evidence of a drug's efficacy. Studies establishing a drug's safety and efficacy that are submitted to the FDA by the drug's sponsor during the drug approval process are referred to as pivotal studies. These are some of the first and most important studies associated with newly marketed drugs. Not all of these studies are published in the medical literature and only about 50% appear in the literature up to a year after approval of the studied drug.¹ Even if the pivotal studies are published, it can be difficult to discern which published studies are the same ones that were submitted to the FDA for the approval of a new drug. Generally, it is a matter of meticulously comparing and matching statistics of the studies in order to find the ones that appear both in the published literature and in the FDA Approval Package.

In the *IDIS* database it is now easier than ever to find studies associated with the FDA new drug approval process and to match them with their published versions. A new descriptor, **162 PIVOTAL STUDY**, has been added. This new descriptor is used to label pivotal studies in the *IDIS* database, both in the FDA Approval Package and the corresponding published studies from the medical literature. A search strategy can include the descriptor 162 PIVOTAL STUDY in the descriptor field and the name of the drug of interest in the drug field. This will retrieve both the pivotal studies published in the medical literature and the section of the FDA Approval Package in which the study appears. Within the *IDIS* database, pivotal study is defined as follows:

162 PIVOTAL STUDY

The U.S. Food and Drug Administration's (FDA) requirements for approval of a new drug application include "sufficient data to demonstrate that the drug is safe and substantial evidence that the drug is effective for its intended use derived from adequate and well-controlled clinical investigations, designed to permit a valid comparison with a control to provide a quantitative assessment of the drug effect . . ." [21 CFR 314.126(a)(2)]. These investigations, Phase IIb or Phase III, are called pivotal studies and are generally randomized controlled clinical trials. This descriptor identifies pivotal studies that appear within the FDA Approval Package, and, if available, the corresponding studies published in the medical literature. (Added April, 2003)

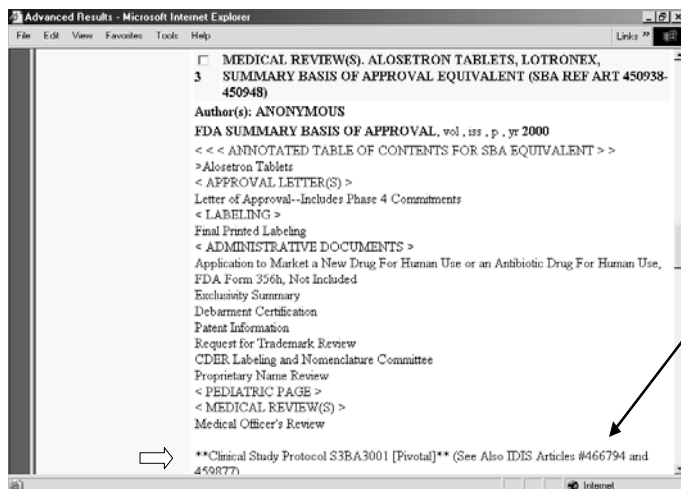
The addition of this descriptor to the *IDIS* database is a work in progress. FDA Approval Packages have appeared in the database since 1997. Thus far, the pivotal study descriptor has been added from 2000 to present. It will soon be added to FDA Approval Packages and associated studies from 1997 to 2000. It is being included in all new FDA Approval Packages as they are indexed and entered into the database and added to the published studies as they are identified.

Nicola Sarrazin, R.Ph., Pharm.D.

