SECOND EDITION

The CenterWatch Directory of Drugs in Clinical Trials

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Drugs in Clinical Trials

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THOMSON HEALTHCARE

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For further information about *The CenterWatch Directory of Drugs in Clinical Trials* or any other CenterWatch publication or service, call (617) 856-5900.

ISBN: 1-930624-18-2

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Preface to the Second Edition

The drug development pipeline continues to produce a great variety of new drugs for the treatment of existing and new indications. These represent only a fraction of those compounds that have been studied in the laboratory. The success of CenterWatch's first edition of *The Directory of Drugs in Clinical Trials* supported the belief that a compendium of drugs in clinical development would be a useful reference source. As the number of agents being actively studied continues to increase, it is important that this reference source be updated and we have done just that. The first edition contained references to approximately 1,100 drugs. This edition presents information on approximately 1,900 drugs and more than 400 indications.

This second edition is written for the health care professional and the sophisticated lay person. Scientific language is used throughout and as much information as could be accumulated from press releases, presentations at meetings, company contacts and medical literature has been included. We have aspired to provide information on as many new therapies as possible—still, this is not an exhaustive resource as information on some drugs has not been made available.

We have expanded the second edition of *The Directory of Drugs in Clinical Trials* to cover all active clinical trials. This edition focuses on drugs in development from phase I, II and III and includes information on some NDAs that have been submitted or withdrawn. Additionally, we have expanded our coverage of active clinical trails to include trials conducted worldwide. It is important to note that this directory does not include the relatively small number of drugs being developed independently by the NIH.

We have also added another index to make the directory an easier searchable resource. Now, there are three indexes: The first is an alphabetical listing of the drugs described in the text. It should be noted that trade names for the same drug compound may vary in different countries. Registration, trademark symbols and designations are not shown to make the presentation of the drug descriptions consistent. The second lists the indications for treatment. Thus, the reader will be able to find new drugs by name or a series of drugs used for treatment of a particular disease. The third lists the company and their drugs alphabetically. It is important to remember, however, that since these compounds are still experimental and in development, there is no guarantee of benefit and these agents can only be obtained through participation in a clinical research study.

A profiled drug may be listed more than once if it has more than one formulation, such as oral pill versus intravenous solution. Multiple indications, if available, are listed in the same record for the same formulation of the clinical test medication. Also, some drug delivery devices have been included since they may represent a significant clinical improvement. In some instances, the descriptions are presented separately for those clinical trials using combination therapies.

Although most of the drugs listed in this edition are still experimental, the FDA may have approved some for use in the United States by the time this book is published. Other drugs have been approved for use in countries outside of the United States and may or may not ever be approved by the FDA. Some of the drugs mentioned in the first edition, and even in

this second edition, may no longer be available because of unfavorable results in clinical studies. Also, companies developing these drugs often merge or move and change their phone numbers and addresses. Thus, all information concerning phase of development, continued availability of the drug, trade and generic name, and contact information needs to be continuously verified.

To keep you abreast of the latest developments in the clinical pipeline, we have incorporated the content of *The Directory of Drugs in Clinical Trials* into an online database located at the company web site www.centerwatch.com. By providing your email address when you purchase the second edition of this book, you will be emailed a protected username and password to freely search the database and view weekly updates on the drugs in the clinical pipeline.

This book can, and should be used in conjunction with the Clinical Trials Listing service provided by CenterWatch. At this web site, the most up-to-date information on clinical studies can be obtained. Many, if not most, of the drugs listed on that web site will be described in this book. Furthermore, both the Trial Result database and FDA Approval database located on the CenterWatch web site will inform you of the latest advances in drug development.

This book contains information on the next wave of medical advances. However, no one knows which of these drugs will be approved, which will make a critical difference in the treatment of specific diseases, and which will fall by the wayside. For patients reading this book and in search of new possible therapies for their condition, we recommend taking this information to their health care providers so that the information can be incorporated into a suitable treatment plan. Participation in clinical studies is often best accomplished when the patient's primary physician helps with explanations and support of the study subject.

