



World of Drug Information

Volume 11, Issue 3 – September 2000

CURRENT CLINICAL
ISSUES

U.S. FDA SUMMARY BASIS OF APPROVAL (SBA): UNEXPLORED AND UNDERUTILIZED

A total of 45 new chemical entities had been approved in 1997 by the Food and Drug Administration (FDA) for marketing in the United States. Drug sponsors apply to the FDA for approval by submitting a New Drug Application (NDA). The NDA contains information accumulated by the sponsor company through its research on the proposed new drug. NDAs consist of a variety of sections including chemistry, manufacturing, pharmacology, pharmacokinetics, safety and efficacy of a drug. Before drug approval, each section of an NDA is reviewed and analyzed by experts at the Center for Drug Evaluation and Research (CDER), a division of the FDA. If a new drug is approved, the FDA is required by federal regulation to make available to the public the information evaluated by the FDA during the drug approval process and a summary of the safety and effectiveness data. This summary is known as the Summary Basis of Approval Equivalent (SBA). An SBA is an amalgamation of the information from the sponsor's NDA and the CDER reviewer's analysis and summary of this information. The SBA for a specific drug may be requested from the FDA through a Freedom of Information Act Request to FOI Services (an agency of the U.S. Federal Government). Recently, a few SBAs have appeared on CDER's web site.

The sections included in an SBA are similar to those in an NDA (Fig. 1). Some of the more informative sections in an SBA from a clinical standpoint include: The Medical Officer's Review, Clinical Pharmacology and Biopharmaceutics Review, and the Statistical Review and Evaluation. Often included within these sections are detailed summaries of the pivotal and supportive studies for a drug.

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Sections Commonly Appearing in an SBA

- Letter of Approval
- Letter of Acknowledgement
- Patent Information
- Patent Certification
- Exclusivity Summary
- Debarment Certification
- Request for Trademark Review
- Drug Studies in Pediatrics
- **Medical Officer's Review**
- Material Safety Data Sheet
- **Clinical Pharmacology and Biopharmaceutics Review**
- Review and Evaluation of Pharmacology and Toxicology Data
- **Statistical Review and Evaluation**
- Review of Chemistry, Manufacturing and Controls
- Environmental Assessment of Finding of No Significant Impact

Figure 1

Pivotal studies are the studies the sponsor or drug company believes show the safety and efficacy of a drug for an indication. The pivotal studies form the basis or foundation for the drug approval. The supportive studies are the studies that reconfirm or substantiate the results found in the pivotal studies.

Surprisingly, the studies that show the safety and efficacy of a drug, the pivotal studies, are not always published in the medical literature. And if they are published, they may not appear in the

literature until many months after the drug has been approved. In order to obtain some objective evidence on the publication status of pivotal studies we conducted a study which is presented below. The objective of this exploratory study was to describe and summarize the drug information content of the Summary Basis of Approval Equivalents (SBA) for 20 new drugs approved in 1997, noting the links or missing links between the SBAs and the published literature.

METHODS

The twenty new drugs selected for the study were chosen because the SBA for these drugs had already been obtained from FOI services (Table 1). The SBAs were obtained by writing or faxing a letter to FOI services requesting the SBA for a newly approved drug. After receiving the SBA, each one was thoroughly reviewed to identify the pivotal studies named by the drug sponsor. If the pivotal studies were identifiable, it was noted whether the trial was randomized, blinded, placebo or active controlled, multi-center, number of patients, protocol number or description, the primary and secondary objectives of the study and the drug sponsor. This information aided in determining if

The 20 drugs selected and the number of indications and pivotal studies identified are:

Drug Name	Indications	Pivotal Studies
Anagrelide HCl	1	2
Bromfenac Sodium*	2	5
Cerivastatin Sodium	1	3
Delavirdine	2	2
Dolasetron mesylate	2	4
Fenoldopam mesylate	1	2
Grepafloxacin HCl	5	8
Imiquimod	1	3
Irbesartan*	1	17
Mibefradil dihydrochloride*	2	17
Nelfinavir mesylate	1	3
Pramipexole dihydrochloride	1	3
Repaglinide	1	6
Tamsulosin	1	2
Tazarotene*	2	9
Tiagabine	1	3
Tiludronate disodium	1	3
Toremifene citrate	1	3
Troglitazone	3	4
Zolmitriptan	1	4
* "Pivotal" not used in SBA		

Table 1

Design Characteristics	N = 103 (100%)
Randomized	98 (95)
Double-Blind	91 (88)
No Control	9 (9)
Placebo Control	46 (45)
Active Control	32 (31)
Placebo and Active Control	16 (15)
Multicenter Study	96 (93)
Duration of studies: 1 day to 8 years	
Number of Subjects/Study: 24 to 1258	

Figure 2

the pivotal studies had been published in a journal by comparing it to the drug's bibliography generated from independent searches of *MEDLINE* and the *Iowa Drug Information Service (IDIS)* databases. The drug sponsor was also contacted by letter requesting information on the publication status of the pivotal studies. Records were kept of the date drugs were approved, the date the SBAs were requested and when they were received from FOI services. The date letters were sent to drug sponsors and

when they replied were also recorded.

