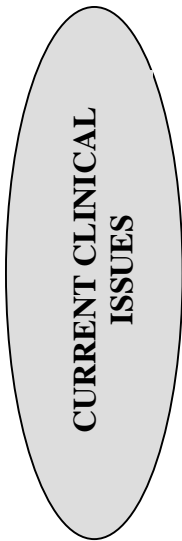




# World of Drug Information

Volume 11, Issue 1 – March 2000



## Efficacy of Alendronate Plus Hormone Replacement Therapy

### Goal:

- ◆ To identify the rationale of adding alendronate therapy to hormone replacement therapy in postmenopausal women with osteoporosis.

### Objectives:

- ◆ Identify the complications of osteoporosis.
- ◆ Explain the bone remodeling process
- ◆ Differentiate between type I and type II osteoporosis
- ◆ Differentiate between the clinical effects of estrogen and alendronate therapy
- ◆ Explain the rationale for combining alendronate to Hormone Replacement Therapy (HRT)

### Drug Information Question:

Are there any additional benefits to bone mineral density (BMD) when adding alendronate to hormone replacement therapy (HRT) in postmenopausal osteoporotic women?

### Introduction:

A clinical study designed to address this question was recently published. However, to fully understand the potential effects of combination therapy with estrogen and alendronate, background information on the pathophysiology of osteoporosis, and the mechanism of action of these drugs is necessary.

Osteoporosis is often referred to as the “silent disease”. In fact, for many women, the first clinical manifestation of osteoporosis is a fracture. Each year in the United States, there are approximately 1.5 million fractures attributable to osteoporosis. The economic impact of these fractures can be enormous. In 1995, the National Osteoporosis Foundation

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(NOF) Physician's Guide estimated that the direct medical costs associated with osteoporotic fractures was \$13.8 billion. Because of the aging population within the United States, it is estimated that the number of hip fractures and the associated cost will more than triple by the year 2040 (National Osteoporosis Foundation: Physician's Guide).

Osteoporosis is defined by the National Osteoporosis Foundation as "low bone mass and microarchitectural deterioration of bone tissue" (National Osteoporosis Foundation: Physician's Guide). These defects lead to fragile bone and

*For many women, the first clinical manifestation of osteoporosis is a fracture.*

an increased risk of fracture. It is estimated that one out of two white women will experience an osteoporotic fracture (National Osteoporosis Foundation: Physician's Guide) with the most common fracture sites being the proximal femur (hip), the vertebrae (spine), and the distal forearm (wrist) (Cooper 1997). The morbidity and mortality associated with these fractures is significant. For example, approximately one quarter of patients who suffer a hip fracture will require long term nursing home care with only one-third of these patients regaining the level of independence that they had before their fracture (National Osteoporosis Foundation). In addition, hip fracture patients are 2 to 4 times more likely to die within one year of their fracture (Schurch 1996). The complications associated with vertebral fractures include height loss, dorsal kyphosis (abnormal backward curvature of the spine) and cervical lordosis (abnormal forward curvature of the spine). Because of these changes in posture and spinal curvature, these patients frequently have pulmonary and cardiopulmonary complications as well.

### ***Bone Remodeling***

The two types of bone cells involved in bone remodeling are the osteoblasts and osteoclasts. The major function of the osteoblasts is forming new bone, whereas the osteoclasts are

considered the bone-resorbing cells. Bone remodeling is a continuous process that couples the removal of old bone with the synthesis of new bone and mineralization (Notelovitz 1997b). The effect of this coupling is to keep bone resorption and formation balanced to ensure bone health and strength. Unfortunately, at approximately the third decade of life we begin to lose this balance with the rate of bone resorption increasing relative to bone formation.

The activity of osteoblasts and osteoclasts is under the influence of various cytokines, growth factors and hormones. Osteoblasts are thought to mediate the regulation of bone turnover. Osteoblasts originate from mesenchymal stem cells and their differentiation may be influenced by interleukin 1 and 6 (IL-1 and IL-6), estrogen, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (O'Connell 1999). In-vitro studies have shown that osteoblasts have receptors for estrogens, androgens, vitamin D, growth hormone (GH), and PTH (Rodan 1995, O'Connell 1999). Cytokines (IL-1 and TNF- $\alpha$ ) secreted by monocytes are thought to be involved with osteoblast activation as well. Mature osteoblasts are involved in bone formation by secreting collagen into the cavities formed from osteoclastic activity. Alkaline phosphatase is needed for the mineralization of the newly formed bone (Rodan 1995, O'Connell 1999). Osteoblasts secrete hormonal compounds that inhibit the activity of osteoclasts, but they also secrete factors necessary for the differentiation of osteoclasts (Rodan 1995).

*It is estimated that one out of two white women will experience an osteoporotic fracture (NOF).*

The differentiation of hematopoietic stem cells to osteoclasts is under the influence of various factors (colony stimulating factor or CSF, IL-1, TNF) secreted by osteoblasts and monocytes (Rodan 1995, O'Connell 1999). The hormonal compounds responsible for the differentiation of these cells include PTH, 1,25 dihydroxyvitamin D, and IL-1. Unlike the osteoblasts, osteoclasts only have receptors for estrogen and calcitonin

(O'Connell 1999). The mechanism of action for osteoclasts as mentioned earlier is bone resorption. Resorption is accomplished by secreting proteolytic enzymes and acids (citric and lactic) to dissolve the organic matrix and mineral of old bone (Notelovitz 1997b).