We encourage reader feedback on this new second edition and hope that the book meets your needs with respect to providing useful information on new drugs in the developmental pipeline.

Kristen Eschman, Managing Editor
Alan Sugar, M.D., Medical Advisor

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Foreword

Today every clinician, health professional, and patient is extremely interested to know about "coming attractions" with regard to medical therapies in their area(s) of interest. Until now it has only been possible to do this for new drugs through a great deal of research in hard-to-find sources, often very expensive ones that are beyond the budget of someone who wants to consult the resource only occasionally.

CenterWatch, a highly respected publisher in the clinical trials industry, has provided just this type of resource. The current book is both inexpensive and easy to use. The most frequently sought information on drugs under development includes:

- Indication(s) for use
- Study phase status
- Clinical trial results
- Mechanism of action
- Formulation
- Manufacturer and contact information

The data for these entries have been verified or have come directly from many research scientists, physicians, and other healthcare professionals in academia, private practice, and industry. The data is then organized by indication, drug name ,and phase, which is very useful and facilitates the book's use as a reference tool.

The number of physicians involved in clinical trials has never been larger. A great deal of this growth has occurred among independent physicians in private practice clinics as well as in various types of managed care clinics outside the traditional academic environment. This rapid growth, in part at the expense of academic medical centers, has led to a reassessment—and confirmation—of interest within the academic centers in sponsored clinical trials being conducted in their setting. Some forward-looking academic centers now have a more "customer-oriented" attitude toward the pharmaceutical industry. Specifically, the process of research contract approvals, protocol, and informed consent reviewed by institutional IRBs (Institutional Review Boards), and the internal administrative procedures of the institution have now been more efficiently organized and operated.

These activities already have helped increase the number of clinical trials conducted by those academic institutions and have helped to re-adjust the balance between trials conducted by academicians and by independent physicians. It is hoped that the remaining academic centers will address this issue for the advantage of faculty and patients—both beneficiaries when new drugs are introduced more rapidly.

Clinical trials have reached a golden age where contemporary views of good science and good medicine are widely understood in regulatory agencies, academic centers, and the pharmaceutical industry.

This coming of age, from the start of modern clinical trials in the late 1940s until the present, is a remarkable achievement for an entire field to reach a mature stage in such a short time. There is still a great deal of research to do in testing new clinical designs, exploring how clinical data can best be analyzed with statistics, and studying many other issues and

questions. Nonetheless, the questions of determining how much data to collect on a new drug, and what type of clinical data to collect prior to marketing is generally understood by regulatory agencies, pharmaceutical companies, and practicing physicians.

This book also serves to educate those less familiar with the process of drug development and clinical trials. At the same time, it is a valuable reference for those more skilled, or at least knowledgeable, in this art and science.

Readers will find periodic updates of this material useful, not only for providing current data, but for telling the story of the many turns and unexpected twists that drugs often take during their development and product lifetime. This varies from those that are never marketed and are "stillborn," to those such as morphine and opium whose lifetime is measured in tens, if not hundreds of generations.

Bert Spilker, PhD, MD
Senior Vice President
Scientific & Regulatory Affairs
PhRMA

1 Cardiovascular Disease

Population with illnesses in this category	**158 million[1]**
Drugs in the development pipeline	**630[2]**
Number of drugs in preclinical testing	**254**
Number of drugs in clinical testing	**188**

Source: 1. World Health Organization, worldwide figures 2. Parexel

The Pharmaceutical Research Manufacturers of America (PhRMA) has estimated the annual cost of cardiovascular disease in the United States as $298.2 billion. This amount includes all health expenditures and estimates of loss of productivity resulting from morbidity and mortality. According to the American Heart Association, almost 61 million Americans suffer from one or more forms of cardiovascular disease, including hypertension, coronary heart disease, myocardial infarction, chest pain, stroke, and rheumatic fever/rheumatic heart disease. These diseases cause close to one million deaths each year.

