Assessing the Safety of Marketed Drugs

Current Issues and Controversies

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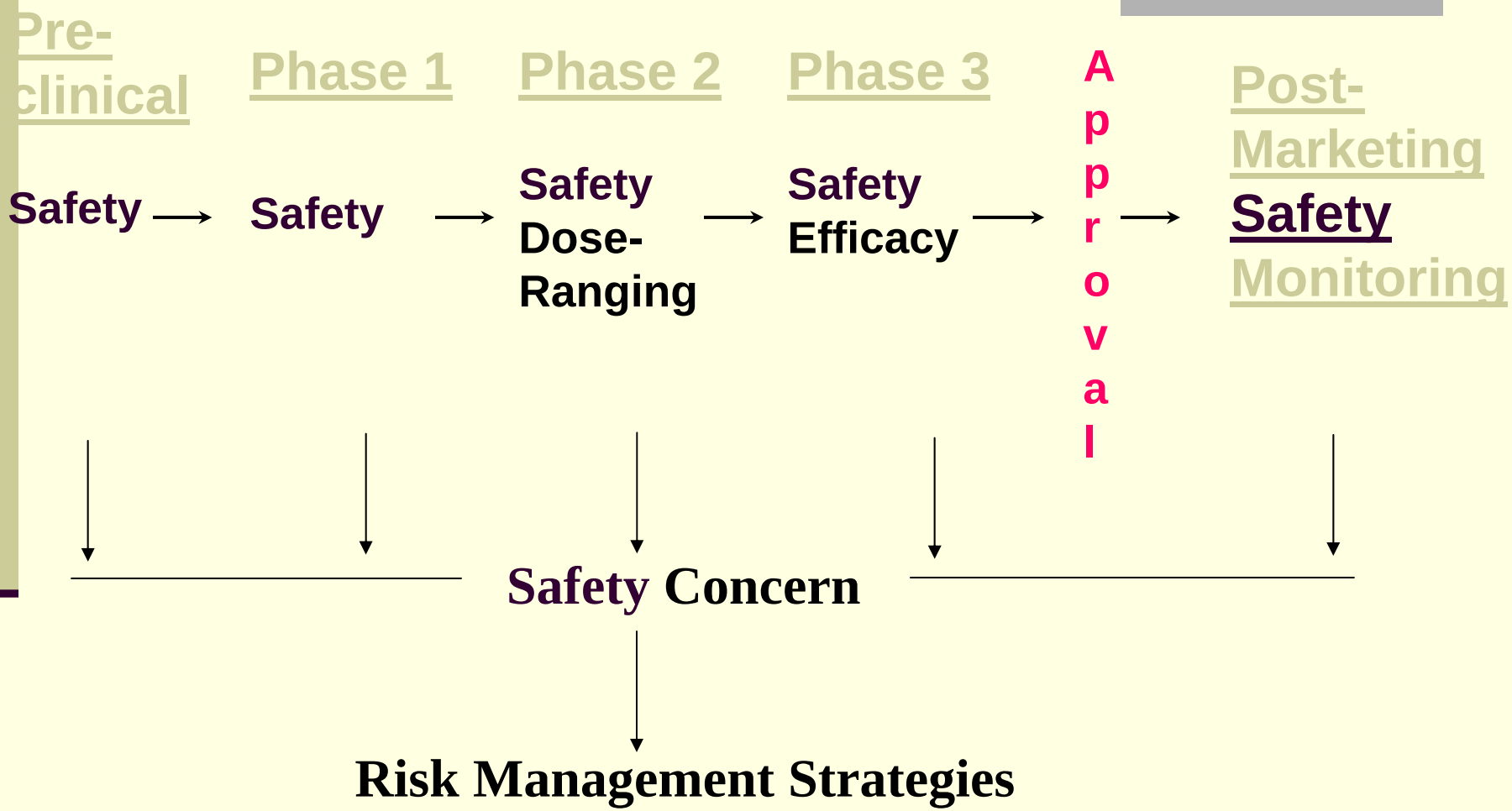
Introduction

- Debates over drug safety have intensified in recent years:
  - Legislative – fundamental changes proposed
  - Congressional investigations
  - Investigative journalism
  - Medical journal editorials
  - Lawsuits
- Observation – poor understanding of current system, strengths & gaps; wide differences in views about risk

