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DRUG INFORMATION 2017

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AHFS® DRUG INFORMATION 2017

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The nature of drug information is that it is constantly evolving because of ongoing research and clinical experience and is often subject to interpretation and the uniqueness of each clinical situation and patient. While care has been taken to ensure the accuracy of the information presented, the reader is advised that the authors, editors, reviewers, contributors, and publishers cannot be responsible for the continued currency of the information or for any errors or omissions in this book or for any consequences arising therefrom. Because of the dynamic nature of drug information, readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician, changing information about a drug (e.g., as reflected in the literature), and changing medical practices.

PREFACE

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 almost 60 years. This notable achievement of almost 6 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, and advancing evidence-based clinical practice. In addition, unlike most compendia, recognition of the authority of AHFS in establishing medically accepted uses of drugs extends far beyond just cancer uses to include the full spectrum of drug therapy.

With the 2017 edition, the *American Hospital Formulary Service®* (*AHFS®*) marks its 59th 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., information on new molecular entities, 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. (See AHFS® Clinical Drug Information™ [AHFS CDI™].)

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. In fact, AHFS' evidence-based assessments of medically accepted uses of drugs predated FDA's authority to evaluate drug effectiveness claims.

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.

As a result of its foundation in a professional and scientific society, the values, editorial standards, and professional priorities of *AHFS DI®* differ importantly from those of commercial drug information publishers. The critical evidence-based assessment and provision of drug information is a core professional activity of ASHP and competency of its members. Despite increased emphasis on provision of evidence-based drug information in all pharmacy practice settings, ASHP and its members remain at the forefront of disseminating such information. As a professional society, ASHP takes a leadership position in influencing health policy, practice, and education toward the goal of assuring that patient care is grounded in accurate, timely, unbiased, and evidence-based drug information. ASHP has been at the forefront of efforts to improve medication use and enhance patient safety for over 70 years.

■ AHFS Patient Medication Information (PMI)

ASHP has a long history of providing patients with meaningful information about medications. AHFS PMI had its origins in 1976 as a collaboration among ASHP, the American Hospital Association (AHA), the US Department of Health, Education, and Welfare (DHEW; now DHHS), and the US Center for Disease Control (CDC; now the Centers for Disease Control and Prevention) and is the only trusted and objective compendium-based database of PMI published by a professional and scientific society in the US. AHFS PMI previously was referred to as AHFS Consumer Medication Information (CMI).

Credibility of sources has been ranked by physicians and other clinicians as the most important characteristic of the Internet related to health information. Consumers also are emphasizing credibility of the health information they obtain on the Internet, trusting safe and effective treatment information from professional societies like ASHP the most and that from pharmaceutical companies the least. AHFS has a clear reputation for credible, valid information based on its history, references, and evidence basis. AHFS PMI, hosted by the National Institutes of Health (NIH), is one of only a few such sites of trusted, accurate medication information.

The trust placed in AHFS PMI has resulted in strategic alliances with groups such as the National Library of Medicine (MedlinePlus® and MedinePlus® Connect) and Consumers Union (Consumer Reports Health and Best Buy Drugs), groups that also place a high priority on the credibility that AHFS PMI provides. In collaboration with Consumer Reports Best Buy Drugs, ASHP has developed a series of off-label drug use reports through a grant from the state Attorney General Consumer and Prescriber Education Grant Program, which was funded by a multistate settlement of consumer fraud claims regarding the marketing of the prescription drug Neurontin® (gabapentin). When accessing any of these sites, consumers can be assured that they are receiving the most trusted and credible medication information available. AHFS PMI also is accessible through ASHP's own website—http://www.safemedication.com.

AHFS PMI also has been adopted as the trusted source of patient medication information by a leading provider of bedside patient engagement and education resources in hospitals—Sonifi® Healthcare (formerly LodgeNet® Healthcare). This service focuses on improving patient satisfaction, outcomes, and quality as measured by the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, care measures, and other indicators.

■ Off-Label Drug Reviews for Oncology

In 2008, *AHFS DI®* introduced a 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 with this oncology process. However, the 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 this 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.