RESULTS

A total of 103 pivotal studies were identified for the 20 drugs (Fig. 2). The number of pivotal studies per drug ranged from 2 to 17. Of the 103 pivotal studies, 95% (98/103) were randomized, 88% (91/103) double-blind, 45% (46/103) placebo controlled, 31% (32/103) active control, 16% (15/103) placebo and active control, and 9% (9/103) no control. Ninety-three percent (96/103) of the studies were multi-center studies. The duration of the studies ranged from 1 day to 8 years. The number of subjects enrolled in the studies ranged from 24 to 1,258.

Of the 103 pivotal studies, 49% (51/103) appeared as journal articles in the medical literature identified through *MEDLINE* or *IDIS* searches. Eleven percent (11/103) appeared as abstracts or posters and 40% (41/103) had not been published (Fig. 3) in journals indexed by *MEDLINE* or *IDIS*. Sixteen of the 51 published pivotal studies were published before the drugs were approved for marketing in the U.S. with 8 of those studies being published a year or more before approval (Fig. 4). Thirty-four of the pivotal studies appeared in the medical literature after the date of the drug approval (Fig. 5). The date of publication was indeterminate for one published pivotal study. Of the 20 drugs, none of the pivotal studies for 6 drugs were published (Fig. 6) in journals indexed by *MEDLINE* or *IDIS*. There were only 5 SBAs in which all of the pivotal studies identified were published (Fig. 7). The number of unpublished pivotal studies per SBA ranged from 0 to 9. The time between requesting the SBA from FOI services and receiving it ranged from 1 to 7 months. Eighteen of the SBAs were received within less than 4 months from time of request (Fig. 8).

Publication Status of Pivotal Studies

	N = 103 (100%)
Journal Article	51 (49)
Abstract or Poster ("unpublished")	11 (11)
Not published	41 (40)

Figure 3

DISCUSSION

The main conclusion to be drawn from this study is that SBAs contain information about newly approved drugs that may not be published in the medical literature. At the time of this study, 40% (41/103) of the pivotal studies, the studies purported to show the safety and efficacy of a given drug, were either unpublished or appeared in journals not indexed by *MEDLINE* or *IDIS*. The majority of information from these studies was most likely unpublished and only available through the SBAs. The information contained in SBAs is valuable. Ninety-five percent of the pivotal studies identified were randomized studies and 91% were controlled. The limitations and inadequacies of these studies are also highlighted in the reviews done by CDER experts.

Pivotal Studies Published After NDA Approval

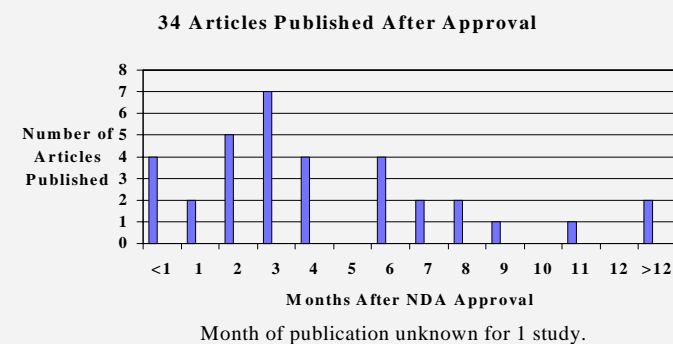


Figure 5

section of the SBA is indexed for side effects, pharmacokinetics, pharmacodynamics, etc. SBAs are found in the *IDIS* database by combining the valid drug term with descriptor *155 SUMMARY BASIS OF APPROVAL*.*

In 1998, bromfenac and mibefradil, two drugs within the list of 20, were withdrawn from the U.S. market for safety concerns. The FDA has also recently requested that troglitazone, another drug on the list, be removed from the market. The SBAs for these drugs contained summaries and critiques of pivotal studies that were unpublished at the time of this study. The information contained in the pivotal studies may or may not have

Pivotal Studies Published Before NDA Approval

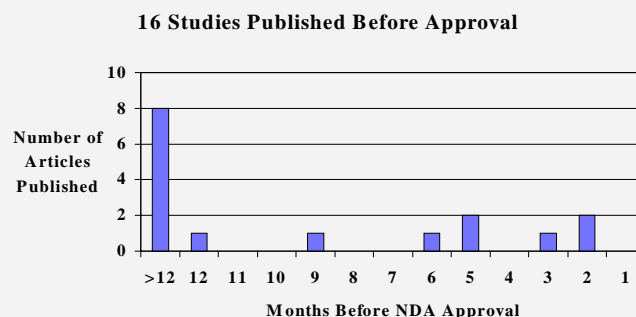


Figure 4

In this study, requests for SBAs were answered within 1 to 7 months. In our experience it is not uncommon to receive an SBA over a year after it has been requested from FOI services. SBAs are not generally available from the drug sponsor or manufacturer.