### ***Type I (Postmenopausal) Osteoporosis:***

Type I osteoporosis is caused by the factors related to menopause (O'Connell 1999, Rubin 1999). A deficiency of estrogen increases bone resorption. Studies indicate that a deficiency of estrogen causes an increase in the release of various factors that induce bone resorption and stimulate the differentiation and maturation of precursor cells to osteoclasts. Also, estrogen reduction increases the sensitivity of bone to the effects of PTH causing bone resorption. This normally occurs in women during the ages 51-75 years. Trabecular bone is the main bone that is lost and the fracture sites associated with this type are vertebrae (crush type fracture) and distal radius. PTH is decreased (due to mobilization of calcium from bone), calcium absorption is decreased, and there is a secondary decrease in the metabolism of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D.

### ***Type II (Age-related or Senile) Osteoporosis:***

The bone loss in type II osteoporosis is gradual and is associated with factors related to the aging process (O'Connell 1999, Rubin 1999, National Osteoporosis Foundation: Physician's Guide). The processes responsible for type II include:

- ◆ Decreased osteoblast function
- ◆ Decreased calcium and vitamin D intake and absorption
- ◆ Decrease in sex hormone concentrations
- ◆ Mechanical bone stress
- ◆ Concomitant disease (e.g. type 1 diabetes, rheumatoid arthritis, gonadal insufficiency)
- ◆ Medications (e.g. anticonvulsants, glucocorticoids, heparin)

Men and women reach their peak bone mineral density between the ages of 25 to 35. After that

time, they lose approximately 3% of their bone per decade. During menopause, women experience an accelerated rate of bone loss (9% per decade) while men continue to lose 3% per decade. Ten to twenty years after menopause, the rate of bone loss returns to normal aging rates. The sites of fracture include the vertebrae

*During menopause, women see an accelerated rate of bone loss (9% per decade)*

(multiple wedge fractures) and hip. Both trabecular and cortical bone are affected. PTH is increased, calcium absorption is decreased, and there is a primary decrease in the metabolism of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D.

### ***Clinical effects of estrogen on bone mineral density:***

Estrogen replacement therapy (ERT) has been shown to slow down the bone loss that occurs during early menopause (Ettinger 1998). The effects of estrogen on the bone remodeling process and calcium regulation include (O'Connell 1999):

- ◆ Decrease osteoclast recruitment and activity
- ◆ Inhibit PTH peripherally
- ◆ Increase intestinal calcium absorption
- ◆ Decrease renal calcium excretion
- ◆ Decrease cytokines and other bone influencing factors leading to decreased bone resorption.

Clinically, estrogen has been shown to reduce the risk of hip, wrist, and vertebral fractures 30 to 50% (observational studies) (Riggs 1992, Col 1997). According to the PEPI trial, women who took estrogen (conjugated estrogen 0.625mg/d) for three years had an increase in bone mineral density of 3.5 to 5% in the spine and 1.7% in the hip. Comparatively, women in the placebo group had a 1.8% loss of bone mineral density in the hip and spine. (Bush 1996). Estrogen increases the bone mineral density in both cortical bone (1 to 3%) and trabecular bone (3 to 5%) (Notelovitz 1997a). Although conjugated estrogen 0.625 mg daily has been considered the

optimal dose for osteoporosis prevention, more recent studies have shown lower doses (0.3 mg). Alendronate has been approved for the prevention (5 mg) and treatment (10 mg) of osteoporosis. It is considered a bisphosphonate and works by the following mechanisms (O'Connell 1999):

- ◆ Adsorb to bone hydroxyapatite, later becoming a permanent part of bone structure (estimated half-life of bisphosphonate bound in bone is 1 to 10 years, similar to bone half-life)
- ◆ Bisphosphonate-bound bone is resistant to osteoclast enzymatic hydrolysis
- ◆ Structure and function of osteoclasts is altered, preventing adherence and resorption

Several studies have shown that patients with osteoporosis or low bone mineral density treated with 10 mg/d of alendronate may see an increase in bone density by 5 to 10% at the hip and spine in up to five years of therapy. Risk of fracture at these sites was reduced by approximately 50% (Black 1996, Karpf 1997, Cummings 1998, Bone 1997). Prevention studies (5 mg daily) demonstrated bone density increases by 3 to 5% (Hosking 1998, McClung 1998). For alendronate to be effective, patients need adequate daily intake of calcium and vitamin D.

### ***Combination Therapy: Alendronate + Estrogen***

Lindsay et al. recently studied the effects of twelve month alendronate therapy in women currently taking estrogen therapy (ERT). Women included in the study had to have a confirmed diagnosis of osteoporosis as determined by a bone mineral density (BMD) measurement by dual X-ray absorptiometry. A total of 428 women on estrogen and with the diagnosis of osteoporosis were randomized to receive either alendronate 10 mg every day or placebo. The two groups had similar baseline characteristics and were similar in their duration of estrogen use (approximately 10 years on average). Primary endpoint was the change in

BMD at the lumbar spine. Secondary endpoints to be effective were the mean percent changes in BMD from baseline at the hip trochanter and femoral neck (Genant 1997, Recker 1999). Efficacy and safety measurements were obtained at baseline, 6 months, and 12 months of therapy. Adverse effects were monitored by the researchers at each study visit.

