

Preface

(AHFS primary)

An Evidence-based Foundation for Safe and Effective Drug Therapy

The mission of *AHFS Drug Information*[®] (*AHFS DI*[®]) is to provide an evidence-based foundation for safe and effective drug therapy. Widely trusted for its established record in refuting unfounded efficacy claims, its rigorous science-based editorial process, and its independence from the influence of pharmaceutical manufacturers, *AHFS DI*[®] has remained true to its mission for more than 50 years. This notable achievement of more than 5 decades of evidence-based medical publishing has gained *AHFS DI*[®] the unique distinction of being the longest published federally designated drug compendium issued by a scientific and professional society. As such, *AHFS DI*[®] maintains a unique role in establishing medically accepted uses of drugs, both labeled and off-label.

With the 2010 edition, the *American Hospital Formulary Service*[®] (*AHFS*[™]) marks its 52nd year of continuous publication by the American Society of Health-System Pharmacists (ASHP). First published in 1959, the *Formulary Service*[™] has evolved to address increasingly complex issues related to drug therapy and formulary management.

AHFS DI[®] is a collection of drug monographs kept current by ongoing electronic updates (e.g., *AHFS*firstReleases[™], MedWatch notices, <http://www.ahfsdruginformation.com>) and by a revised master print volume issued each year. The *AHFS DI*[®] database is maintained continuously throughout the year for the purpose of disseminating comprehensive, evaluative drug information to the entire medical and paramedical community, and updates are issued frequently on an ongoing basis in electronic formats.

AHFS[™] was first published in 1959 as an adaptation from the *Hospital Formulary of Selected Drugs* by Don E. Francke. *AHFS*[™] had its roots in the hospital formulary system, which was intended to establish a sound therapeutic and economic basis for drug policy. Originally, the *Formulary Service*[™] was conducted through the Committee of Pharmacy and Pharmaceuticals of the American Society of Hospital (now Health-System) Pharmacists to assist the pharmacy and therapeutics committee of each hospital in preparing its hospital formulary. Since then, *AHFS DI*[®] has developed beyond its original purpose to become the most comprehensive, authoritative source of evaluative, evidence-based drug information available. Paramount to providing such information is the critical, evidence-based evaluation of pertinent clinical data concerning drugs, with a focus on assessing thoroughly the advantages and disadvantages of various therapies, including interpretation of various claims of drug efficacy.

■ Off-Label Drug Reviews for Oncology

In 2008, *AHFS DI*[®] introduced a new process for publishing structured, codified, evidence-based determinations for off-label cancer uses. The decision to create a separate method resulted from the unique characteristics of evidence-based decisions that are applied to serious and life-threatening conditions such as cancer. This process supplements the long-standing evidence-based process used by AHFS to evaluate off-label uses of drugs and biologics, and incorporates the desirable characteristics for cancer-specific compendia outlined by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC). The cancer-specific codified method developed by AHFS is consistent with distinctions applied to evidence-based assessments of cancer treatments by other authoritative sources such as the National Cancer Institute (NCI) and FDA.

The principles of the *AHFS DI*[®] evidence-based editorial development process have not changed. However, the new codified determinations supplement and enhance the traditional *AHFS DI*[®] evaluation of off-label uses with structured determinations that summarize ongoing assessments of new and changing evidence. ASHP appointed an Oncology Expert Committee, comprised of oncologists, oncology pharmacists, and oncology nurses, to assist with the independent review and final recommendations for off-label cancer determinations. Final decisions are made solely by the Oncology Expert Committee for determinations emanating from the newly introduced supplementary process for oncology uses and by AHFS staff for other information, taking into account the advice of other expert reviewers. All processes related to the review and publication of determinations are transparent and designed to mitigate any potential conflict of interest in order to preserve the integrity of *AHFS DI*[®] and to minimize bias.

New federal regulations for transparency and conflict of interest disclosure and management became effective January 1, 2010. In the case of balloted determinations made by the AHFS Oncology Expert Committee as of this date, conflict of interest disclosure policies follow the definition of a publicly transparent process for identifying potential conflicts of interest as established in Section 414.930(a) of the Code of Federal Regulations (CFR).

Documents describing this process for off-label oncology uses, including levels of evidence, transparency, and conflict of interest disclosure and management,

may be viewed under the Off-label Uses section of the *AHFS DI*[®] website at <http://www.ahfsdruginformation.com>. Subscribers may access details about specific determinations of medical acceptance for these uses at this website location.