SBAs are available within the *IDIS* database. To make SBAs more manageable, a Table of Contents is created for each SBA. The pivotal studies are identified and an abstract for each pivotal study is created. Each

swayed a practitioner's decision to recommend or prescribe these drugs. Whether ordered directly from FOI services or viewed in the *IDIS* database, the SBA offers clinical practitioners an alternate source of critical information on new drugs.

**Note: There are currently over 45 SBAs in the IDIS database. The majority of the SBAs in the database, are from 1998 and 1999. Three SBAs from 1997(mibefradil, becaplermin and nelfinavir) appear in the database. SBAs were not routinely added to the IDIS database until 1998.*



Brad Gilchrist, R.Ph.

Number of Unpublished Pivotal Studies Per SBA Document

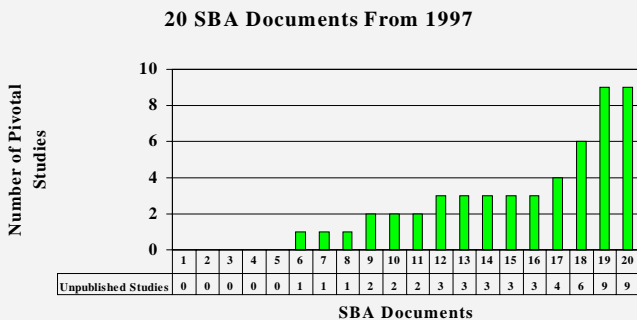


Figure 7

Time Between Request for SBA From FDA FOI and Receipt

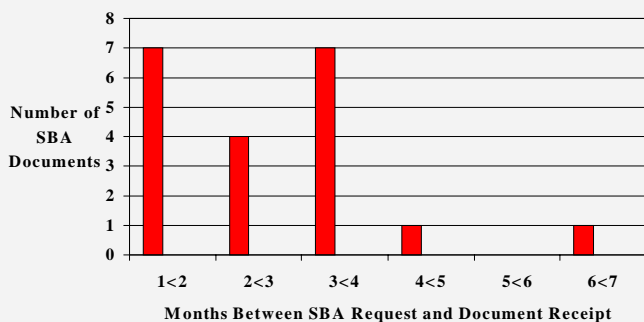


Figure 8

Number of Pivotal Studies Published Per SBA Document

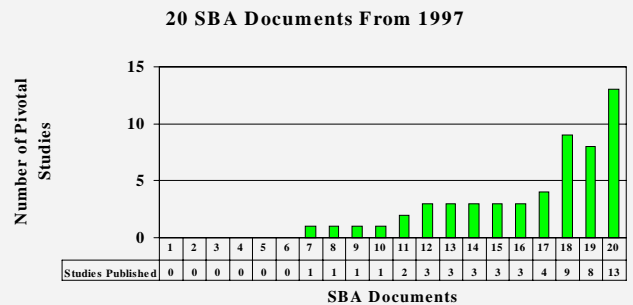


Figure 6

IDIS/Web

Featured in Search Tips.

See next page for details.

IDIS/Web

SEARCH TIPS

IDIS/Web will be available soon. *IDIS* subscribers have been provided with a User Identification and Password to access *IDIS/Web*. Notice of availability of *IDIS/Web* and a link to the database appear on our web site: <http://www.uiowa.edu/~idris>.

Please take this opportunity to explore this new media format for *IDIS*. We look forward to your comments and suggestions—they will shape future development of the web version of the database.

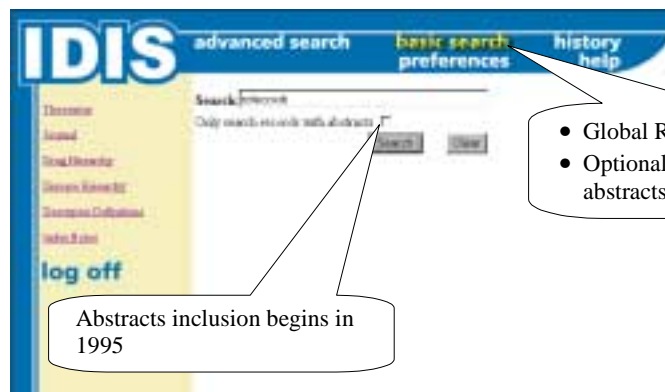
—Hazel H. Seaba, Director

IDIS/Web program opens with two search options: **Advanced Search** or **Basic Search**. Auxiliary searchable files such as Thesaurus, Drug Hierarchy, Journal, Disease Hierarchy, Descriptor Definitions and Index Notes offer additional tools for effective search retrieval. Online search help is also available.

Auxiliary Searchable Files



The **Basic Search** template allows a **global** retrieval. The program retrieves citations containing the search term or its cross reference term(s) anywhere in the index record. It will search the whole database as a default. You can restrict your search to articles having abstracts by selecting the check box.



With the **Advanced Search** template distinct fields within an *IDIS* index record can be searched individually or combined with each other by a Boolean connector. Advanced search offers more flexibility and specificity.

Advanced search example: Are there any review articles related to Vioxx used in the treatment of rheumatoid nodules in *IDIS*?