Significant increases in lumbar spine BMD were found at 6 months and 12 months for the alendronate + HRT group as compared to HRT alone. Mean percent changes in lumbar spine BMD was 3.6% in twelve months for the alendronate + HRT group compared to 1.0% change for HRT alone. The mean percent changes in BMD of the hip trochanter was significantly greater at twelve months for the alendronate + HRT group vs. HRT group (2.7% vs. 0.5%). The researchers found that the two groups were similar in their adverse effect

Significant increases in lumbar spine BMD were found at 6 months and 12 months for the alendronate + HRT group as compared to HRT alone.

profile (alendronate + HRT: 85% vs. HRT alone: 83%). Four percent of the alendronate + HRT patients discontinued the study drug as compared to 7% of patients in the HRT alone group. Incidence of gastrointestinal adverse effects were identical for each group (10.7%). The incidence of fractures was greater for the alendronate + HRT group vs. HRT alone (15 vs. 9) though this was not significant. Neither group had a patient who experienced a hip or symptomatic vertebral fracture.

### ***Conclusion:***

Some patients who are on hormone replacement therapy will continue to lose BMD. In those patients, alternative treatments need to be identified. Although estrogen and alendronate are both antiresorptive medications, their mechanisms of action are different. Therefore, studying the combination of alendronate + HRT therapy is rational. In the study by Lindsay et al. they demonstrated that women taking

alendronate with HRT had significantly better improvement in their BMD (lumbar spine and hip trochanter) measurements as compared to HRT alone. Since this study was done for only twelve months, larger studies for longer duration will need to be done to determine the safety and efficacy of this combination. Until then, this study provides us with new information that we can incorporate into our practice and help us with our treatment decisions regarding the care of our postmenopausal patients with osteoporosis.

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Randy McDonough, R.Ph., M.S.

## Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

1. Complete the answer sheet.
2. Print or type your name, address, social security number and pharmacy license number(s) in the space provided on the CE registration form.
3. Complete the program evaluation.

**Mail with processing fee of \$5.00 made out to the College of Pharmacy, your completed answer sheet, registration form and evaluation to:**

**Iowa Drug Information Service  
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The University of Iowa  
100 Oakdale Campus N330 OH  
Iowa City, IA 52242-5000**

Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified, and no credit will be recorded. Allow four weeks for processing.

## Assessment Questions:

### 1. Which statement is FALSE?

- a) Because of earlier diagnosis and our understanding of the pathophysiology of osteoporosis, hip fractures are predicted to significantly decrease by the year 2040.
- b) Hip fracture patients are 2 to 4 times more likely to die within one year of their fracture.
- c) Each year in the United States, there are approximately 1.5 million fractures attributable to osteoporosis.

### 2. Each of the following are considered complications of osteoporosis EXCEPT?

- a) Cervical lordosis
- b) Bone spurs
- c) Dorsal kyphosis
- d) Hip fracture
- e) Wrist fractures

### 3. Which statement is FALSE regarding bone remodeling?

- a) Osteoblasts are the cells thought to be responsible for the regulation of bone turnover
- b) Monocytes secrete cytokines to activate osteoblasts
- c) Estrogen receptors exist on both osteoblast and osteoclast cells

### 4. Each of the following is involved in regulation of bone turnover EXCEPT?

- a) Interleukin 1 and 6 (IL-1 and IL-6)

- b) Parathyroid Hormone (PTH)
- c) Growth Hormone (GH)
- d) Aldosterone
- e) Alkaline Phosphatase

### 5. Which statement is FALSE regarding type I osteoporosis?

- a) It is associated with a deficiency of estrogen
- b) PTH and calcium absorption is decreased
- c) Rheumatoid arthritis patients are at increased risk of developing type I osteoporosis

### 6. All of the following are true statements regarding type II osteoporosis EXCEPT?

- a) It is associated wedge type fracture of the vertebrae
- b) Rheumatoid arthritis has been associated with this type of osteoporosis
- c) On average, men have accelerated loss of bone after age 70

### 7. Which of the following is NOT an effect of estrogen?

- a) Adsorbs to bone hydroxyapatite and becomes a permanent part of bone structure
- b) Inhibits osteoclast recruitment and activity
- c) Increases intestinal calcium absorption
- d) Decreases renal calcium excretion

**8. All of the following statements are true EXCEPT?**

- a) Bisphosphonate-bound bone is resistant to osteoclast enzymatic hydrolysis
- b) Alendronate alters the function of osteoclasts, preventing adherence and resorption
- c) For alendronate to be effective, patients need adequate intake of calcium and vitamin D.

**9. Which statement is TRUE regarding the Lindsay et al trial comparing alendronate + HRT to HRT alone?**

- a) A significant increase in mean percent change in BMD was seen in lumbar spine, hip trochanter, and femoral neck.
- b) Patients in the Alendronate + HRT group experienced more gastrointestinal side effects as compared to HRT alone.