Overview of Drug Safety

- Current Status of Safety Assessment
  - Strengths & Challenges
- Issues in Drug Safety
  - Science/regulatory/public health perspective
- The Future

Safety in the Lifecycle of FDA-Regulated Products



Current FDA – Operated Systems: Premarket Safety Evaluation

- Significantly more information generated about investigational drugs than in the past
- Common conditions: 5-6,000 patient exposures, 3-4 months of use. Some exposures of 1-2 years; common side effect profile
- Special studies: drug metabolism; studies in renal and liver failure; drug-drug interactions; cardiac repolarization effects
- Less common diseases: Fewer patients in trials

FDA Drug Safety: Premarket Review Process

- Complete submission by industry required:
  - All animal studies
  - All safety results from all human trials
  - Any relevant marketing experience
  - Any relevant literature

FDA Premarket Drug Safety Review

- Assigned to medical reviewer or review team
- Thorough review of safety findings per "safety review guidance"
- Includes evaluation of remaining uncertainties
- Documented in written review—posted on FDA web page after drug approval
- Safety assessment is about 50% of FDA resources in premarket program

What Has Changed in Review Process in Past Decade?

- More rapid FDA review process means that many fewer drugs have a safety track record from marketing abroad—previously a big safety factor
- Massive promotional efforts (primarily detailing-related) accelerate uptake and increase patient exposure – Billions spent vs FDA's resources

What Has Changed in Review Process in Past Decade?

- Extensive DTC advertising has affected public expectations about drug safety and usage
- Despite these factors, drug withdrawal rate has remained stable, although the rapidity of withdrawal has increased

Safety of Marketed Drugs

- Continued evolution of understanding of benefits and risks after approval. Inevitable with current testing schemes.

- Drug label information usually updated multiple times in 5 years post-approval

Postmarketing Commitments and Risk Management Plans

- Postmarket commitments about safety usually address specific issues or populations
- Risk management plans – address specific preventable risks (e.g., use in contraindicated populations) identified during premarket workup
  - FDA attempts to limit the number of such exceptional programs
- Requirements for explicit randomized postmarket safety trials rare in drug development

Current U.S. Pharmacovigilance System

- FDA operates “spontaneous reporting system” or “MedWatch”
  - Reporting and follow-up mandatory for manufacturers
  - Voluntary direct reporting to FDA by healthcare professionals and the public
  - More than 400,000 reports yearly
- This system generates signals for unusual drug-related adverse events: not very effective for detecting increased frequency of common events like MIs

Current U.S. Pharmacovigilance System

- Manufacturer may conduct studies in additional populations (e.g., pediatrics) or indications
- FDA may conduct population-based studies to follow up on Medwatch signal
- Comparative trials or explicit outcome studies (e.g., NIH-sponsored) are relatively uncommon
- FDA cannot mandate new safety trials

Summary: Capacities of Current System

- Generate profile of common adverse events in tested populations during drug development
- Understand drug metabolism and common metabolism-based drug-drug interactions
- Develop plans for managing/evaluating certain anticipated risks after marketing
- Identify rare serious adverse events after marketing