Search Steps:

- Click on the **Drug Look Up** button, enter the drug term Vioxx,
- Click on Submit to bring the list of valid terms.
- Click on Rofecoxib to highlight the term.
- Click on **Submit**.

Rofecoxib will be automatically pasted in the drug field.

- Repeat the same steps with the **Disease Look up** and the term “rheumatoid nodule”
- Click on the **Descriptor Look Up**

button. Scroll to choose and click on “review, adult” to generate an automatic transfer into the descriptor search field

- **Logical Operators** choice: “and”
- Click on search

Diagram illustrating the search process flow: Specific Searchable Fields + Boolean Operator → Relevant Citations.

Callouts on the right side of the screenshot describe search features:

- ◆ Searchable defined term(s)
- ◆ Automatic selected term transfer
- ◆ Valid term pick list
- ◆ Multiple picks possible
- ◆ Journal titles
- ◆ Correct titles abbreviations

Search Results:

The result template shows the citations, the number of citations retrieved and the number of result pages. The **results** are displayed according to your preset preferences. The number of citations per page and citation format can be changed during a search session by selecting the appropriate option and clicking “adjust.” The results can be **viewed** on screen, **printed** or **e-mailed** to yourself under a short bibliographic or a full record format. The full article can be read on screen by clicking on the article number. Search strategies can be **saved** for future use.

Callouts on the screenshot describe search result options:

- Index Record Selection for printing or E-mail
- Output Display Format Options
- Result Summary
- Index Record
- Save Search History
- Results:**
 - Print
 - Read on screen
 - Self E-Mail

Online Help: provides detailed explanation of our database and search guidance. If you have any questions regarding *IDIS/Web*, please do not hesitate to contact us and an *IDIS* pharmacist will gladly assist you.



ThaiBinh TonThat, R.Ph., Pharm.D.

Specialized Residency Pharmaceutical Informatics/ Drug Information

University of Iowa College of Pharmacy
University of Iowa Hospitals and Clinics
Iowa City, Iowa

This 12-month specialized residency is a collaborative program offered by the University of Iowa College of Pharmacy and the University of Iowa Hospitals and Clinics Department of Pharmaceutical Care.

This specialized residency focuses on developing mastery level skills in:

- verbal and written communication
- critical literature evaluation and interpretation
- problem solving in information management and therapeutics
- use of technology for storage, retrieval, analysis, and distribution of information
- medication use evaluation and policy development

Requirements for Admission

Candidates must have a Pharm.D. or M.S., and be eligible for licensure in the State of Iowa. Applicants for this specialized residency should have completed a pharmacy practice residency or have comparable experience. An on-site interview is required.

Who Should Apply

Individuals interested in a career in the areas of: drug information practice; pharmaceutical benefits management; information services in pharmaceutical industry; clinical research organizations; outcomes research; health care technology assessment; pharmacoconomics; and pharmacoepidemiology.

Application

To obtain application materials contact one of the Co-directors. The application deadline is February 1, 2001.

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Perspective from an *IDIS* Subscriber



Re: Late occurring “flu-like or serum sickness-like” syndrome in a 36 year old male with a history of cardiac problems and dysthymia. Possibly drug related?

HISTORY OF PRESENT

ILLNESS: On 4/12/00 the patient presented to the emergency room with a two day history of sub-sternal chest pain radiating to the left arm and jaw accompanied by mild nausea and shortness of breath. He was treated in the emergency room with beta blockers and nitroglycerin which provided relief. His cardiac enzymes were negative. He was admitted to medicine service. The discharge diagnosis was non-cardiac chest pain.

During the second or third week of May 2000 the patient noticed the presence of more widespread skin lesions, which began on his arms and eventually spread to his back, trunk, thighs and legs over several weeks. He had been treated for several years for recurrent folliculitis with cephadrine and dicloxacillin. Many of these new lesions were not in the area of hair follicles and all were pruritic. On excoriation clear fluid drained from the lesions. Until early July he reported no other new symptoms.

In the afternoon of July 21, 2000 he described the sudden onset of a “flu-like” syndrome of malaise and fatigue with minor myalgia, pain on movement, and headache. By that evening he was experiencing a “cold-sweat” over his whole body, his headache and pain were worse and he had become nauseous. He described pain in all joints including jaw, shoulders, elbows, wrists, fingers, hips, knees, L ankle (R ankle in cast), and toes. Over the next 48 hours the myalgias and arthralgias severity worsened. By the time he presented to the ER on July 24, 2000 at 7:23PM, the pain in his joints was severe, all his joints were tender and he described “whole body” pain which was equal in all areas. His appetite began to decline at the onset of the syndrome and was virtually gone by the time he presented to the ER. He had no history of prior appetite disturbances. He also reported the new onset of “achy” abdominal pain in the middle left quadrant and in the right pubic area. He had no history of prior abdominal or pubic area pain. He also described the new onset of headache with dull non-throbbing pain in the frontal, fronto-occipital, and occipital areas. His headache pain was moderate intensity, constant, present upon awakening and throughout the day until he fell asleep. He also

reported edema in both wrists, his watch no longer fit, and a tight feeling in his throat. There were no chart entries describing either the presence or absence of lymphadenopathy. He reported four episodes of semi-solid diarrhea over the past two weeks, and other episodes since the syndrome began. He described the syndrome as constant for the past 19 days. Throughout the past 19 days new skin lesions have appeared, his headache, joint and muscle pain, and pruritis have not diminished.