- c) The mean percent change in the BMD of the lumbar spine after twelve months of Alendronate + HRT was 3.6%

**10. Which statement is true regarding the use of the combination of alendronate with estrogen replacement therapy?**

- a) The results of this trial were unexpected since alendronate and estrogen have the same mechanisms of action.
- b) The incidence of fractures was greater for the alendronate + HRT group vs. the HRT alone.
- c) More patients in the combination therapy group discontinued the study drug as compared to the ERT alone group



## 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 ACEP program number is 020-000-99-901-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 Iowa Drug Information Service with a processing fee of \$5.00 made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists completing this program by September 1, 2000 can receive credit.

# ANSWER SHEET

Circle the most appropriate answer

- |     |   |   |   |   |   |  |  |  |  |  |
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| 1.  | a | b | c |   |   |  |  |  |  |  |
| 2.  | a | b | c | d | e |  |  |  |  |  |
| 3.  | a | b | c |   |   |  |  |  |  |  |
| 4.  | a | b | c | d | e |  |  |  |  |  |
| 5.  | a | b | c |   |   |  |  |  |  |  |
| 6.  | a | b | c |   |   |  |  |  |  |  |
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| 8.  | a | b | c |   |   |  |  |  |  |  |
| 9.  | a | b | c |   |   |  |  |  |  |  |
| 10. | a | b | c |   |   |  |  |  |  |  |

## CE REGISTRATION

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## 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
	Agree				Disagree
Important to pharmacists	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.

# **2000 EXHIBIT SCHEDULE**

You're Invited . . .

Please visit the IDIS/IDIN booth at the upcoming professional meetings:

**Federation Internationale Pharmaceutique (FIP)  
World Congress of Pharmacy and Pharmaceutical Sciences  
Vienna, Austria  
August 26-31**

**American College Clinical Pharmacy (ACCP) Annual  
Meeting  
Los Angeles, California  
November 5-8**

**American Society of Hospital Pharmacists (ASHP)  
Midyear Clinical Meeting  
Las Vegas, Nevada  
December 3-7**

# *IDIS Hosts WHO Study Tour*



**Mr. Tryambak A. Thool**

During the fall of 1999, IDIS again hosted a World Health Organization and Pan American Health Organization (WHO/PAHO) Fellow at the Division of Drug Information Service. During September and October Mr. Tryambak A. Thool studied at DDIS. Mr. Thool is currently the Assistant Commissioner of the State of Maharashtra Food & Drug Administration in Mumbai, India. His education includes a B. Pharm., M. Pharm., MA in Public Administration and a degree in law.

The fellowship program presented the technical aspects of the *IDIS* database, an overview of other drug information databases, study of the drug approval system adopted by the U.S. FDA, postmarketing surveillance, drug labeling and

advertising regulations in the U.S. He also visited an FDA approved manufacturing facility, two contract research organizations, a community pharmacy and the Department of Pharmaceutical Care at the University of Iowa Hospitals and Clinics (UIHC). Mr. Thool plans to use the knowledge he gained during his visit to the U.S. to modify the Maharashtra FDA drug product database and incorporate changes into their current system.

When asked to compare the similarities and differences in pharmacy practice in India and the U. S., Mr. Thool responded, "Pharmacy practice is very different in India. There the FDA rather than State Boards of Pharmacy controls the practice of pharmacy. The government also controls the price of medicines. Unit of doses required by patients generally are prepackaged by manufacturers and many solid dose forms come in strip packs. There is no system of patient registration within the pharmacy and no compounding of drugs. Patient counseling is negligible." Mr. Thool went on to explain that in India, the state FDA controls drug manufacturing except for certain categories which are controlled by both Central as well as State governments. These categories include: Vaccines and Sera, Blood Products and Large Volume Parenterals. Drug manufacturing is regulated by a licensing system and drugs must be approved every two years. Medicines are generally inexpensive compared to U.S. prices.

During his fellowship at IDIS, Mr. Thool spent a weekend in Pella, Iowa, visiting a farm family. At the conclusion of his study tour, he visited a friend in Chicago, Illinois and traveled on to see Disney World in Orlando, Florida.

*Candidates interested in participating in WHO Fellowships, need to contact the WHO directly for application information. Information about customized drug information study programs is available from our office.*



Donna Brus, Editor

# Access to Unpublished Information on Recently Approved New Drugs: The Summary Basis of Approval Equivalent (SBA)

The Summary Basis of Approval equivalent (SBA) is a document created from information generated during the U.S. New Drug Approval process. An SBA is made up of the information collected by the drug's sponsor through their research and combined with the comments and analyses of reviewers at the Center for Drug Evaluation and Research (CDER) or at the Center for Biologics Evaluation and Research (CBER) branch of the U.S. Food and Drug Administration (FDA). Included in the SBA are the "pivotal" studies. These are the studies which the sponsor believes convincingly show the safety and efficacy of their new drug or biologic. Often supportive studies as well as pharmacokinetic studies are also summarized within an SBA. Many of the studies reviewed and summarized in the SBA are never published in the medical literature. For this reason, we feel it is very important to include these documents in IDIS. How to retrieve these documents and what is included in them is the focus of this search tip.

SBAs are large documents, some are over one thousand pages. Before indexing these documents, they are divided into sections and an annotated table of contents is created to make the SBA more manageable. A typical SBA in the *IDIS* database contains ten to fourteen sections. A few of the earlier SBAs were only separated into one or two sections. Each section is assigned an Article Number. The simplest way to retrieve all sections of an SBA is to search a specific drug combined with descriptor 155 SUMMARY BASIS OF APPROVAL. This search will identify the complete SBA for a drug.