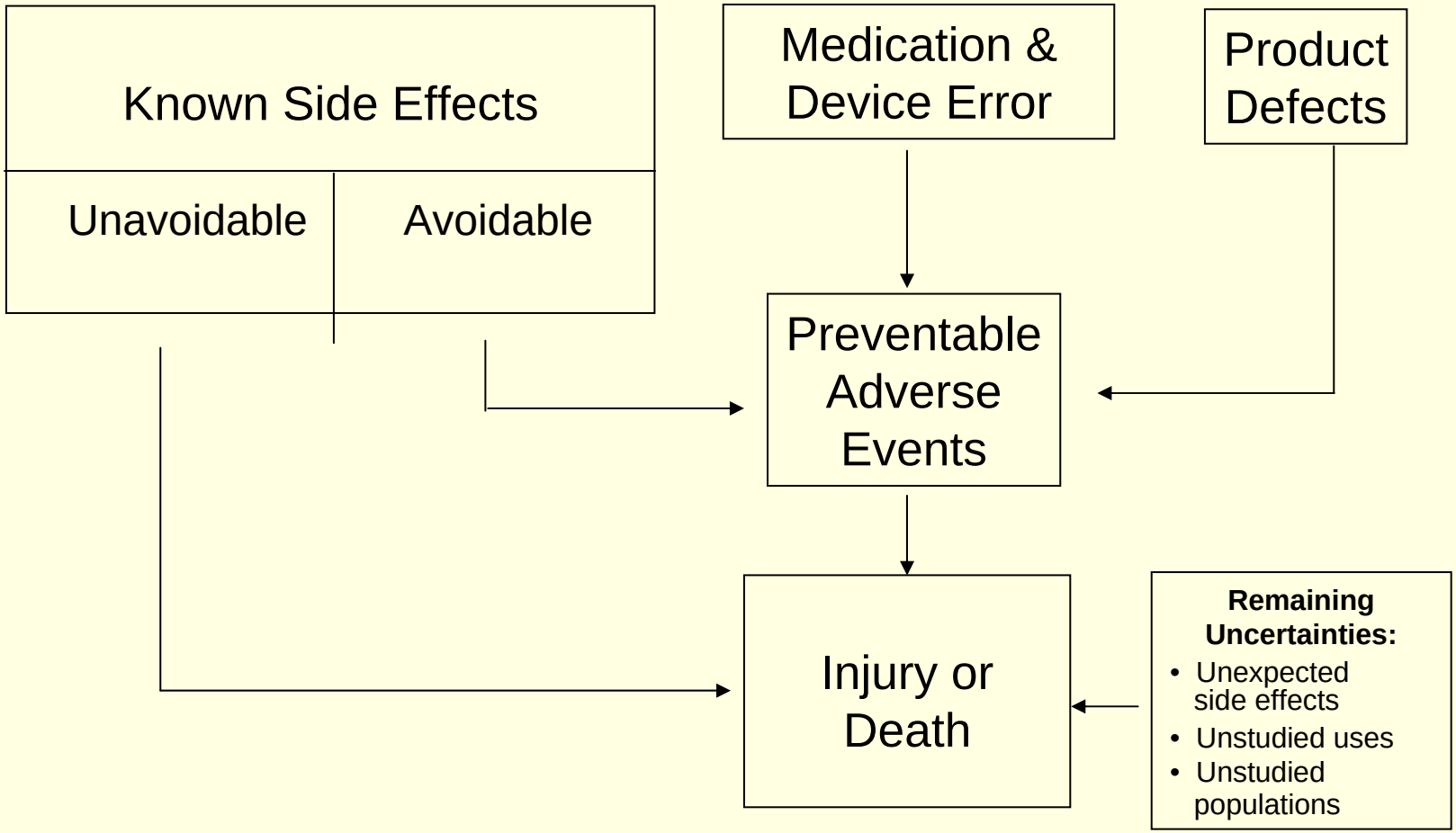
Current System May Not Identify

- Increased frequency of drug-related events that occur otherwise in population
- Time-dependent events
- Events occurring more frequently in populations not tested in trials: the very sick, those on polypharmacy, multiple medical problems, etc.
- Events that are much more frequent with off-label use
- Events related to medical errors or abuse
- Detailed understanding of who should take the drug and who should not
- Rare events, chronic use, complicated patients (co-morbidities, co-prescribing), pregnancy

Drug Safety: The Big Picture

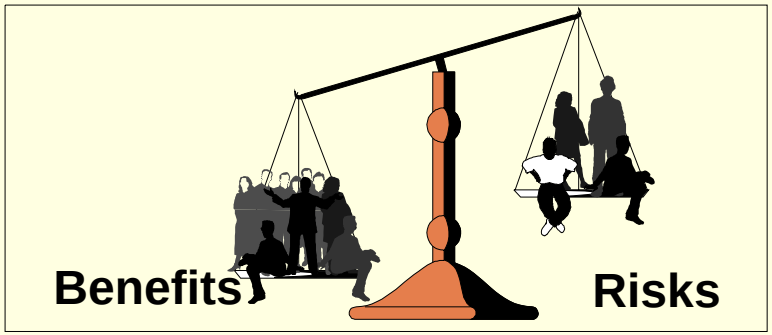
- 1.5 million preventable ADEs/year
- $3.5 billion among hospitalized patients
- Drug therapy for individuals still largely empiric