PRIOR MEDICAL

HISTORY (PMH): He reported several attacks of non-cardiac chest pain in the past dating back to before a 11/97 hospital visit. He had a cardiac catheterization in 1997 which he understood was normal. His recent medicine admission work up added mild GERD to his history.

Other PMH includes allergic or vasomotor rhinitis; long standing uncontrolled hypertension; mild abnormalities on his echocardiogram; hyperlipidemia, and dysthymia. (first drug therapy for depression in our records is citalopram 20 mg qd starting on 9/27/99.)

MEDICATIONS: Dicloxacillin NA 500mg tid for 30 days. (folliculitis); Erythromycin 2% topical soln (skin lesions); triamcinalone 0.1% cr. (skin lesions); atenolol 50 mg qd (HTN); HCTZ 25/triamterine 37.5 (HTN); felodipine 10 mg bid (HTN); isorbide dinitrate 10 mg 1 tid (angina) NTG 0.4mg SL (angina); lansoprazole (non-cardiac chest pain vs GERD); citalopram 40 mg qd (dysthymia);**recently discontinued simvastatin 80 mg 0.5 tab qd (hyperlipidemia).

LITERATURE: Erffmeyer reviewed serum sickness including the common clinical and laboratory findings, which include the following symptoms (Erffmeyer, 1986). He described fever which is usually mild, arthritis or arthralgia usually of multiple large joints with occasional involvement of the small joints, edema may be present usually around the face and neck. The primary syndrome usually occurs within a few days, however both signs and symptoms may persist for several weeks.

Roujeau and Stern reviewed adverse cutaneous reactions due to drugs (Roujeau, 1994). Included was a discussion of “serum sickness” which due to its delayed onset, slow evolution and clinical similarity to many infectious illnesses the diagnoses is often missed or delayed. They report that the skin findings are distinctive with erythema first, on the sides of fingers, toes, and hands before a more widespread eruption which is often morbilliform.

Cefadrine

Vial reviewed cephadrine associated serum sickness like reactions (Vial, 1992). Almost all of the reports were in children of less than 5 years of age. Polyarthralgia occurred in approximately half of reported cases with the knee, shoulder and elbow joints being most often affected. Recurrence of the syndrome has not been described following rechallenge with cephadrine without any similar flu-like syndrome are against it being the cause of his recently described syndrome.

Zimeldine

Zimeldine, a relatively unknown SSRI (in the US) was removed from the worldwide market due to suspected hypersensitivity reactions in September 1983. It had been introduced in five European countries and given to about 200,000 patients. According to Ruiz and colleagues, approximately 2% of clinical trial patients treated with zimeldine developed a multi-systematic reaction characterized by fever, joint pain and/or muscle pain and transient increases in serum transaminases (Ruiz, 1987). In most cases the symptoms appeared 14-21 days after initiation of therapy (Langlois, 1985). Langlois and associates discussed the possibility of a direct cellular toxic mechanism and suggested that the syndrome appeared to be dose related. In their case series all seven patients developed the syndrome a few days after the zimeldine dose had been increased from 200 mg to 300 mg daily (Langlois, 1985). Other authors favor an immunological mechanism, because the total dose was low in all patients at the time of the influenza-like reaction. Many other patients have received zimeldine for many months with very high cumulative doses without the emergence of any side effects (Fagius, 1985).

Fluoxetine

There have been at least four published and 32 unpublished reports of so called “serum sickness” associated with fluoxetine. (Beer, 1994, Lezhoff, 1992, Miller, 1989, Sapiro, 1997, Vincent, 1991).

In one case, fluoxetine was discontinued; the syndrome was thought to be infectious. One week later fluoxetine was restarted and several features of the syndrome returned. A personal communication with Eli Lilly and Company indicated they were aware of 32 cases described

as “serum sickness” among 2.5 million patients treated with fluoxetine (Vincent, 1991).

In another case a patient developed a rash, eosinophilia and arthralgias believed to be associated with fluoxetine. The syndrome remitted when fluoxetine was discontinued and steroids were given. On rechallenge with fluoxetine the dermatitis recurred. About two months later she decided to take a dose of fluoxetine to help her sleep. One day later she began to have a similar but less severe cutaneous eruption. She had been on fluoxetine for about 36 months prior to the first presentation of the rash (Beer, 1994).

A 16 year-old girl on no other medications was treated for depression with fluoxetine 20mg daily. Four weeks later she presented with a generalized urticarial eruption, arthralgias, difficulty swallowing, and a fever of 39 C. She had stopped the fluoxetine 48 hours before presentation. Seventy-two hours after admission her fever had resolved and the exanthem and arthralgia were improved (Sapiro, 1997).