The sections most commonly appearing within an SBA include: *Approval Letters, Labeling, Administrative Documents, Medical Review(s), Pharmacology Review(s), Statistical Review(s), Microbiology Review(s), Chemistry Review(s), Memoranda and Correspondence*. The sections within an SBA that usually contain the most clinical information are "*Medical Review(s)*" and "*Statistical Review(s)*." These sections often provide in-depth information on the clinical trials performed with a new drug.

## SBA Description

Approval Letter(s)	Includes the letter from the FDA to the manufacturer notifying them of the approval. The approvable letter is sometimes included too.
Labeling	The final printed labeling for the approved drug.
Administrative Documents	Contains the Debarment Certification, Patent Information, Exclusivity Summary.
Pediatric Page	A page indicating whether studies in children are needed or not.
Medical Review(s)	Generally a review by the Medical Officer from CDER of the pivotal and supportive trials submitted by the drug sponsor.

Pharmacology Review(s)	Primarily reviews of pharmacology and toxicology studies in animals.
Statistical Review(s)	A statistical reviewer from CDER analyzes and comments on the studies submitted by the drug sponsor.
Microbiology Review(s)	Review of in vitro studies of antiinfectives.
Chemistry Review(s)	One or two page documents describing the chemical formula and structure, indication, pharmacological category, dosage form/strength and route of administration of a new drug.
Memoranda/ Correspondence	Communications between a drug sponsor and the FDA during the drug approval process.

By federal law, the FDA must make these documents available to the general public. SBAs may be requested through a Freedom of Information Act request. Our experience has been that the response time to a request for an SBA can vary from a few weeks to many months. This variance in response time makes it impossible to guarantee when a specific drug SBA will appear in the *IDIS* database. Alternatively, the FDA has begun putting some of the SBAs on their website (<http://www.fda.gov/cder/approval/index.htm>). The time from new drug approval to the appearance of the SBA or “Review” as it is referred to on the webpage, is highly variable.

**The SBAs for the following drugs are available in the *IDIS* database:**

AMLEXANOX	EPTIFIBATIDE	ORLISTAT	SODIUM FERRIC GLUCONATE COMPLEX
BENTOQUATAM	FOMIVIRSEN SODIUM	PARICALCITOL	TEMOZOLOMIDE
BRINZOLAMIDE	GANIRELIX	PIOGLITAZONE	THALIDOMIDE
BUTENAFINE	LEFLUNOMIDE	RABEPRAZOLE	TIROFIBAN
		SODIUM	
CALFACTANT	LEPIRUDIN	RIFAPENTINE	TOLTERODINE TARTRATE
CANDESARTAN	LOTEPREDNOL ETABONATE	RISEDRONATE	VALRUBICIN
CILEXETIL			
CAPECITABINE	MIBEFRADIL	RIZATRIPTAN	ZALEPLON
	DIHYDROCHLORIDE	BENZOATE	
CITALOPRAM	MODAFINIL	ROSIGLITAZONE	ZANAMIVIR
DOXERCALCIFEROL	NELFINAVIR MESYLATE	SACROSIDASE	
EFAVIRENZ	NEVIRAPINE	SILDENAFIL CITRATE	

As you read through various SBAs you will find that not all drugs are unanimously recommended for approval. Concerns and questions are raised by the CDER reviewers. This information is often not published anywhere else. Access to this information requires only a simple search of the *IDIS* database. Descriptor 155 SUMMARY BASIS OF APPROVAL is the key to retrieving these well-organized, well-indexed conglomerations of drug information. Pick a drug from the list above and take a look. You may be surprised at what you find.



Brad Gilchrist, R.Ph., Staff Pharmacist II

# Perspective from an *IDIS* Subscriber



## Drug Induced Lupus Syndrome: Case Report

**Re:** A 64 year old white male who presents on [1/2/00] w/ chest pain and pleural effusion. Diagnostic impression pleural effusion 2<sup>nd</sup> to CHF vs. r/o pulmonary embolism vs. angina pectoris. [Most probable diagnosis is procainamide associated lupus syndrome.]

**Data:** [on admission] T100.5;R-28;P-120;BP 142/80; accucheck - 211 V-Q scan [-] + ANA [speckled pattern]

[Date:]	BUN/Cr	WBC/bands	CK	Pleural fluid culture & sensitivity
1-2	19/1.0	7.4/10	--	--
1-3	17/0.6	6.4/	29	Bact. no growth
1-3	Thoracentesis	[200ml from R lung]		Fungus no growth
1-4	19/0.9			
1-5	21/0.9	5.3/-		Lupus anti-coag [-]
1-5		5.3	RBC 4.22	MCV 95.7 MCHC 33.4
1-6		4.1	RBC 4.4	MCV 95.1 MCHC 33.7

**PRIOR MEDICAL HISTORY:** CHF; L sided pleurisy; IDDM; HTN; s/p AMIx2 [2<sup>nd</sup> in March of previous year]; CAD; chronic angina; COPD; s/p permanent pacemaker; s/p mural thrombus

**CHIEF COMPLAINT:** Severe pain in R lower rib cage, worse on inspiration, increasing over past three weeks [did not seek help - wanted to be home over the holiday season], different than cardiac pain from AMI or angina. He took frequent short breaths to avoid worse chest pain.