Sources of Harm From Medical Products – Systems Problem

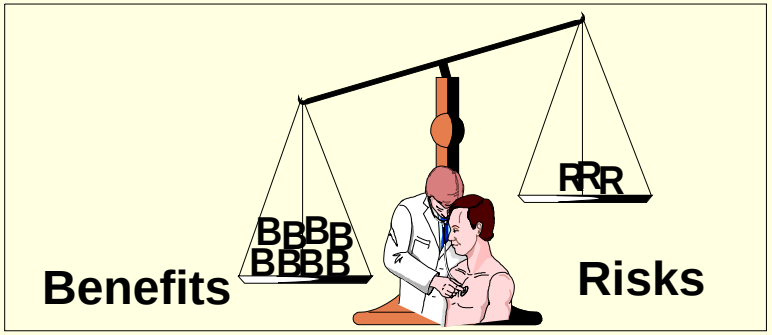


Balancing Benefits vs Risks

FDA
evaluates
benefits/risks
for the population



Provider
evaluates
benefits/risks
for a patient



Patient
evaluates
benefits/risks
in terms of
personal values

The Future of Drug Safety: Improving the Quality of Healthcare

- Implement Quality Improvements outlined in landmark IOM reports
- Decrease “medication errors” and inappropriate prescribing through modifying prescriber behavior and automation
- Improve recognition and management of emerging side effects
- Improve training/education of physicians on pharmacology & best practices

The Future of Drug Safety: Improving Surveillance

- Utilization of emerging electronic medical record systems for surveillance
- Studies or registries conducted in practice settings after marketing
- More surveillance systems in specialized settings: e.g., ER, nursing homes, etc.

These Approaches Should Be Implemented, But They are Not Sufficient

- Traditional focus on detection, communications, (warnings, precautions), management
- Need to add where possible: prediction; prevention; monitoring; mitigation
- Avoid treatment of individuals at high risk for event: serious side effects occur in only a small fraction of patients
- Develop new ways of monitoring for emerging toxicity before it becomes severe

The Future of Drug Safety
Improved Drug Development

- Drug development (e.g., animal & human testing) is largely empirical in nature
- This tradition focuses on population means & observations of outliers
- Directly translated into “trial and error” approach in clinical medicine
- Major loss of information, eg. Why did drug fail to work in patient?

The Future of Drug Safety

- These are significant limitations on the number of questions that can be answered via empirical testing (imposed by # of patients, changing practice patterns, cost, etc)
- Despite hundreds of millions of dollars invested in a development program – we often lack key information at approval.
- Many of the patients subsequently exposed will not benefit from the Rx
- Some will be exposed unnecessarily to risks

FDA's Critical Path Initiative and Drug Safety

- Incorporate cutting-edge science into clinical drug development
- Better predictive tools for safety outcomes (e.g., side effects such as liver or renal toxicity)
- Genomic or other tools to identify the subgroups with high probability of positive response (targeted therapy)

Example: Drug Metabolism in Drug Development

- Development of in vitro human cell models and animal models over last 15 years have enabled manufacturers to predict human metabolism
- Avoid candidates with problematic metabolism/drug-drug interactions
- These have dropped in same timeframe from leading cause of late clinical failures to minor cause
- Many fewer products pulled from market because of interactions

Example: New Technologies

- Genomic, proteomic, metabolomic markers
- Status in patients with serious side effects vs those without?
- Study in prospective trials and from MedWatch reports
- Develop ability to avoid high risk patients or monitor for development before overt toxicity occurs