CenterWatch has identified approximately 150 drugs in clinical development for cardiovascular treatment. Indications with the largest number of drugs being tested include congestive heart failure, myocardial infarction, and hypertension. According to PhRMA, these new medicines represent a 20% increase in drug development efforts for cardiovascular disease since 1999. Many of these new therapies in the pipeline use cutting-edge technologies and new scientific approaches to these diseases. These include a vaccine that may be able to increase levels of "good" cholesterol, or HDL, by blocking its transition into "bad" cholesterol, or LDL; a medicine now used to treat rheumatoid arthritis that may be able to block a substance that damages the heart and causes congestive heart failure; and a gene therapy that prompts the growth of new blood vessels to bypass clogged arteries.

Coronary heart disease is the most common cause of death in both men and women in the United States. Of the one million cardiac fatalities seen each year, about half are caused by coronary heart disease. Coronary heart disease occurs when the coronary arteries become thickened or clogged by deposits of cholesterol, and cannot supply enough blood to the heart. A heart attack results when a blood clot obstructs a coronary artery supplying blood to the heart. This causes an inadequate flow of oxygenated and nutrient-enriched blood and results in the death of a portion of the heart muscle.

As many as 1.1 million Americans suffer heart attacks each year. Every 29 seconds, someone in the U.S. will suffer a heart attack, and every minute, someone will die from one. It is estimated that 7.3 million Americans over the age of 20 have a history of myocardial infarction. There are currently an estimated 15 drugs in the clinical pipeline for the prevention and/or treatment of myocardial infarction. Annual costs for such development are estimated by CenterWatch to be between $70 million and $90 million.

The FDA has approved five new drugs indicated for the treatment of cardiovascular disease. One of these products, TNKase, may help to reduce the growing number of heart attack victims. TNKase (tenecteplase), a thrombolytic, has been FDA approved for the reduction of mortality associated with acute myocardial infarction. It is the first thrombolytic to date that can be administered over five seconds and in one dose, which

is selected based on the weight of the patient. TNKase works by stimulating the innate clot-dissolving mechanism by activating plasminogen, a naturally occurring substance secreted by endothelial cells in response to injury to the artery walls that contributes to clot formation. When TNKase activates plasminogen, it converts into plasmin, which breaks down the fibrin mesh that binds the clot together. The clot is then dissolved, restoring blood flow to the heart.

Despite the advances put forth from such efforts, cardiovascular illness and death can be prevented most effectively by controlling the risk factors associated with heart disease. The list of controllable factors is led by high blood pressure, also known as hypertension. Over 50 million Americans ages six years and older, and one in four adults, suffer from high blood pressure. Along with high blood cholesterol and smoking, hypertension doubles a patient's chance of developing heart disease. Hypertension seldom causes symptoms but it can cause severe damage to major organs over time—leading to heart attack, stroke, or kidney failure. Exercising regularly, maintaining a healthy weight, and not smoking can help control one's blood pressure. Others need assistance from blood pressure medications.

In September 2000, the FDA approved Atacand HCT for the treatment of hypertension. Atacand HCT consists of an angiotensin II receptor antagonist and the diuretic, hydrochlorothiazide. This combination medication has a dual mechanism of action: inhibition of the effects of angiotenisin II, an agent that causes vasoconstriction and hypertension, and increased sodium and water elimination through the effects of the diuretic.

CenterWatch has identified an estimated 20 drugs currently involved in clinical trials for the treatment of hypertension. Expenditure for this indication will range from $80 million to $100 million this year. These drugs are categorized as diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, alpha blockers, and centrally acting drugs that act on the brain to reduce neural impulses that may cause blood vessels to constrict. Many of these products treat other types of heart conditions in addition to lowering blood pressure.