**HISTORY AND PHYSICAL:** A & O x 3. ROS negative except for arthralgia, myalgias

and chest pain syndrome which is slightly worse on movement, mild DOE; breath sounds diminished at the bases. Denies productive cough, chills or fever. Chest x-ray showed r-basilar plate like atelectasis.

### **HISTORY OF PRESENT ILLNESS:**

He was hospitalized here for 3 days, 21 days prior to this admission, for a similar episode of pleurisy, which resolved with NSAID therapy. The etiology of the pleurisy during the 1<sup>st</sup> admission was unclear, however the V-Q scan and venogram were negative. One week after discharge, in early December, he began having worsening R lower chest pain on inspiration. During the week prior to admission, the pain

moved to the R side [was across whole lower chest] and became worse. Also c/o ↑ SOB and can not sleep while laying flat, needs to raise the head of his bed. The chest pain, which was unlike his cardiac pain, had been slowly worsening, and was localized to the lower left side of his chest with radiation to the back. Pulmonary service thought the likely diagnosis was PE. He was temporarily anticoagulated. After the negative lung scan, anticoagulation was discontinued. ANA was positive w/homogeneous [speckled] pattern consistent with procainamide use. Chest x-ray revealed a left basilar pleural effusion.

He was seen in primary care clinic on 12/4 w/new complaint of constant L rib [anterior] pain unrelieved by 2 NTG; and was worse on deep inspiration. Sometimes the chest pain goes through to his back. He usually had pain in the L arm, but now complains of a new different sharp pain [elbow to hand]. He also c/o new sharp pain in the posterior aspect of his RLE from the R knee distally. He denies recent or old injury or over use of either L arm or R leg.

He was seen in medicine clinic on 11/27 w/ a new complaint of ↑ "arthritic pain of the joints" during the previous week. In early November he began to notice stiffness and pain in both hands and fingers. At that time there was no pain in other areas, except his well-known cardiac pain syndromes.

**MEDICATIONS:** Diltiazem 30mg q8h, procainamide 500mg q6h [since previous March], NTG 0.4/hr, furosemide 40 mg qd, lente + regular insulin, ASA 325 mg/day, heparin IV full dose.

**HOSPITAL COURSE:** On admission pain was relieved by meperidine and ibuprofen. Thoracentesis was done on 1/3 [report indicated exudate]. Procainamide was discontinued on 1/4 and by 1/6, lungs were clear and chest pain was resolving. His chest pain was much improved except when coughing. He still had some complaints of arthralgia and myalgia. On 1/8 he was discharged to a medical ward on a

Holter monitor. On ibuprofen, the pain in his hands, L arm, and R leg had resolved. The ibuprofen was not continued after discharge.

**FOLLOW UP:** He was seen in medicine clinic 3 months after discharge, at which time he still had bilateral pleuritic chest pain. There was no mention of any other painful arthralgias or myalgias. An NSAID was started for his pleuritic chest pain. When seen 5 months after discharge, his pleuritic chest pain was intermittent. Later, 7 months after discharge, his pleuritic chest pain occurred only with deep inspiration and sneezing. At his clinic visit 11 months after discharge, there was no mention of any chest pain syndrome or any pain other than angina.

**LITERATURE:** Systemic Lupus Erythematosus (SLE) is the most common connective tissue disease with an annual incidence ranging from about 6 cases per 100,000 population to 35 cases per 100,000 in low and high risk populations. Drug induced lupus syndrome [DILS] is considered a rare variant of (SLE) which may account for 5% of known cases DILS shares some of the common features of systemic SLE including the presence of ANAs, arthralgia, myalgia, and pleurisy. Most patients with DILS will have less than 4 of the 11 American College of Rheumatology criteria for SLE. Central nervous system involvement is not believed to occur and renal involvement is found in less than 20% of cases. Skin rashes are much less prominent in DILS than in SLE and occur in less than 25% of cases. Lymphadenopathy, which is common in SLE, is absent in DILS. Generally DILS is a much less severe disease than SLE with the syndrome completely resolving within days or weeks of discontinuing the suspect drug (Hess, 1988; Harmon, 1982; Cush, 1985; Price, 1995).

Cush and Goldings report that 50-83% of patients on procainamide develop a positive ANA with a speckled pattern but only 12-29% develop DILS (Cush, 1985).

Specific diagnostic criteria for DILS have not been developed, however several findings should be made before the diagnosis is seriously considered:

- ❑ the suspect drug is one of the drugs with a proven or probable association w/DILS;
- ❑ no history suggestive of SLE before the suspect drug was started;
- ❑ +ANA should be present with a speckled pattern;
- ❑ at least one of the clinical features of SLE should be present during sustained treatment with the suspect drug;
- ❑ rapid improvement in clinical symptoms should occur when the drug is withdrawn;
- ❑ gradual fall in the ANA and other serologic changes after the drug is withdrawn.