■ Editorial Independence

Information included in *AHFS DI*[®] shapes treatment decisions made by clinicians and influences public and private health-care policies and decisions. As a result, it is important that the information be authoritative, objective, and free of undue influence from pharmaceutical manufacturers and other third parties who may seek to use the compendium to promote their own vested interests. Final decisions are made solely by the Oncology Expert Committee for determinations emanating from the newly introduced supplementary process for oncology uses and by *AHFS* staff for other information, taking into account the advice of other expert reviewers.

AHFS DI[®] is the only remaining official drug compendium published by a non-commercial, nonprofit professional and scientific society. ASHP is an IRS 501(c)(6) tax-exempt entity. ASHP is the national professional association that represents pharmacists who practice in inpatient, outpatient, home-care, and long-term-care settings. ASHP has a long history of fostering evidence-based medication use as well as patient medication safety. *AHFS DI*[®] is published in part to support the mission of pharmacists helping people make the best use of medications.

AHFS DI[®] is published by ASHP under the authority of its elected Board of Directors. As such, the Board exercises oversight through its ongoing Society considerations as well as through its Committee on Publications. This oversight by the Board also involves review and approval of relevant recommendations originating from its appointed Council on Therapeutics and the advisory and best practices developments of its other Councils, House of Delegates, and other policy-recommending bodies.

In addition, hundreds of experts, principally physicians but also other clinicians, medical scientists, pharmacists, pharmacologists, and other professionally qualified individuals, participate in an ongoing extramural review process for *AHFS DI*[®]. Participation is solicited but voluntary, and no honorarium nor other benefit other than limited access to the *AHFS DI*[®] database is provided. These experts must provide full disclosure of interest, including any affiliation with or financial involvement in the manufacturer of the drug(s) under consideration and directly competitive products.

ASHP considers it essential that interactions between *AHFS* and pharmaceutical manufacturers be limited to the legitimate exchange of the scientific and medical information needed to fulfill the mission of *AHFS DI*[®]. To maintain independence from the undue influence of the promotional interests of pharmaceutical manufacturers, communications are directed to the scientific and medical information areas within the companies; contact with marketing areas is avoided.

ASHP holds in high regard the responsibilities attendant to the public and private trust placed in the evidence-based editorial deliberations of *AHFS DI*[®]. As such, ASHP also considers it essential to protect the integrity and independence of the editorial decisions of *AHFS* staff by separating the Society's business activities with pharmaceutical manufacturers (e.g., exhibits at educational meetings, journal advertising) from the editorial activities of its drug compendium. An editorial independence statement, approved by ASHP's Board of Directors and available at <http://www.ahfsdruginformation.com>, outlines the principles that *AHFS* staff apply in ensuring such independence.

■ Comparative, Unbiased, Evaluative Drug Information

AHFS DI[®] is a tested and proven source of comparative, unbiased, and evidence-based drug information containing a monograph on virtually every molecular drug entity available in the US. Drug monographs are prepared by a professional editorial and analytical staff, who critically evaluate published evidence on the drug. The monographs incorporate the advice of leading medical experts in the specific field of therapy under consideration, including experts from major research and clinical institutions as well as public bodies such as the National Institutes of Health (NIH) and US Centers for Disease Control and Prevention (CDC) and professional associations with therapeutic authority; there currently are approximately 500 expert reviewers. It is this preparation by a professional staff and the exhaustive review process that make *AHFS DI*[®] monographs unbiased and authoritative.

Using an independent, evidence-based, evaluative process, *AHFS DI*[®] monographs incorporate information from pertinent references in the literature and expert therapeutic guidelines. The monographs also address the labeling approved by the FDA, in some cases challenging outdated and clinically irrelevant information that may persist in the approved labeling. *AHFS DI*[®] monographs continue to include information on uses, dosages, and routes and/or methods of administration that may not be included in the FDA-approved labeling for the drug ("off-label/unlabeled uses"). (See Uses in the Users Guide, p. xiii.) A typical monograph on a new drug incorporates information from several hundred published references, and some general statements and individual monographs incorporate information from several thousand references. The current database includes almost 80,000 uniquely cited references linked to over 560,000 statements. Tens-of-thousands of additional references from the *AHFS*[™] archives provide support for monographs on drugs introduced into the US market prior to 1984. It is this point-by-point analysis and evaluation of the literature that make *AHFS DI*[®] monographs comprehensive, evaluative, and considerably beyond the FDA-approved labeling in their scope.