Angina

abciximab, c7E3
ReoPro

MANUFACTURER
Centocor

DESCRIPTION
ReoPro is an antiplatelet drug being tested for acute ischemic stroke, acute myocardial infarction, and angina. This biological drug is a fragment (Fab) of a monoclonal antibody that binds to the glycoprotein (IIb/IIIa) receptor of human platelets and inhibits their clumping together.

ReoPro has recently completed a phase II trial for acute ischemic stroke and the overall results have shown that it improves the subject's clinical condition. ReoPro is unique because it can work when given up to 24 hours after a stroke, unlike other drugs that must be given within the first three hours. Also, none of the subjects suffered from symptomatic intracranial bleeding (ICH), a potential fatal side effect of current therapy.

A preliminary analysis showed that after three months of treatment, 35 percent of the subjects treated with any dose of abciximab had minimal or no remaining disability, compared with the 20 percent of subjects who received the placebo. In addition, half of the subjects treated with abciximab showed improved function in carrying out daily activities compared with 40 percent that were given the placebo. There was also a trend toward improved neurological functioning.

ReoPro is also being tested in a phase III trial for acute myocardial infarction and for angina. It is approved by the FDA as an add-on therapy to heart procedures (percutaneous coronary interventions, such as balloon angioplasty and stent placement) for the prevention of heart blood flow problems.

INDICATION(S) AND RESEARCH PHASE
Angina – Phase III
Heart Disease – Phase III
Strokes – Phase II completed
Myocardial Infarction – Phase III
Cardiac Surgery – FDA approved

amlodipine besylate
Norvasc

MANUFACTURER
Pfizer

DESCRIPTION
Norvasc is the besylate salt of amlodipine, a long acting calcium channel blocker. The drug blocks the flow of calcium ions across the cell membrane into vascular smooth muscle and cardiac muscle. Additionally, Norvasc is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to reduce peripheral vascular resistance and blood pressure.

Norvasc has been approved by the FDA for the treatment of hypertension, chronic stable angina, and vasospastic angina in adults.

It is currently in phase III trials for hypertension in children between the ages of six and 17 years.

INDICATION(S) AND RESEARCH PHASE
Pediatric, hypertension – Phase III
Hypertension – FDA approved
Angina – FDA approved

AR69931
unknown

MANUFACTURER
AstraZeneca

DESCRIPTION
AR69931 is an enzyme inhibitor of thrombin that may help block this protein's ability to form blood clots. This drug is currently in a phase II study to prevent angina and thrombosis.

INDICATION(S) AND RESEARCH PHASE
Angina – Phase II
Thrombosis – Phase II

bivalirudin
Angiomax

MANUFACTURER
The Medicines Company

DESCRIPTION
Angiomax, formerally called Hirulog, is a synthetic derivate of hirudin, an anticoagulant from the leech medicinals that inhibits the formulation of blood clots. Angiomax is in a phase II trial at the Duke University Medical Center testing 50–100 subjects with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS).

The FDA approved Angiomax on May 17, 2000 for use as an anticoagulant in subjects with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Angiomax is intended for use with aspirin and has been studied only in subjects receiving concomitant aspirin. The FDA approval was based on data from double-blinded clinical trials of 4,312 subjects.

INDICATION(S) AND RESEARCH PHASE
Thrombosis – Phase II
Angina – FDA approved

diltiazem HCl/ hydrochlorothiazide
Cardizide SR

MANUFACTURER
Elan Pharmaceutical Research

DESCRIPTION
Cardizide SR is a sustained release (SR) oral drug made to slowly deliver the combination therapy of a calcium blocker (diltiazem hydrochloride) and a diuretic (hydrochlorothiazide) to treat angina. The diltiazem is thought to work by inhibiting the movement (influx) of calcium ions during membrane depolarization of heart muscle and vascular smooth muscle in blood vessels. In effect, this calcium antagonism decreases cardiac muscle contraction and lowers vascular resistance. In turn, oxygen demand decreases on the heart giving relief from angina. Cardizide SR also combines the water reducing effect of a traditional diuretic, which may help relieve heart pain. Clinical trials testing for relief from angina are in phase III.