Federal regulations for transparency and conflict of interest disclosure and management became effective January 1, 2010 for off-label oncology determinations. AHFS employs a process for evaluating therapies that is publicly transparent as defined by CFR Section 414.930(a) and that includes criteria used to evaluate the use, a listing of evidentiary materials reviewed by the compendium, and a listing of all individuals who participated substantively in the development, review, or disposition of the request. 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 this section of the 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 companies and other third parties who may seek to use the compendium to promote their own vested interests. Editorial decisions are evidence-based and made independent of such third parties.

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 organization that represents pharmacists who serve as patient care providers on healthcare teams in acute and ambulatory settings spanning the full spectrum of medication use. ASHP has a long history of fostering evidence-based medication use as well as patient medication safety. *AHFS DI®* and PMI are published in part to support the mission of pharmacists in helping people achieve optimal health outcomes.

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. 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 with the manufacturer of the drug(s) under consideration and directly competitive products.

ASHP considers it essential that interactions between AHFS staff and pharmaceutical companies 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 companies, 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 companies (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. It is this process for establishing medically accepted uses of drugs that makes *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 *AHFS DI®* database includes more than 89,000 uniquely cited references linked to more than 637,000 statements and provides direct links to more than 56,000 supporting evidence sources. 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 (DHEW), including DHEW'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 DHEW 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, pharmaceutical company 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 the Department of Health and Human Services (DHHS) 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., Omnibus Budget Reconciliation Act [OBRA] of 1990 and 1993) 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 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, the American Medical Association (AMA), and the United States Pharmacopeia (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.

In 2013 and 2014, ASHP's AHFS staff, as part of a team of highly specialized Life Sciences Subject Matter Experts, led by Reed Technology, performed a key role in the Prescription Drug Labeling Improvement and Enhancement Initiative (PDLI-EI) under a contract (Contract # HHSF223201310225C) with FDA. The purpose of this contract was to provide FDA's Center for Drug Evaluation (CDER) with the necessary services to complete a number of projects aimed at improving and enhancing prescription drug labeling.

■ Widely Used in Print and Electronic Formats

AHFS DI® and its point-of-care derivative database *AHFS DI® Essentials™* are used widely as sources of authoritative drug information by physicians, pharmacists, dentists, nurses, and other health-care professionals and by schools of pharmacy, nursing, and medicine and are available in a variety of formats. Electronic formats include Lexicomp ONLINE with AHFS®; First DataBank's (FDB Health's) AHFS Drug Information monographs available from multiple vendors (e.g., McKesson); *AHFS Drug Information®* from STAT!Ref®, Pepid's Pharmacist Pro with AHFS DI®, and Medicines-Complete®; *Drug Information Fulltext®* (*DIF®*); ePocrates Rx Online™ + AHFS DI®; and AHFS DI® Powered by Skyscape Medpresso and Physicians Interactive. *AHFS DI® Essentials™* is available electronically in online and mobile applications.

In hospitals, clinics, 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 ambulatory care and professional practice settings and is available in most medical libraries.

■ AHFS® Clinical Drug Information™ (AHFS CDI™)

In 2016, ASHP released a comprehensive, electronic suite of its leading drug information databases, including *AHFS DI®*. The new product, AHFS® Clinical Drug Information™ (AHFS CDI™), expands the availability of these trusted ASHP resources, providing clinicians with real-time drug and safety updates and direct links to more than 56,000 supporting evidence sources, as well as easy access to the detailed drug information and in-depth coverage of off-label uses found in *AHFS DI®*. In addition to the monographs of *AHFS DI®*, subscribers to AHFS CDI™ have access to AHFS DI Essentials™, which offers quick, point-of-care answers. Additional ASHP drug information resources are included in the new product, including ASHP's drug shortages resources (which are prepared in conjunction with the University of Utah Drug Information Service). ASHP's *Handbook on Injectable Drugs™* also can be integrated into the suite. AHFS CDI™ features additional links to prescribing information, drug images and imprints, updates on FDA black-box warnings and REMS, and other clinical information.

AHFS® Clinical Drug Information™ is available for individual and institutional subscribers via Web browser, as well as iOS and Android apps. The user interface will also integrate into clinical workflow solutions in hospitals and ambulatory care settings. An application programming interface (API) is available.

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.

■ 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 coverage 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 the Medicare Catastrophic Coverage Act. 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.