■ Widely Vetted Editorial Process in Support of Compendial Recognition

The *American Hospital Formulary Service*[®] grew out of the concept of the Formulary System in institutions. The ASHP Minimum Standard for Pharmacies in Hospitals, which described principles of the formulary system, was approved in 1951 by ASHP and the American Pharmaceutical Association, American Hospital Association, American Medical Association, and American College of Surgeons and served as the cornerstone for Joint Commission standards on formularies.

The broad-based vetting and recognition of ASHP's editorial standards over several decades are unparalleled. (See also the section "Highly Recognized Authority" below.)

In the mid-1960s through the mid-1970s, recommendations from the US Department of Health, Education, and Welfare (HEW), including HEW's Task Force on Prescription Drugs and FDA's Bureau of Drugs, proposed the creation of a Federal drug compendium. Key people involved in promoting the concept of a national formulary included FDA Commissioner James Goddard and HEW Secretary Caspar Weinberger. Congressional Committees involved included the Senate Monopoly Committee (Senator Gaylord Nelson, Chair) and the Senate Subcommittee on Health. Various physician proponents of the quality and scope of *AHFS*[™] and others corresponded and met with most of the Federal principals involved in these deliberations and proposed *AHFS*[™] as meeting the goals for such a compendium. ASHP also provided comments at the Drug Information Association's symposium on a Federal Drug Compendium held in Washington, DC June 11-12, 1970. At the time, *AHFS*[™] was "the only constantly updated compendium of edited, organized, unbiased, and evaluated information on virtually all drugs used in the United States."

The National Academy of Sciences–National Research Council (NAS–NRC) was contracted by FDA in 1966 to evaluate efficacy claims being made by manufacturers for drugs cleared for marketing from 1938–1962 (prior to Kefauver–Harris amendments). Analysis of existing conclusions in *AHFS*[™] found remarkable similarities with the NAS–NRC findings and spoke well for *AHFS*[™] as an evaluative, unbiased drug compendium. (*Am J Hosp Pharm.* 1968; 25:483-4.)

Based on ASHP's demonstrated expertise as a scientifically based group that reviewed drug data in an ongoing program and that could provide a continuum of experience and evaluation of drug information, FDA contracted with ASHP in 1975 to develop a class prescription labeling system. ASHP exhaustively applied this system to 20 major therapeutic classes and subclasses of drugs (e.g., antipsychotics, antidepressants, various anti-infective and endocrine classes, analgesics, antihypertensives), developing standard, objective professional class labeling for safe and effective use that FDA applied to numerous individual drug products included in these classes. At the time, manufacturers' labeling for drug products within the same class and even for the same generic drug included inconsistent information, including that about efficacy of the drugs.

The Medicare Catastrophic Health Coverage Act of 1988 (Public Law 100-360) required that the Secretary of Health and Human Services (HHS) establish outpatient standards for prescribing drugs that were based on accepted medical practice. In establishing such, the Secretary was directed to incorporate standards from current authoritative compendia for the prescribing, dispensing, and utilization of covered outpatient drugs. The editorial policies and procedures, scope, and evidence-based analyses applied to *AHFS DI*[®] content were exhaustively scrutinized by Congressional staff as part of this process. To assist the Secretary in making a determination of official compendial designation, *AHFS DI*[®] was required to establish that it met the criteria identified by the Conference Committee as an appropriate source of information for establishing the prescribing standards based on accepted medical practice. The activities surrounding this legislation, including intense analysis by Congressional staff and that of the Health Care Financing Administration (HCFA; now the Centers for Medicare & Medicaid Services [CMS]), ultimately resulted in the designation of *AHFS DI*[®] as a source for establishing these drug prescribing standards. This set the precedent for recognition by Federal, State, and private sector entities of *AHFS DI*[®] as an authoritative source for establishing drug use standards in subsequent legislation (e.g., OBRA 90 and OBRA 93) and guidelines. Federal compendial recognition continues under part 456 of CMS regulations governing utilization control for Medicaid and under section 1927 of the Social Security Act.