Bupropion

Peloso described a young man who had begun bupropion at 300mg/day for 10 days to quit smoking. He presented to the ER with a diffuse achiness of the shoulders and hips. The next day he had diffuse swelling of fingers, toes, knees and eyelids. His symptoms progressed to include a sense of throat tightness. He denied taking any other drugs. His temp was 37.8 C, there was no adenopathy, no evidence of joint swelling, there was nonpitting edema of the hands and feet. Joint pain was present in the shoulders, elbows, wrists, hands, hips, knees, and feet. The urticaria was widespread involving his trunk, upper extremities, and abdomen. He was treated with steroids and experienced marked improvement within 24 hours (Peloso, 1999).

Canadian clinical trial data lists myalgias and arthralgia in 4-5% of bupropion patients compared with 2-3% of persons taking placebo (Peloso, 1997).

Yolles and colleagues reported a case of serum sickness associated with bupropion (Yolles, 1999). On day five after beginning bupropion the patient developed a temperature of 39 C and reported joint pain (worse in elbows) and pain in his chest. The following day a nonpruritic morbilliform rash developed on his upper and lower extremities and flanks.

Citalopram, (Celexa™)

The following information is from the FDA NDA summary (SBA) for citalopram: (SBA)

Musculoskeletal events unlikely to be citalopram related:

- ❑ 43 year old female with polymyalgia rheumatica after 8 months of therapy;
- ❑ one patients with arthritis? Who discontinued therapy;

- two patients one with arthritis and one with arthrosis

Events considered possibly, probably, or definitely related to citalopram:

- study 94001 #183: 34 year old female developed a rash with itching over the whole body fever, and swollen lymphatic glands 11 weeks after starting citalopram.
- Post marketing: Seven (7) cases of allergic reaction, one of which was serious and led to hospitalization.

***Rash and urticaria are included in the labeling as “frequent events.”

Dropouts due to SAEs in the “body as a whole” category:

- Non-cardiac chest pain (2);
- Malaise (1)

Other SAEs under “body as a whole” category:

- Non-cardiac chest pain (2);
- Anaphylactoid reaction (2)

Events reported by at least two percent of patients treated w/citalopram:

- Musculoskeletal system disorders;
- Arthralgia;
- Myalgia

COMMENT:

My impression is that the work up for infectious causes of the patient’s syndrome was unrewarding. A major confounding factor is the history of folliculitis. It is unlikely, but possible, that the dicloxacillin or cephadrine could be responsible for a serum sickness like syndrome.

Beta-blockers, especially those with intrinsic sympathomimetic activity, have been reported to cause muscle cramps in the calves (Imia, 1995). They have also been associated with proximal muscle weakness, (Stone, 1979) and are said by some to have caused arthritis (Waller, 1985). We are unaware of any cases which have described “flu” or “serum sickness” like syndromes. It is unlikely that atenolol which was begun in April 2000 is responsible for the syndrome.

Although many of the reported cases with various SSRI’s use the terms “serum sickness” or “serum sickness-like” it is not clear that the mechanism for this syndrome is immune mediated. In fact many of the cases occurred after only a few days and other appeared as late as three or four weeks after the drug was introduced. In other cases lower doses were tolerated, but within a few days of dose increase the syndrome emerged. Bakish described a patient who experienced a syndrome of myalgia, fever, and malaise which occurred after exposure to zimeldine, nomifensine, and trazodone (Bakish, 1986). Interestingly nomifensine has no serotonin reuptake inhibition activity.

I have experience with only one other case of an acute onset polyarthralgia syndrome associated with an SSRI. Sertraline had been restarted in October after about a six-month period off. The patient, a 47 year old white male, presented with a 4-5 day history of migratory arthralgia which began in his L shoulder and eventually spread to all his joints. The pain was relieved by Toradol 30 mg IM. (Mace, 1995).

The most likely toxic explanation for the recent dermatological lesions not in the area of hair follicles and his “flu like syndrome” is an adverse reaction to citalopram. For clinical details of the recent syndrome see Table 1 and the discussion under the history of present illness.

This syndrome which began thirty-seven days after the order for the citalopram dose increase (uncertain when he actually started taking the higher dose) is similar to the prodromal phase reactions described for zimeldine an SSRI which was removed from the market, and the few published cases reported for fluoxetine. The possibility that his syndrome could progress to the Guillain-Barre’ syndrome described in a few of the zimeldine patients is unknown.

Bengtsson and colleagues described no crossover reactions in three patients who had experienced flu-like reactions to zimeldine (Bengtsson, 1991). Seven weeks after a toxic syndrome due to zimeldine had resolved a 70 year old female was given citalopram 20mg daily with good effect. After six months of citalopram she had reported no adverse effects. The second patient, a 77 year old female, had reacted to 100mg of zimeldine daily. Three days after zimeldine was discontinued her syndrome resolved. After a course of electro-convulsive therapy, citalopram 20mg daily was started. At her five month follow up visit, there was no sign of any adverse reaction. The third patient, an 85 year old female, developed the toxic syndrome 14 days after zimeldine was started. Within two weeks after zimeldine was discontinued her syndrome resolved. She did not respond to ECT and was eventually treated with citalopram 30mg daily without the development of any adverse reaction.