Continuously Updated and Revised

The *AHFS DI®* database and annual print edition are updated extensively, incorporating revised information on uses, therapeutic perspectives, cautions, drug interactions, new products, and other new developments. In addition, the database is expanded by dozens of new drug monographs over the course of the year.

■ Recognition and Increased Granularity of the AHFS Pharmacologic-Therapeutic Classification©

The *AHFS®* Pharmacologic-Therapeutic Classification© is the most widely used formulary-structure drug classification in the US and Canada. The AHFS classification is maintained continuously by ASHP and allows the grouping of drugs with similar pharmacologic, therapeutic, and/or chemical characteristics in a 4-tier hierarchy.

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 2017 edition. New this year are subclasses: 48:10.20 Interleukin Antagonists; 56:22.32 Neurokinin-1 Receptor Antagonists; and 92:26 Carbonic Anhydrase Inhibitors. **For additional details on the new subclasses and affected drug monographs, see the link to the AHFS Classification Drug Assignments and Reassignments 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 Prescription Drug Benefit Manual: Part D Drugs and Formulary Requirements" describe use of the *AHFS®* Pharmacologic-Therapeutic Classification© as the only named alternative to USP's Model Guidelines for use by prescription drug 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

The *AHFS DI®* database is expanded, revised, and updated extensively throughout the year to add new monographs and address evolving therapeutic guidance and perspective through review of newly published studies and authoritative guidelines from government and professional organizations. This information is reflected in the revised print edition published each January.

■ Major Cautionary Information

The *AHFS DI®* database is revised and updated extensively throughout the year to address evolving information on medication safety. Manufacturer labeling, FDA safety communications such as MedWatch notices and Risk Evaluation and Mitigation Strategy (REMS) information, published studies and reports, and other safety information are addressed throughout the course of the year. Through semi-automated processes, much of this information is updated on an ongoing basis in electronic versions of the database to reflect more contemporaneously changes made by FDA.

■ www.ahfsdruginformation.com

Some monographs have been omitted from the print version of *AHFS DI®* because of space limitations. Associated index entries for these monographs are followed by "see www.ahfsdruginformation.com." Copies of these monographs are available on the "For Subscribers" page of the AHFS Drug Information website, www.ahfsdruginformation.com, in the "Electronic Only Monographs" section. A username and password are required to access the subscriber-only portions of the website. For the 2017 edition, the username and password for accessing electronic-only content are as follows:

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* Category is currently not in use in the printed version of *AHFS Drug Information®*.

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Organization of the Book

AHFS Drug Information® (*AHFS DI®*) is a collection of drug monographs on virtually every single-drug entity available in the United States. *AHFS Drug Information®* is a tested and proven source of comparative, unbiased, and evaluative drug information.

AHFS DI® monographs are written principally on single-drug entities; information on various trademarked preparations and brands of a drug is contained in a single monograph. Drug *combinations* are described in the monographs on the principal ingredients or, rarely, appear as separate monographs (e.g., Co-trimoxazole 8:12.20) when the combinations are considered important because of therapeutic rationale and/or frequency of use. There also are general statements on groups of drugs (e.g., Salicylates 28:08.04.24) whose activities and uses permit their discussion as a class. Information on older and prototype drugs is another feature of *AHFS DI®*.

Drug monographs are arranged by the widely recognized and used *AHFS®* Pharmacologic-Therapeutic Classification©. (See p. viii.) This arrangement permits easy review of information on a group of drugs with similar activities and uses and allows the reader to determine quickly the similarities and differences among drugs within a group.

A *table of contents* precedes each major class of drugs (e.g., 8:00 Anti-infective Agents) in the book. The table of contents lists each drug monograph included in that major class according to the specific subclass (e.g., Cephalosporins 8:12.06). Within each subclass, monographs are arranged alphabetically by nonproprietary (generic) name and are preceded by the general statement, when present, for that subclass. The names of the drugs are the United States Adopted Names (USAN) and other names for drugs as described in the *USP Dictionary of USAN and International Drug Names*.