In January 1989, HCFA began developing regulations to implement section 202 of the Medicare Catastrophic Coverage Act of 1988 aimed at establishing standards for prescribing outpatient drugs based on accepted medical practice. In establishing these standards, HCFA required ASHP to describe the extent to which *AHFS DI*[®] met each of the criteria outlined in the Congressional Conference Report. HCFA was required by Congress to designate as official only those compendia that based such medical practice standards on review of published scientific and medical information and that provided adequate assurances that the expert reviewers who assisted in establishing the standards were free of financial (or other) conflicts of interest. ASHP participated in a public hearing conducted by HCFA's Bureau of Eligibility, Reimbursement, and Coverage on the use of authoritative compendia to determine prescribing standards for the new Medicare outpatient drug coverage. In September 1989, HCFA published its determination that *AHFS DI*[®] met the selection criteria as an official compendium. HCFA's determination was subject to broad-based public scrutiny and comment via

the *Federal Register* (1989; 172:37190-246). HCFA also established the expectation that such designation of any compendium in the future would require evaluation by the Agency as to whether the compendium met the established standards as well as publication for public comment in the *Federal Register* of their selection decision in the form of a proposed rule.

In 1989, the Health Insurance Association of America (HIAA; now America's Health Insurance Plans [AHIP]) recommended that insurers use *AHFS DI*[®] as well as certain other resources (e.g., peer-reviewed literature, medical specialty organizations, consultants) for making determinations about off-label uses. In 1994, ASHP met with the HIAA Health Care Technology Committee regarding the use of *AHFS DI*[®] as a standard for making determinations on reimbursement of off-label uses.

In 1989, ASHP also was invited to the National Blue Cross and Blue Shield Association's Technology Management Conference for the purpose of addressing the individual member Plan Medical Directors and senior Plan management regarding the use of the compendia for evaluating the efficacy of off-label uses. As a result, the National Blue Cross and Blue Shield Association changed its previous position that off-label uses be considered investigational and therefore ineligible for reimbursement. The revised position stated that off-label uses should be eligible for reimbursement based on evaluation of efficacy and that *AHFS DI*[®] was a valuable resource for use in the evaluation process.

In September 1991, ASHP was invited to participate in Medicaid's National Medical Directors' Conference to provide information on the use of *AHFS DI*[®] for making decisions regarding which drugs to pay for and under what clinical circumstances. This conference was a forum for the medical directors to discuss HCFA's national drug coverage determination.

Section 4401 of the Omnibus Reconciliation Act of 1990 (OBRA 90; Public Law 101-508) specified requirements for a Drug Use Review program as part of Medicaid. As a result of OBRA 90, section 1927(g) of Title XIX of the Social Security Act required State Medicaid programs to assess data on drug use against standards established by ASHP, AMA, and USP (the latter 2 no longer publish a drug compendium). Once again, the *Federal Register* (1992; 57:49397-412) provided an opportunity for public comment; the rule was finalized in September 1994.

Section 9401 of HCFA's State Medicaid Manual required that State Medicaid programs use *AHFS DI*[®] as a predetermined standard against which to assess drug use. In June 1992, this revision to the Manual was submitted to the State Medicaid Directors for comment prior to being finalized. The authority of *AHFS DI*[®] as an official compendium was further recognized under OBRA 93 for use by State Medicaid programs for information on medically accepted off-label uses of drugs and under the Medicare provisions of this Act for medically accepted indications of antineoplastic drugs.

Section 1861(t) of the Social Security Act established *AHFS DI*[®] as an official compendium for use in determining medically accepted indications of drugs and biologics used in anti-cancer chemotherapeutic regimens under Medicare Part B and section 1927(k) established such compendial recognition for all Medicare Part D drugs.

Because of its long-standing record in evidence-based evaluation of information on drug use, ASHP was requested by FDA in 1993 to assist the Agency in attempting to identify important off-label uses. ASHP was the only professional pharmacy organization requested to assist FDA in this effort.

In 2003, *AHFS DI*[®] was specified by the National Association of Insurance Commissioners as a standard reference compendia in their model Health Carrier Prescription Drug Benefit Management Act that provides standards for the establishment, maintenance, and management of prescription drug formularies and other pharmaceutical benefit management procedures used by health plans that provide prescription drug benefits.