References

1. Gilchrist B. U.S. FDA Summary Basis of Approval (SBA): Unexplored and underutilized, *World Drug Info* 2000;11:1-5.

Approval Package



Published Version

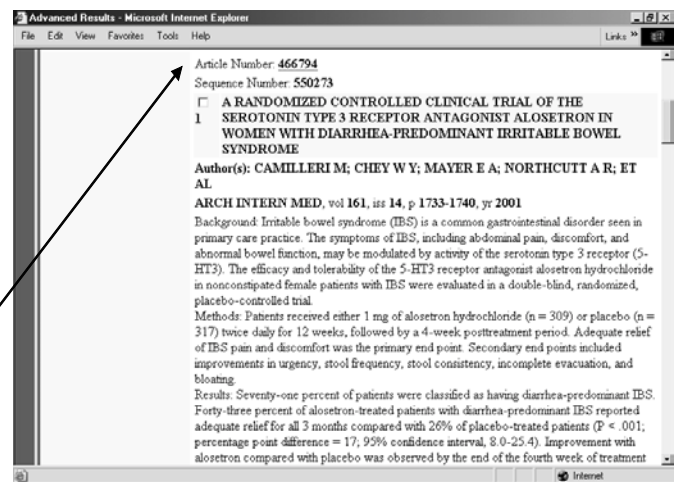


Figure 1. Results of Alosetron and Pivotal Study Search

New Descriptor:

163 MODIFICATION OF EFFECT SEX/GENDER



163 MODIFICATION OF SEX/GEND, has been added to the *IDIS* database. This addition will enable *IDIS* users to easily retrieve articles that focus on sex or gender differences, either physiologic or psycho-social.

Physiologic differences, referring to those determined by a person's sex, include both pharmacokinetics and pharmacodynamics. Gender generally refers to psycho-social elements of a person's sexuality. This might be seen in drug usage or prescribing practices. To facilitate retrieval of articles that focus on gender issues, those articles will be indexed with the new descriptor *plus* the descriptor 128 DRUG UTILIZATION.

The new descriptor has been added to applicable articles from 1966 to present. The *IDIS* database now contains over 500 articles that highlight sex/gender differences in medication use.

Definition:

163 MODIFICATION OF SEX/GEND

Variation in the pharmacokinetics or pharmacodynamics of a drug based on the sex of the person receiving the drug. Also, variations in drug use or prescribing practices based on gender. When gender differences are indicated, this descriptor is used in conjunction with descriptor 128 DRUG UTILIZATION.

DDIS EXHIBIT SCHEDULE 2003

American Association of Colleges of Pharmacy
July 18-23, 2003
Hyatt Regency Minneapolis
On Nicollet Mall
Minneapolis, MN
Booth # 28

American College of Clinical Pharmacy
2003 Annual Meeting
November 2-5, 2003
Hyatt Regency Atlanta
Atlanta, GA
Booth #212

American Society for Health-System Pharmacists
39th Midyear Clinical Meeting
December 7-11, 2003
New Orleans, LA

IDIS

Iowa Drug Information Service

Telephone: 319-335-4800

US Toll-Free: 800-525-IDIS

Fax: 319-335-4440

E-mail: IDIS@uiowa.edu

Web Site: <http://www.uiowa.edu/~idis>

IDIN

Iowa Drug Information Network

Telephone: 319-335-4199

US Toll-Free: 800-525-4347

Fax: 319-335-4440

E-mail: IDIN@uiowa.edu

Web Site: <http://www.uiowa.edu/~idin>

World of Drug Information is published quarterly

(March, June, September, December) by the Division of Drug Information Service.

Editor-in-Chief Hazel Seaba

Editor Donna Brus

Production/Design Coordinator Julie Tomash

Photographer David Luck

ISSN# 1529-4331

Division of Drug Information Service

The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000 USA

The University of Iowa prohibits discrimination in employment and in its educational programs and activities on the basis of race, national origin, color, creed, religion, sex, age, disability, veteran status, sexual orientation, gender identity, or associational preference. The University also affirms its commitment to providing equal opportunities and equal access to University facilities. For additional information on nondiscrimination policies, contact the Coordinator of Title IX, Section 504, and the ADA in the Office of Affirmative Action, (319) 335-0705 (voice) or (319) 335-0697 (text), The University of Iowa, 202 Jessup Hall, Iowa City, Iowa 52242-1316.