Because of the unique arrangement of the book, information on a particular drug can be located by several methods. Information can be located via the Index by using any of the following index terms:

- proprietary (trade) name
- nonproprietary (generic) name
- synonym (e.g., British Approved Name [BAN])
- abbreviation (e.g., INH for isoniazid)
- pharmacy equivalent name (PEN) (e.g., co-triamterzide for the fixed combination of hydrochlorothiazide and triamterene)
- former name (e.g., glyceryl guaiacolate for guaifenesin)

The Index also includes entries for all *AHFS®* Pharmacologic-Therapeutic Classification© terms; therefore, a specific class of drugs (e.g., cephalosporins) can be located by referring to the Index. Once the table of contents for a specific major class of drugs has been located, the page number for the beginning of each drug monograph is listed alongside the monograph title in the table; thus, the list of drug monographs in a given subclass can be quickly scanned to locate a specific drug or drugs of interest. Synonyms for drug classes and other cross-references for classes of drugs (e.g., ACE inhibitors) also may be included in the Index.

Some monographs have been omitted from the print version of *AHFS DI®* because of space limitations. Associated index entries and listings in the table of contents for each major class of drugs in the printed book refer users to the website www.ahfsdruginformation.com to see these monographs. A username and password are required to access these electronic-only monographs. (See the Preface for information on subscriber access to this website.) Each year after publication of the print edition of *AHFS DI®*, new monographs are created, and revisions to existing monographs continue. At the end of the subscription year, any new or revised monographs that were published electronically usually will become incorporated into the upcoming annual edition of *AHFS DI®* within the appropriate AHFS Pharmacologic-Therapeutic class©. Such revised monographs carry the statement "Selected Revisions January 2017" or some other appropriate revision date in the Copyright notice at the end of the monograph. Because information about a drug frequently changes, the manufacturer's labeling should be reviewed periodically.

■ Organization of Full-length Monographs

Information within each drug monograph is divided into the following sections and subsections:

- Monograph Title and Synonyms
- REMS
- Introductory Description
- Uses
- Dosage and Administration
  - Reconstitution and Administration
  - Administration
  - Dosage
  - Dosage in Renal (and Hepatic) Impairment
- Cautions
  - Adverse Effects
  - Precautions and Contraindications
  - Pediatric Precautions
  - Geriatric Precautions
  - Mutagenicity and Carcinogenicity
  - Pregnancy, Fertility, and Lactation
- Drug Interactions
- Laboratory Test Interferences
- Acute Toxicity
  - Pathogenesis
  - Manifestations
  - Treatment
- Chronic Toxicity
  - Pathogenesis
  - Manifestations
  - Treatment
- Pharmacology
- Mechanism of Action (for anti-infectives)
- Spectrum (for anti-infectives)
- Resistance (for anti-infectives)
- Pharmacokinetics
  - Absorption
  - Distribution
  - Elimination
- Chemistry and Stability
  - Chemistry
  - Stability
- Preparations

Not all sections or subsections are included in each monograph. The information is divided only when applicable and necessary. Other subsections not listed above also are used within Pharmacology, Uses, Cautions, and Dosage and Administration.

The presence or absence of a particular drug or use should *not* be interpreted as indicating any judgment by *AHFS DI®* on its merits.

Described below are the types of information that may be included in each major section and subsection within a monograph. Individual monographs may not contain all of the information described below, and the absence of specific information within an individual monograph does not imply that such information is unavailable.

■ **Monograph Title and Synonyms**—Lists the USAN name or other name for the drug(s) described; salts generally are included even when omitted from the USAN name. If multiple forms (e.g., salts, esters) of the same drug are available, all forms are described within the monograph; the title may include all forms (if only a few) or just the base (active moiety). Occasionally, when several drug entities are described in a single monograph, an alternative title descriptive of the group (e.g., Antacids 56:04) is used. Common synonyms for the drug are listed alongside the USAN or other names. When a graphic formula of the drug or prototype (if multiple drugs) is present, it is in the style adopted by the USAN Council and United States Pharmacopeial Convention.

Occasionally, certain synonyms (e.g., pharmacy equivalent names [PENs]) that apply to specific preparations or combinations rather than to the drug itself are noted parenthetically alongside various preparation headings. (See the discussion on Preparations.)

■ **Introductory Description**—Provides a brief chemical, structural, and/or pharmacologic/therapeutic description for the purpose of orientation and introduction.