■ Widely Used in Print and Electronic Formats

AHFS DI[®] is widely used as a source of complete drug information by physicians, pharmacists, dentists, nurses, and other health-care professionals and by schools of pharmacy, nursing, and medicine and is available in a variety of formats. Electronic formats include Lexi-Comp ONLINE with *AHFS*[®]; First DataBank's *AHFS Drug Information* monographs available from multiple vendors (e.g., McKesson); *AHFS Drug Information*[®] from STAT!Ref[®] and from MedicinesComplete[®]; *Drug Information Fulltext*[®] (*DIF*[®]); ePocrates Rx Online[™] + *AHFS DI*[®]; and *AHFS DI*[®] Powered by Skyscape. In hospitals, extended-care facilities, nursing homes, health maintenance organizations, and other organized health-care settings, *AHFS DI*[®] as print and/or electronic databases is accessible in patient-care areas for ready use by physicians, nurses, pharmacists, and other health-care professionals. *AHFS DI*[®] also is used in community pharmacies, chain drugstores (e.g., CVS), and other professional practice settings and is available in most medical libraries.

Expanded Point-of-Care Access in Support of Drug Therapy Decisions

During 2007, ASHP[®] and Lexi-Comp[®] launched a new collaboration that integrates the evidence-based information from the *AHFS DI*[®] and *AHFS DI Essentials*[®] databases with Lexi-Comp's industry-leading databases and enhanced searching technology in Lexi-Comp[®] ONLINE[™] to provide time-sensitive clinical information at the point of

care. Lexi-Comp® ONLINE™ with AHFS® drug information provides quick access to clinical information and is an indispensable solution for every hospital and health-system.

■ Highly Recognized Authority

AHFS DI® is supported solely through subscriptions. AHFS DI® has been officially adopted by the US Public Health Service and the Department of Veterans Affairs; recommended by the National Association of Boards of Pharmacy as part of the standard reference library; recommended by the American College of Physicians as part of a library for internists; included in the Standards for Medicare; approved by the American Pharmaceutical (now Pharmacists) Association, American Health Care Association, American Hospital Association, and Catholic Health Care Association of the United States; recognized by the US Congress, CMS, AHIP, National Blue Cross and Blue Shield Association, National Association of Insurance Commissioners, and various third-party health-care insurance providers for reimbursement decisions on off-label (unlabeled) uses; and included as a required or recommended standard reference for pharmacies in many states.

The authority of AHFS DI® also includes Federal recognition through legislation and regulation as an “official” compendium for information on medically accepted uses of drugs. The Federal compendial recognition for AHFS DI® originated in Public Law 100-630 (Medicare Catastrophic Coverage Act) following careful consideration by Congressional staff and establishment of standards for such designation. HCFA (now CMS) determined that AHFS DI® met the compendial selection criteria established by Congress and adopted the compendium for carrying out certain aspects of the Act and in meeting the need of the US Secretary of HHS to establish standards based on accepted medical practice for the prescribing, dispensing, and utilization of covered drugs. This established the Federal precedent for use of AHFS DI® as a compendial standard in subsequent legislative and regulatory initiatives, including for drug coverage under Medicaid and Medicare Parts B and D.

For additional information on official recognition, see the section on Widely Vetted Editorial Process in Support of Compendial Recognition above.

Highlights of 2010 Revisions

The 2010 edition has been updated extensively, incorporating revised information on uses, therapeutic perspectives, cautions, drug interactions, new products, and other new developments. Each year more than 60% of the monographs are revised. In addition, the coverage in the 2010 edition has been expanded by 51 new drug monographs.

■ Increased Granularity of the AHFS Classification® and CMS Medicare Part D, HL7, and NCPDP Recognition

Additional subdivision of the AHFS™ Pharmacologic-Therapeutic Classification® to provide more specific subgroupings of certain drugs along therapeutic and pharmacologic lines is implemented with the 2010 edition. New this year are 7 subclasses in 12:16 (Sympatholytic [Adrenergic Blocking] Agents). In addition, a new subclass 28:40 (Fibromyalgia Agents) has been created. **For additional details on the new subclasses and affected drug monographs, see the link to the AHFS Classification on the homepage at <http://www.ahfsdruginformation.com>.**

In the printed version of the classification in AHFS DI®, a drug monograph generally is only printed under one classification. Multiple classifications for a drug in print are represented by cross-references in the table of contents for each chapter/class. If cross-referenced, the drug name is given followed by the classification number that it is printed under. Electronically, all applicable classes for a drug are listed.