Fakhro and colleagues described 15 cases of procainamide associated DILS within four years (Fakhro, 1967).<sup>5</sup> Procainamide had been administered in daily doses of 0.75 - 6.0 gm for periods ranging from two weeks to three years. None of their patients had any history of connective tissue disease. The earliest and most frequent complaints were polyarthralgias associated with myalgia and general malaise. The arthralgia was migratory and symmetrical, affecting in order of frequency: small joints of hands, shoulders, wrists, knees, and ankles. Persistent pain radiating from the shoulder down the arm suggested a shoulder-hand syndrome. Joint presentations varied from slight stiffness to bursitis to arthritis with disabling pain. Joint syndromes were relieved by discontinuing procainamide. All 15 patients had a positive ANA with a median titer of 1:256. There was no correlation between the height of the ANA titer and the severity of the syndrome.

Byrd and Schanzer reviewed the extent and time of recovery in 16 cases of procainamide-associated lupus syndrome (Byrd, 1969). Time to full recovery of the pulmonary involvement

ranged from within a few days in patients on steroids to 10 weeks or more if not on steroids. Alarcon-Segovia also reported in some cases of procainamide DILS, pulmonary symptoms have tended to persist for 4-6 weeks or have required steroids for relief after the drug was discontinued. On the other hand, musculoskeletal symptoms usually resolve promptly within a few days after the procainamide is discontinued (Alarcon-Segovia, 1969).

### **COMMENT:**

This case meets all the criteria for diagnosis of procainamide DILS. Rechallenge was not necessary. There was no prior history of connective tissue disease. Procainamide had been started nine months before the admission and several months before the emergence of any symptoms. All of the clinical findings were consistent with procainamide DILS including: chest pain, pleural effusion, arthralgias, and myalgias. The rapid clinical resolution of the arthralgias and myalgias, within 4 days after the drug was discontinued, is consistent with procainamide DILS. The persistence of chest pain several months after drug withdrawal, with eventual resolution 11 months after drug withdrawal, is also consistent with procainamide associated DILS.

Five years after resolution of the syndrome, there has been no recurrence.

### **REFERENCES:**

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Price EJ and Venables PJW. Drug-induced lupus. *Drug Safety* 1995;12:283-290.

Dave Mace R.Ph., Drug Information Specialist.

*Dave Mace, R.Ph., Drug Information Specialist, reviewed 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.*

**EDITOR'S 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](mailto:donna-brus@uiowa.edu).



Donna Brus, Editor



## New Policy on Indexing Book/Software Reviews

Beginning with the January 2000 update, book and computer software reviews are no longer indexed into *IDIS* database. This will allow our staff more time to evaluate and include more clinically oriented articles from the medical literature. Originally, these types of reviews were included in the database because they were difficult to find elsewhere. Now book and computer reviews are easily retrievable from various Internet sites such as <http://www.medbooksnow.com>

## New Descriptor - 158 MEDICATION ERROR

The descriptor list will have a new addition starting with the March update. The new descriptor is 158 MEDICATION ERROR and it has been indexed starting with journals received in January 2000. The nature of medication errors will be denoted by existing descriptors, such as those for routes of administration, patient compliance or side effects/adverse reactions.

The addition of this new descriptor will simplify searches for articles in which medication errors are either a main or an important topic. To retrieve articles concerning drug errors for a specific drug, enter the name of the drug into the Drug Field of the Main Search screen along with the descriptor number 158 in the Descriptor Field. The addition of this new descriptor brings the total number of descriptors to 151.

## FDA DRUG/BIOLOGIC APPROVALS

<b>Generic Name (FDA Therapeutic Classification) Trade Name</b>	<b>Sponsor (Approval Date)</b>	<b>Valid IDIS Drug Term Drug Number (IDIS Citations)*</b>	<b>Indication/Use</b>	<b>Valid IDIS Disease Term Modified ICD-9-CM Number</b>
<b>Aminolevulinic Acid HCl</b> (1S)** <i>Levulan Kerastick</i>	DUSA Pharm (December 3)	AMINOLEVULINIC ACID 95000173 (51 citations)	For use with the BLU-U blue-light illuminator for photodynamic therapy of nonhyperkeratotic actinic keratoses of the face and scalp	Dermatosis NEC 702.
<b>Bexarotene</b> (1P)*** <i>Targretin</i>	Ligand Pharm (December 29)	BEXAROTENE 10120176 (4 citations)	For the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy	NEOP, MGN-Lymph/Histio NEC 202.
<b>Dexmedetomidine HCl</b> (1S) <i>Precedex</i>	Abbott (December 17)	DEXMEDETOMIDINE 28240845 (51 citations)	For sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting	Nervousness 799.2 Therapy, Respiratory 93.9
<b>Gadoversetamide</b> (1S) <i>OptiMARK</i>	Mallinckrodt (December 8)	GADOVERSETAMIDE 36680054 (2 citations)	For use with magnetic resonance imaging (MRI) in patients with an abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues; and to enhance visualization of liver lesions with abnormal vascularity	Magnetic Resonance Imaging 88.9
<b>Gatifloxacin</b> (1S) <i>Tequin</i>	Bristol Myers Squibb (December 17)	GATIFLOXACIN 8122025 (29 citations)	For treatment of community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis; acute bacterial sinusitis; complicated and uncomplicated urinary tract infections; uncomplicated gonorrhea; and pyelonephritis	Pneumonia, Bacterial NEC 482. Infection, Urinary Tract 599.0 Sinusitis, Acute 461.
<b>Levetiracetam</b> (1S) <i>Keppra</i>	UCB Pharma (November 30)	LEVETIRACETAM 28122040 (1 citation)	For adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy	Epilepsy, Part No Impair Consc 345.5