■ **REMS**—Provides a brief description of a Risk Evaluation and Mitigation Strategy (REMS) approved by the US Food and Drug Administration (FDA), including a list of the components. Because REMS frequently are modified or rescinded, a cross reference to FDA's list of "Approved Risk Evaluation and Mitigation Strategies (REMS)" is provided to refer users to the most current information. REMS for drug *combinations* are described in the monographs on the principal ingredient.

■ **Uses**—Provides information on uses included in the labeling approved by FDA and those that are not (i.e., "off-label" [unlabeled] uses). Off-label uses are identified with daggers† within the text of the monograph; a footnote that describes the use as unlabeled appears at the end of the monograph. Comparisons with other forms of therapy and limitations on use are included when appropriate. This section usually is subdivided by major indication.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the labeling approved by FDA for a drug is limited to those uses for which the sponsor has

submitted information regarding the safety and efficacy of that product and which has been reviewed by the FDA; other uses for which the sponsor has chosen not to submit data to the FDA may be demonstrated in the clinical literature before and after the product is approved by FDA. The FD&C Act does not, however, limit the manner in which a clinician may use an approved drug. Once a drug has been approved for marketing, the clinician may prescribe it for uses or in treatment regimens or patient populations (e.g., children) that are not included in approved labeling. Such off-label uses may be appropriate and rational, and may reflect approaches to drug therapy that have been reported extensively in the medical literature. Valid new uses for drugs often are first discovered via serendipitous observations and therapeutic innovations, and then subsequently may be confirmed by well-designed and controlled studies. Inclusion of such new uses in the FDA-approved labeling for a drug may take considerable time and, without the initiative of the sponsor whose product is involved, may never occur. Therefore, accepted medical practice (state-of-the-art) often includes drug use that is not included in FDA-approved labeling. Accordingly, *AHFS DI®* monographs attempt to describe most uses for a drug, whether or not they are included in FDA-approved labeling; however, the presence or absence of a particular use should *not* be interpreted as indicating any judgment by *AHFS DI®* on its merits. Coverage of off-label uses in *AHFS Drug Information®*, an official Federal drug compendium, has been recognized by the US Congress (e.g., in OBRA 90 and OBRA 93), the Centers for Medicare & Medicaid Services (CMS; Section 1861 and 1927 of the Social Security Act), third-party health-care providers, and others. (See Off-label Uses at http://www.ahfsdruginformation.com for additional information.)

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.

Drugs designated as orphan drugs by FDA and those otherwise considered as orphans are described. An orphan drug is one that is used for the treatment of a rare disease or condition that either occurs in fewer than 200,000 individuals in the US or is more prevalent but for which there is no reasonable expectation that the cost of developing and marketing the drug in the US for such disease or condition would be recovered from US sales. An orphan drug also may be a vaccine, diagnostic drug, or preventive drug if the individuals to whom it will be administered in the US are fewer than 200,000 per year

AHFS Grades of Recommendation

During 2008, *AHFS DI®* introduced a new process for publishing structured, codified, evidence-based determinations for off-label cancer uses. In some monographs that subsequently were revised based on Final Off-label Determinations for cancer uses, text describing such uses based on AHFS Grades of Recommendation may be noted. Following are the categories of AHFS Grades of Recommendation and the definitions of each:

A: Recommended (Accepted) (e.g., should be used, is recommended/indicated, is useful/effective/beneficial in most cases)

B: Reasonable Choice (Accepted, with Possible Conditions) (e.g., treatment option) (e.g., is reasonable to use under certain conditions [e.g., in certain patient groups], can be useful/effective/beneficial, is probably recommended/indicated)

C: Not Fully Established (Unclear risk/benefit, equivocal evidence, inadequate data and/or experience) (e.g., usefulness/effectiveness unknown/unclear/uncertain or not well established relative to standard of care)

D: Not Recommended (Unaccepted) (e.g., considered inappropriate, obsolete, or unproven; is not useful/effective/beneficial; may be harmful)

Documents describing the current process for off-label oncology uses, including levels of evidence, 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.

■ **Dosage and Administration**—Includes information on reconstitution and administration of specific dosage forms and on dosage. In addition, restricted distribution programs for certain drugs may be described when requirements for prescribing and dispensing a drug exist or where distribution is otherwise limited (e.g., orphan drugs).