CMS’ “Guidelines for Reviewing Prescription Drug Plan Formularies and Procedures” and “Medicare Part D Manual” describe use of the AHFS® Pharmacologic-Therapeutic Classification® as the only named alternative to USP’s Model Guidelines for use by prescription drugs plans (PDPs) in implementing the formulary portion of the outpatient prescription drug benefit in the Medicare Modernization Act (MMA) of 2003. These Guidelines are part of the MMA Final Guidelines for Formularies that address the “CMS Strategy for Affordable Access to Comprehensive Drug Coverage.”

The AHFS Classification is a registered external code system in the HL7 Vocabulary Repository. (OID: 2.16.840.1.113883.6.234.)

The AHFS Classification also is an approved value code of the External Code List for use in the Formulary & Benefit, Telecommunication, Post-Adjudication, & SCRIPT e-Prescribing standards of the National Council for Prescription Drug Programs (NCPDP)

■ Evolving Therapeutic Guidance and Perspective

Antidiabetic agents: Results of several randomized, controlled trials (ADVANCE, ACCORD, and VADT) have raised questions about the benefit of intensive antidiabetic therapy (target HbA_{1c} <7% in nonpregnant adults) on macrovascular complications in type 2 diabetes mellitus; however, delayed benefits (e.g., at 10-year follow-up) on macrovascular outcomes (e.g., reduction in MI and all-cause mortality) have been shown in type 1 or type 2 diabetes mellitus (UKPDS, DCCT-EDIC) who began early intensive therapy. The results of these trial affected therapeutic information in over a dozen antidiabetic agent monographs.

Heparin: New USP heparin reference standard and test method used to determine potency was implemented in 2009, resulting in 10% decreased potency of marketed heparin products in the US compared with products tested under the previous USP

standard. There are potential implications for dosage adjustment to maintain therapeutic efficacy in instances where rapid onset of heparin effect is needed (e.g., treatment or prevention of life-threatening thromboembolic events); however, heparin dosage generally is titrated to therapeutic effect.

Evolving information on combined antilipemic therapy with simvastatin and ezetimibe.

AHFS DI® monographs also are updated each year to include the current recommendations of numerous authorities. For example, many monographs in the 2010 edition have been revised to include:

- Updated *US Department of Health and Human Services (HHS)* guidelines for the management of HIV infection in adults, adolescents, and children and guidelines for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission. New emphasis on early initiation of antiretroviral therapy in adults.
- Updated recommendations from *US Centers for Disease Control and Prevention (CDC)* and *World Health Organization (WHO)* for influenza vaccination and management, including those for H1N1 influenza (swine flu). Information on Emergency Use Authorization for oseltamivir in children younger than 1 year of age, including instructions on use of an oral syringe that could deliver the appropriate dose and avoid dosing errors associated with the manufacturer-provided oral-dosing device.
- The latest (January 2010) *US Recommended Immunization Schedules for Children and Adolescents*, which was issued by the *CDC*, *AAP*, and *American Academy of Family Physicians (AAFP)*, as well as the revised (January 2010) *US Recommended Immunization Schedules for Adults* that incorporates the recommendations of *CDC*, *AAFP*, *American College of Physicians (ACP)*, and *ACOG* has been added for the 2010 edition.
- Information on the new HPV vaccine and expanded *CDC* recommendations on the use of HPV vaccines, including use in males to prevent genital warts.
- New *CDC* recommendations for Hib, Hepatitis A, HPV, Poliovirus, Meningococcal, MMR, MMRV, Rotavirus, and Varicella immunization.
- *CDC* health information for international travel, including information on the treatment and prevention of malaria.
- *Infectious Diseases Society of America (IDSA)* guidelines for treatment and prevention of candidiasis and aspergillosis and revised *CDC*, *National Institutes of Health (NIH)*, and *IDSA* guidelines for prevention and treatment of opportunistic infections in HIV-infected individuals.
- Differing position statements from *AHA* and *AAP* regarding the need for routine ECG screening in all pediatric patients being considered for or currently receiving stimulant therapy.