Improving Drug Safety: Possibilities

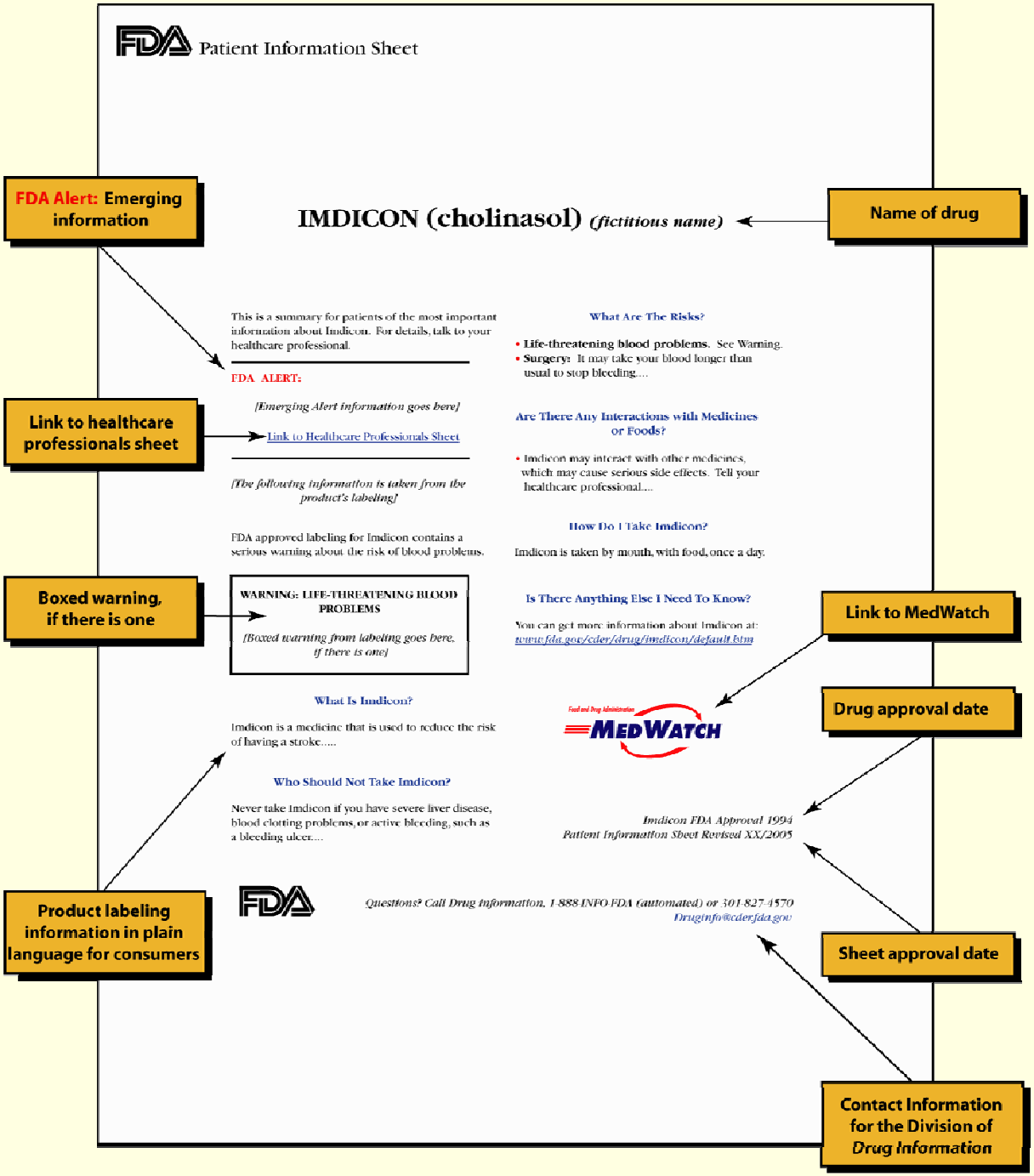
- Improve current surveillance systems
- Access additional data sources as they develop
- Improve quality of healthcare system
- Move clinical drug development from empirical, trial and error approach towards mechanistic “personalized” approach

Drug Safety – Specific Actions

- Institute of Medicine (IOM) Study of the Drug Safety System
- Established Drug Safety Oversight Board
  - Emerging information for providers & patients
- Published three guidance documents – March 2005
  - Premarketing Risk Assessment
  - Good Pharmacovigilance Practices and Pharmacoepidemiogic Assessment
  - Development and Use of Risk Minimization Action Plans (RiskMAP)

IOM Study

- Study began in January 2005
- Committee has had public meetings (June, July, October, Jan)
- Detailed information about each of the meetings http://www.iom.edu/CMS/3793/26341.aspx
- Have interviewed large number of stakeholders, including many FDA staff
- Final report - Fall 2006