The Administration subsection describes the routes of administration and, when necessary for clarity, the appropriate dosage form for each route. Instructions for administering the drug (e.g., after meals, with food) and specialized methods of administration are given. Occasionally, instructions for extemporaneous preparation of a dosage form that is not commercially available (e.g., preparation of a pediatric oral suspension from the contents of capsules) are included. For injectable drugs or other dosage forms requiring reconstitution, the Administration subsection is replaced by the Reconstitution and Administration subsection. In addition to information described for the Administration subsection, instructions for reconstitution and, when applicable, further dilution of the dosage form are presented. The rate of injection or infusion of the drug is described, as well as any precautions associated with administration. Generally, compatibility and stability information is described under Chemistry and Stability.

The Dosage subsection describes recommended and alternative dosage schedules for each dosage form and route of administration, and condition being treated. Information in this subsection often is divided by use. When applicable, dosage equivalencies are described. The initial, maintenance, and maximum dosages are given. When available and applicable, specific dosages for children, geriatric or debilitated patients, or patients with renal and/or hepatic impairment are described. Occasionally, when use of a fixed-dosage combination preparation or concomitant use of the drug with another drug is considered rational, specific regimens may be described. Because information about a drug frequently changes, the manufacturer's labeling should be reviewed periodically.

■ **Cautions**—Includes information about adverse effects, precautions and contraindications, pediatric and geriatric precautions, mutagenicity and carcinogenicity, and pregnancy, fertility, and lactation.

Adverse reactions of a drug are undesirable effects, reasonably associated with use of the drug, that may occur as part of its pharmacologic action or may be unpredictable in occurrence. The general Adverse Effects subsection usually is replaced by multiple subsections that are specifically divided by body system affected (e.g., GI, CNS, Hematologic) or by type of effect (e.g., Sensitivity Reactions).

The Precautions and Contraindications subsection includes any special care to be taken by practitioners and/or patients for safe and effective use of the drug and describes serious adverse effects and potential safety hazards, limitations on use imposed by them, and actions that should be taken if they occur. Those situations or conditions for which the drug should not be used because the risk clearly outweighs any possible benefit also are described. Additional precautions and contraindications are included in other appropriate sections of the drug monograph (e.g., Pediatric Precautions; Pregnancy, Fertility, and Lactation; Drug Interactions). Because precautionary information about a drug frequently changes, the manufacturer's labeling should be reviewed periodically.

The Pediatric Precautions subsection describes those pediatric age groups for which safety and/or efficacy of the drug have not been established from adequate and well-controlled studies. Risks associated with use of the drug in pediatric age groups also are described.

The Geriatric Precautions subsection includes precautions, warnings, and contraindications associated with use of the drug in geriatric individuals and provides some perspective regarding study and experience in this population, including factors that may affect response and tolerance.

Pediatric and geriatric information also may be described within the appropriate major sections of the monograph. For example, information on age-dependent pharmacokinetics of the drug would be described within the Pharmacokinetics section and that on age-specific dosage recommendations would be described in the Dosage and Administration section of the monograph. When relevant information on use of the drug in pediatric or geriatric patients is readily available in the medical literature and/or the drug is labeled specifically for use in this age group, details about efficacy generally are described in the Uses section.

The Mutagenicity and Carcinogenicity subsection describes data derived from long-term animal studies evaluating carcinogenic potential of the drug as well as data derived from in vitro tests of mutagenic potential. Pertinent evidence from human data regarding the mutagenic and/or carcinogenic potential of the drug also is included.

The Pregnancy, Fertility, and Lactation subsection describes the safety of the drug in pregnant and/or lactating women and any potential effects on male and female reproduction capacity. Precautionary information regarding use of the drug during pregnancy, as described in FDA's previously designated pregnancy categories A, B, C, D, and X, is included when available. (See Overviews: Pregnancy Precautions for a description of the previously used FDA categories.) In 2014, FDA amended the requirements for pregnancy and lactation labeling, eliminating these lettered categories and replacing the letters with a narrative structure for pregnancy labeling. During the transition period, labeling may contain either the letters designating categories of risk or a text description. Therefore, *AHFS DI®* monographs also may have varying styles depending on the available information. Additional pertinent information regarding use of the drug during pregnancy or effects on labor and delivery also is presented. A description of whether the drug is distributed into milk is included when available, and any associated precautions regarding use of the drug in nursing women are described. Effects of the drug on lactation and/or the nursing infant also are described. Evidence from animal studies regarding effects of the drug on fertility is given, and relevant advice regarding the importance of these animal findings is included when available. Pertinent evidence from humans regarding effects of the drug on fertility also is described.