Chouinard and colleagues described a 41 year old female who developed a flu-like syndrome one week after starting zimeldine 200mg daily. One week after stopping the zimeldine her syndrome had resolved. Therapy with fluoxetine 20mg the first day, 40mg the second day and then 100mg daily was continued for four months without any symptoms similar to her previous syndrome (Chouinard 1984).

I would suggest a withdrawal of the citalopram. The patient has been given information on possible citalopram withdrawal symptoms. Resolution of the syndrome has occurred within 3-10 days after the SSRI was discontinued. In most cases recovery was complete. Some consideration might be given to a rechallenge. Several patients who experienced the syndrome and took

single doses of the drug at a later time had a rapid, mild, similar syndrome emerge.

FOLLOW UP:

The patient will be seen in clinic and the citalopram discontinued. If citalopram is the cause of his syndrome, remission should be complete within a few weeks.

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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.

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.



Donna Brus, Editor

Table 1.

CLINICAL FEATURE	PATIENT	FLUOXETINE	ZIMELDINE	BUPROPION
Onset: (speed/time frame)	Sudden; by day 4 full blown (onset 7/21/00)	Sudden; by day 5 (4/6 & 2 unknown)	Sudden (7/30); probably sudden (23/30)	Sudden (2/2)
Progression:	New skin lesions; otherwise constant from day 5-day to day 21	Similar (6/6)	No data	96 h p med dc'd (1/2) no data (1/2)
Resolution: (time frame)	N/A	3 days (1/6) unknown (5/6)	4-10 days (7/30) no data (23/30)	11 days after d/c'd (1/2); no data (1/2)
Abdominal pain	Yes (no prior history)	(1/6)	Yes (4/30); no data (23/30)	(0/2)
Arthralgia: (list joint)	Neck, shoulders, elbows, wrists, fingers, hips, knees, ankles, toes? (no prior history)	Polyarthralgia (4/6)	Polyarthralgia (24/30)	(0/2)
Diarrhea	Semi-solid x 4 over past 14 days; several similar episodes since onset	(2/6)		
Headache	Constant; tension-type distribution (no prior history)	(2/6)	(20/23) & (7/7)	(1/2)
Myalgia	Whole body: PH did not wish to be more specific. (no prior history)	(1/6)	(26/30)	(0/2)
Nausea	Constant (no prior history)	(0/6)	(18/30)	(1/2)
Rash: (description/location)	Pruritic lesions spread from the forearms to the back, trunk and LE's	(6/6)	(19/30)	Trunk, arms and abdomen (2/2)
Fever:	No data	101/3-102/2 F (3/6)	>100.4 (14/23) 99/5-101.3 (7/7)	100.4 (1/2); 102.2 (1/2)
Abdominal pain	Yes-middle and left upper quadrant & R pubic area. (no prior history)	(1/6)	Yes (3/7); no data (23)	(0/2)
Edema extremities: (location)	Wrists and LLE (no prior history)	Non-pitting in hands and feet (1/6)	(4/30)	Extremities (1/2)
Appetite:	Early reduction-by the 2-3 rd day almost total absence – still absent (no prior history)	(1/6)	No data (30/30)	

You're Invited ...

Visit the *IDIS* booth at the upcoming professional meetings:

American College Clinical Pharmacy (ACCP)

Annual Meeting
Los Angeles, California
November 5-8

American Society of Health-System Pharmacists (ASHP)

Midyear Clinical Meeting (MCM)
Las Vegas, Nevada
December 3-7

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Argatroban (1S)** <i>Acova</i>	Texas Biotech (June 30)	ARGATROBAN 20120410 (27 citations)	For prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia	Thrombocytopenia, Secondary 287.4 TX/AE-Drug/Chemical E999. Embolism/Thrombosis, VN NEC 453.
Balsalazide Disodium (1S) <i>Colazal</i>	Salix (July 18)	BALSALAZIDE 56400016 (26 citations)	For treatment of mildly to moderately active ulcerative colitis	Proctocolitis, Idiopathic 556.
Colesevelam HCl (1S) <i>Welchol</i>	GeITex (May 26)	COLESEVELAM 24060012 (2 citations)	For reduction of elevated LDL-cholesterol, alone or in combination with an HMG-CoA reductase inhibitor, in patients with primary hypercholesterolemia (Frederickson Type IIa)	Hypercholesterolemia, Pure 272.0
Gemtuzumab Ozogamicin (1P)*** <i>Mylotarg</i>	Wyeth Ayerst (May 18)	GEMTUZUMAB OZOGAMICIN 10120201 (3 citations)	For the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years or older and are poor candidates for cytotoxic chemotherapy	Leukemia, Myeloid, Acute 205.0
Insulin Aspart (1S) <i>NovoLog</i>	Novo Nordisk (June 7)	INSULIN ASPART 68200822 (8 citations)	Treatment of adult patients with diabetes mellitus for control of hyperglycemia	Diabetes Mellitus 250.
Tenecteplase (NA)**** <i>TNKase</i>	Genentech (June 2)	TENECTEPLASE 20400014 (20 citations)	For reduction of mortality associated with acute myocardial infarction	Infarction, Myocard, Acute 410.
Tinzaparin Sodium (1S) <i>Innohep</i>	Dupont (July 14)	TINZAPARIN 20120422 (102 citations)	Treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium	Embolism/Thrombosis, VN NEC 453. Embolism, Pulmonary 415.1
Triptorelin Pamoate (1S) <i>Trelstar Depot</i>	Debio Recherche (June 15)	TRIPTORELIN 68180008 (255 citations)	For the palliative treatment of advanced prostate cancer	NEOP, MGN-Prostate 185.