FDA Patient Information Sheet
FDA Alert: Emerging information
IMDICON (cholinasol) (fictitious name)
Name of drug
This is a summary for patients of the most important information about Imdicon. For details, talk to your healthcare professional.
FDA ALERT:
[Emerging Alert information goes here]
Link to healthcare professionals sheet
Link to Healthcare Professionals Sheet
[The following information is taken from the product's labeling]
FDA approved labeling for Imdicon contains a serious warning about the risk of blood problems.
Boxed warning, if there is one
WARNING: LIFE-THREATENING BLOOD PROBLEMS
[Boxed warning from labeling goes here, if there is one]
What Is Imdicon?
Imdicon is a medicine that is used to reduce the risk of having a stroke.....
Who Should Not Take Imdicon?
Never take Imdicon if you have severe liver disease, blood clotting problems, or active bleeding, such as a bleeding ulcer....
What Are The Risks?
• Life-threatening blood problems. See Warning.
• Surgery: It may take your blood longer than usual to stop bleeding....
Are There Any Interactions with Medicines or Foods?
• Imdicon may interact with other medicines, which may cause serious side effects. Tell your healthcare professional....
How Do I Take Imdicon?
Imdicon is taken by mouth, with food, once a day.
Is There Anything Else I Need To Know?
You can get more information about Imdicon at: www.fda.gov/cder/drug/imdicon/default.htm
Link to MedWatch
MEDWATCH
Drug approval date
Imdicon FDA Approval 1994
Patient Information Sheet Revised XX/2005
Product labeling information in plain language for consumers
FDA
Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570
Druginfo@cder.fda.gov
Sheet approval date
Contact Information for the Division of Drug Information

FDA

U.S. Food and Drug Administration

Department of Health and Human Services

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News from CDER

- May 11. FDA warns the public about the sale of counterfeit Lipitor, Viagra, and an unapproved product promoted as "generic Evista" at pharmacies in Mexican border towns. FDA Talk Paper.
- May 5. FDA approves Requip (ropinirole) to treat moderate to severe Restless Legs Syndrome (RLS). FDA Talk Paper.
- April 28. Famotidine Injection - Recall of one lot of Famotidine Injection, 20 mg/2 mL due to a lack of sterility assurance. MedWatch Safety Info.
- April 28. Eli Lilly and FDA notify healthcare professionals of the stopping of enrollment in a randomized, double-blind, placebo-controlled trial of Xigris in pediatric patients with severe sepsis. Xigris is not indicated for use in pediatric severe sepsis. MedWatch Safety Info.
- April 14. FDA approves first-time generic Niacin Extended-Release to treat hypercholesterolemia. The reference listed drug is Niaspan.
- April 14. FDA approves first-time generic Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets as an antihistamine/decongestant. The

Drug Safety

About FDA's New Drug Safety Initiative

Safety Information for Patients & Healthcare Professionals

- Drug Specific Information

Consumer Information

Let Us Hear from You

Featured Links

- The FDA Process for Approving Generic Drugs (online tutorial)
- Genomics at FDA

Quick Info Links

- Drugs@FDA
- Drug Information Pathfinder
- Drug Shortages
- Inactive Ingredient Database
- MedWatch
- National Drug Code Directory
- Orange Book
- Postmarketing Study Commitments

- Advisory Committees
- Bioterrorism
- CDERLearn (Online Courses)
- Drug Application Process
- FDA Patient Safety News with Videos

Societal Disputes on Risk/Benefit Contributing to Debate

- Even with perfect information there will be sharp disagreements
  - Isotretinoin & SSRI antidepressant examples
  - Differing views about:
    - Who should make risk decisions
      - Role of government regulators, practitioners, patients
    - Regulatory policy/constitutional issues
      - Power vested in FDA by Congress
      - Role of states
- Risk/benefit : analytic and communications methodology limits ability to communicate

Lively Public Debate

- Changing development paradigm
  - Conditional approval pending completion by sponsors of required post-approval studies (Strom)
- New institutions/organizations
  - Independent institute dedicated to post-marketing studies funded by healthcare insurers (Reidenberg)
- Expanding role for public health agencies
  - Increase funding/authority for agencies such as FDA/AHRQ/CMS/CDC to conduct studies

Summary of Recent Actions

- FDA responsive to concerns about drug safety decision-making and communication
- While comprehensive review underway, we will implement important changes to improve public knowledge, internal management and outside involvement
  - Reorganization, Congress increased drug safety budget $10 million
- Changes will not be free of controversy and may raise important new issues for resolution
- Clinicians must stay informed and involved

Improving Overall Drug Safety is a Systems Problem

- Many of the risks of drugs related to use patterns-e.g., prescribing habits, drug-drug interactions, errors, etc.
- No entity—government or otherwise—is charged with investigating and resolving safety issues—i.e., comparative safety, long term outcomes of therapy, etc
- Focus on drug withdrawals and high profile AEs obscures many components of systems problem
- To a large extent – drug safety is a function of the safety of the healthcare system

Questions?

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