■ Major Cautionary Information

Some major cautionary information added or revised for AHFS DI 2010® includes dozens of FDA MedWatch notices and risk evaluation and mitigation strategies (REMS), such as the interaction between ceftriaxone and calcium-containing IV solutions and associated neonatal fatalities; ongoing risk evaluation of cefepime; the potential for serious, life-threatening adverse effects (e.g., irregular heart beat, seizures, breathing difficulties, coma, death) associated with topical overdosage of local anesthetics; increased risk of reactivation of latent viral infections, including cases of BK-virus associated nephropathy, in immunocompromised patients receiving sirolimus, mycophenolate, cyclosporine, or tacrolimus; possible reduced efficacy of clopidogrel associated with genetic polymorphism of CYP 2C19 or concurrent use of drugs such as omeprazole that inhibit this isoenzyme; expanded discussion on the risks of serious systemic toxicity, including toxicity resembling botulism, with botulinum toxin; a voluntary, phased withdrawal of efalizumab (used to treat psoriasis) from the US market due to a potential risk of progressive multifocal leukoencephalopathy (PML), a rare brain infection; and ongoing concerns that the risks of propoxyphene therapy outweigh the benefits.

Other major cautionary information added as revised for 2010 includes the risk of tardive dyskinesia with long-term or high-dose use of metoclopramide; risk of serious liver injury, including liver failure and death, associated with propylthiouracil use; results of the ANDROMEDA study which showed more than a 2-fold increase in mortality in patients with severe heart failure receiving dronedarone; increased mortality in stable liver transplant patients after conversion from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus; metabolic acidosis associated with zonisamide; serotonin syndrome and possible neuroleptic malignant syndrome (NMS)-like reactions with selective serotonin-reuptake inhibitors (SSRIs) and serotonin- and norepinephrine-reuptake inhibitor (SNRIs); serious neuropsychiatric symptoms with bupropion and varenicline in smoking cessation; ongoing safety review for orlistat concerning reports of liver-related adverse events, including several cases of liver failure; ongoing safety review of stimulant medications used in children and adolescents with ADHD and of leukotriene modifiers concerning behavior/mood changes; interim data from a 5-year observational study (EXCELS) suggesting a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic, and thrombophlebotic associated withomalizumab; and adverse effects reported in children following secondary exposure to testosterone through contact with another person being treated topically with the drug.

New safety information for erlotinib including risk of GI perforation (sometimes fatal); bullous, blistering and exfoliative skin conditions (e.g., suggestive of Stevens-Johnson syndrome); toxic epidermal necrolysis (sometimes fatal); and ocular disorders, including corneal perforation or ulceration.

Several tumor necrosis factor (TNF) blocking agent monographs (adalimumab, certolizumab, etanercept, golimumab, and infliximab) were revised to address new risk information on lymphoma and other malignancies in children and adolescents; leukemia in adults, adolescents, and children; other malignancies in children and adolescents; and new-onset psoriasis.

Increased concerns about misuse and abuse of propofol (e.g., by anesthesiologists and other physicians), with potentially fatal consequences. Reformulation of the product to contain EDTA as a preservative and sodium metabisulfate because of the risk of bacterial contamination associated with inappropriate reuse of injections intended for single use.

A cautionary statement has been added to the product listings section of each monograph to remind clinicians that excipients present in some formulations may have clinically important effects in some patients.

This is just a small sampling of the numerous revisions that are included in *AHFS Drug Information 2010*[®].

■ **www.ahfsdruginformation.com**

With the 2010 edition, *AHFS DI*[®] print subscribers will continue to have free access to ASHP's ahfsdruginformation.com, a companion website designed to provide timely ongoing updates as part of their subscription service.

The username "59first" and password "essentials" will be required to access the subscriber-only portions of the website.

By providing post-publication updates to *AHFS DI*[®] electronically via this website, timely notification of critical updates (e.g., MedWatch information) as well as information on newly approved drugs (same-day coverage for most drugs) will be ensured. Information on new molecular entities (NMEs) will be posted on the website as soon as possible following FDA approval, initially as part of the news service and then in the form of an *AHFS/firstRelease*[™].

In addition, access to information on drugs that are deleted from the printed book because of space constraints will be maintained on this website. Occasionally, monographs on drugs with extensive information (e.g., Botulinum Toxin) will be posted on the website for space considerations. In most cases, drugs that are not used commonly will be the focus of such space-saving web postings. Index entries in the printed book for all these monographs refer users to the web site.

The Editorial staff wishes to express appreciation to the many consultants and reviewers for their excellent guidance and cooperation and to our subscribers for their support and comments.