<b>Generic Name (FDA Therapeutic Classification) Trade Name</b>	<b>Sponsor (Approval Date)</b>	<b>Valid IDIS Drug Term Drug Number (IDIS Citations)*</b>	<b>Indication/Use</b>	<b>Valid IDIS Disease Term Modified ICD-9- CM Number</b>
<b>Moxifloxacin HCl</b> (1S) <i>Avelox</i>	Bayer (December 10)	MOXIFLOXACIN 8122029 (36 citations)	For treatment of acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis and mild-to-moderate community-acquired pneumonia	Pneumonia, Bacterial NEC 482. Sinusitis, Acute 461. Bronchitis, Chronic NEC 491.
<b>Nitric Oxide</b> (1P) <i>INOmax</i>	INO Therapeutics (December 23)	NITRIC OXIDE 24120055 (483 citations)	For the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension	Condition, Resp, Newborn NEC 770.

\* Through February 2000 Update. Complete bibliographic citations will be provided upon request.

\*\* (1S) New Molecular Entity given standard review by FDA

\*\*\* (1P) New Molecular Entity given priority review by FDA

*World of Drug Information* is published quarterly (March, June, September, December) by the Division of Drug Information Service.

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Production/Design Coordinator .....Julie Tomash  
Photographer ..... David Luck

# New Drug Selected Bibliography

This new drug selected bibliography provides key clinical studies and reviews of new drugs approved by the FDA in November and December 1999. *IDIS SYSTEM/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

## Bexarotene

Miller VA, Benedetti FM, Rigas AL et al. Initial clinical trial of a selective retinoid X receptor ligand, LGD1069. *J Clin Oncol*, 1997;15:790-795. (*IDIS* Article Number 381296). *Investigators conducted a dose ranging study to evaluate the safety, clinical tolerance and pharmacokinetics of LGD1069 (Bexarotene) in 52 patients with advanced cancer including cutaneous T-cell lymphoma.*

## Dexmedetomidine

Belleville JP, Ward DS, Bloor BC et al. Effects of intravenous dexmedetomidine in humans: I. Sedation, ventilation, and metabolic rate. *Anesthesiology*, 1992;77:1125-1133. (*IDIS* Article Number 306925).

*In a double-blind, placebo-controlled study, investigators assessed the sedative, ventilatory and metabolic effects of intravenous dexmedetomidine (0.25-2.0 microgram/kilogram over 2 minutes) in 37 healthy male volunteers.*

## Gadoversetamide

Terk MR and Rozenberg D. Gadolinium-enhanced MR imaging of traumatic hepatic injury. *AJR* 1998;171:665-669. (*IDIS* Article Number 410525). *Investigators evaluated the safety, tolerability and efficacy of gadoversetamide with gadopentetate dimeglumine in magnetic resonance imaging of five patients with hepatic abnormalities who had also undergone CT scans.*

## Nitric Oxide

Kinsella JP, Walsh WF, Bose CL et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic

respiratory failure: a randomised controlled trial. *Lancet* 1999;354:1061-1065. (*IDIS* Article Number 434259). *In a double-blind, randomized controlled multi-center trial, investigators studied the effect of low dose inhaled nitric oxide on survival in 80 premature neonates with unresponsive severe hypoxemic respiratory failure.*

Ehrenkranz RA, Finer NN, Avery G et al. Inhaled nitric oxide in full-term and neraly full-term infants with hypoxic respiratory failure. *N Engl J Med*, 1997;336:597-604. (*IDIS* Article Number 380409). *The Neonatal Inhaled Nitric Oxide Study Group conducted a randomized, multi-center, controlled study to assess the effect of inhaled nitric oxide on mortality and the initiation of extracorporeal membrane oxygenation in 235 neonates with hypoxic respiratory failure.*

Roberts JD, Fineman JR, Morin FC et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. *N Engl J Med*, 1997;336:605-610. (*IDIS* Article Number 380410). *Investigators conducted a randomized, prospective, multi-center study to study the efficacy of inhaled nitric oxide (80 parts per million) mixed with oxygen to decrease severe hypoxemia in 58 full-term neonates with severe hypoxemia and persistent pulmonary hypertension.*

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



Ruth Calloway, R.Ph., M.S.



STAFF  
PROFILES

Two University of Iowa College of Pharmacy students, Jenny Jamison and Chase Zaputil, work at DDIS helping with several production tasks and identification of new drug nomenclature.

Jenny Jamison moved to Iowa from Illinois in 1996 to attend the University of Iowa. She is currently working on her PharmD degree. Upon completion of her degree she plans to continue her education through a residency program. She enjoys reading, walking, listening to music, and spending time with her family.



Chase Zaputil joined the DDIS staff as a production assistant in July of 1998. Originally from Mystic, Iowa, Chase has been a resident of Iowa City since starting school at the University of Iowa in 1995. Chase is currently a third year pharmacy student at the University and plans to graduate in May of 2002. At DDIS, Chase is involved in many production tasks to prepare the articles for the database. These tasks include, scanning and proofing the articles, as well as proper identification of drug database numbers. In his spare time Chase enjoys writing and recording his own music, spending time with friends and family, and watching the stock market.

Jenny Jamison and Chase Zaputil

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