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

** New molecular entity given standard review by FDA.

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

**** Not applicable.

New Drug Selected Bibliography

This new drug bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA May through July 2000. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

Balsalazide

Green JRB, Lobo AJ, Holdsworth CD et al. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. *Gastroenterology* 1998;114:15-22. (*IDIS* Article Number 399117). ***In a randomized, double-blind study, investigators compared balsalazide, 6.75 daily, to mesalamine, 2.4 g daily, administered for 4, 8 or 12 weeks in 101 patients with symptomatic, sigmoidoscopically verified ulcerative colitis.***

Colesevelam

Davidson MH, Dillon MA, Bordon B et al. Colesevelam hydrochloride (Cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999;159:1893-1900. (*IDIS* Article Number 433533). ***In a multi-center, randomized, double-blind, placebo controlled study, investigators compared colesevelam hydrochloride (1.5, 2.25, 3.0, or 3.75 g/d) for 6 weeks with placebo, following diet and placebo lead-in periods, in 137 patients with hypercholesterolemia.***

Gemtuzumab Zogomicin

Sievers EL, Appelbaum FR, Spielberger RT et al. Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: a phase I study of an anti-CD33 calicheamicin immunoconjugate. *Blood* 1999;93:3678-3684. (*IDIS* Article Number 427265). ***In a phase I study, investigators assessed the effect of gemtuzumab zogomicin infusions, 0.25, 0.5, 1, 2, 4, 5, 6, 9 mg/m², in 40 patients with relapsed or refractory CD33⁺ acute myeloid leukemia.***

Insulin Aspart

Raskin P, Guthrie RA, Leiter L et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 2000;23:583-588. (*IDIS* Article Number 448663). ***Investigators conducted a randomized open label six-month study (882 subjects) with a six-month extension period (714 subjects) to assess long-term glycemic control and safety of insulin aspart compared with regular human insulin as the mealtime***

component of an intensive insulin regimen in subjects with type 1 diabetes.

Home PD, Lindholm A, Hylleberg et al. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. *Diabetes Care* 1998;21:1904-1909. (*IDIS* Article Number 416069). ***In a multi-center, randomized, double-blind crossover study, (4-week study periods), investigators compared glycemic control obtained with insulin aspart to that of human insulin using algorithm-driven dosage adjustment in 90 male subjects with type 1 diabetes.***

Tenecteplase

Van de Werf F, Adgey J, Ardissino D et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double blind randomised trial. *Lancet* 1999;354:716-722. (*IDIS* Article Number 432644). ***In a multi-center, randomized, double-blind controlled trial, investigators compared the efficacy and safety of tenecteplase (single-bolus 30-50 mg according to bodyweight) with alteplase (rapid infusion <100 mg) in 16,949 patients with acute myocardial infarction of less than 6 hours duration.***

Van de Werf F, Cannon CP, Luyten A et al. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. *Am Heart J* 1999;137:786-789. (*IDIS* Article Number 430336). ***Investigators evaluated the safety of 30, 40, and 50 mg single-bolus doses of tenecteplase administered to 3235 patients within 12 hours onset of myocardial infarction.***

Cannon CP, Gibson M, McCabe CH et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998;98:2805-2814. (*IDIS* Article Number 450788). ***In a multi-center, randomized controlled trial, investigators compared the angiographic efficacy and safety of 30 or 50 mg single bolus tenecteplase with front-loaded alteplase in a 1:1:1-ratio in 886 patients with acute ST-elevation myocardial infarction presenting within 12 hours.***

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.



Mike Conrey and Steve Hancock

**STAFF
PROFILE**

Mike Conrey (front) joins the DDIS staff as a drug information assistant in May 2000. Originally from Cedar Rapids, Iowa, Mike has been a resident of Iowa City since starting school at the University of Iowa in 1998. He is currently working on his PharmD degree. Upon completion, Mike hopes to continue his education in medicinal chemistry, with aspirations of one day working in the development and manufacturing end of the drug industry. In his spare time Mike enjoys playing basketball, tennis, and spending time with friends and family.

Steve Hancock (back) joined the DDIS staff as a production assistant in May of 2000. Originally from Epworth, Iowa, Steve plans to pursue a major in Communications. Steve is involved in many of the duties concerning the production tasks associated with the drug information database. These tasks include CD proofing, journal cutting and stamping, and data entry. In addition to contributing to DDIS, Steve is also involved with Security/Investigation for a regional casino. Steve enjoys writing, swimming, and social events shared with friends and family.

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