■ **Acute Toxicity**—Describes toxic effects of the drug associated with intentional or accidental ingestion or administration of a large dose. Information on the amount of drug in a single dose that usually is associated with symptoms of overdosage and the amount of drug in a single dose that is likely to be life-threatening is included when available. Manifestations, laboratory findings, and potential complications of acute overdosage are described. Plasma concentrations associated with toxicity are included when well described.

Recommendations for management of acute toxicity, including those for supportive and symptomatic treatment, are described.

■ **Chronic Toxicity**—Includes well-described toxic effects of the drug associated with prolonged use. When information on chronic toxicity is limited, it often is described in the appropriate subsection under Cautions. The pathogenesis, manifestations, and treatment of chronic toxic effects are discussed. Also included is a description of tolerance to and/or physical or psychologic dependence on the drug. Adverse effects associated with abrupt withdrawal of the drug are described, and appropriate measures for management are included.

■ **Drug Interactions**—Describes clinically important drug/drug and drug/food interactions, including adverse and therapeutically useful interactions. The mechanism of the interaction, associated clinical importance, precautions to be observed, and management of the interaction are described. Generally, potential interactions supported only by animal or in vitro data are not described. Occasionally, theoretical interactions are presented because of the likelihood of their occurrence (e.g., based on evidence from similar drugs) or the potential severity of the effect should it occur.

■ **Laboratory Test Interferences**—Includes information on common, well-established drug/laboratory test interferences. The mechanism of the interaction, effects on test results, and effects on interpretation of these results are included. Alternative laboratory tests are described when appropriate. Alterations in laboratory test results that reflect a pathologic effect of the drug (e.g., aminoglycoside-induced increase in serum creatinine concentration) are described in the appropriate subsections under Cautions. Because of the nature of information on laboratory tests, appropriate specialized references on laboratory methods should be consulted when detailed information is required.

■ **Pharmacology**—Includes a brief statement of pharmacologic activity and/or mechanism of action, often compared with other similar drugs, for the purpose of orientation and introduction. Expanded descriptions of all pharmacologic activities and effects are included. When relevant to human pharmacology and therapeutics, animal or in vitro data are presented. Data from human studies are not specified as such unless needed for clarification. Quantitative and qualitative comparative (with other drugs) information is provided when appropriate. Pharmacology usually is subdivided by pharmacologic effect (e.g., Anti-inflammatory, Analgesic) and/or body system affected (e.g., CNS, GI, Hematologic).

For anti-infectives, pharmacology is described under Mechanism of Action, Spectrum, and Resistance.

■ **Mechanism of Action**—Describes the mechanism of anti-infective activity for anti-infective agents.

■ **Spectrum**—Describes the in vitro spectra of activity of anti-infectives. The subsection on Susceptibility Testing describes factors (e.g., pH, test media, inoculum size) affecting susceptibility tests and defines susceptible and resistant organisms in terms of in vitro susceptibility test results (e.g., zone diameters for the Kirby-Bauer method, MICs for the tube dilution method). MIC values for clinically important organisms are included in the spectra subsections. Spectra often are divided according to class of organism (e.g., Gram-negative Bacteria, Anaerobic Bacteria).

In general, nomenclature for microorganisms follows that presented in the current edition of *Bergey's Manual of Systematic Bacteriology* and the "Approved Lists of Bacterial Names" published in the *International Journal of Systematic and Evolutionary Bacteriology*. Other standard sources (e.g., Bacterial Nomenclature Up-to-date at http://www.dsmz.de/microorganisms/main.php?contentleft_id=14), as described by the American Society for Microbiology in the January issue of *Antimicrobial Agents and Chemotherapy*, also are used. When available, in vitro susceptibility information generally is described according to the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards [NCCLS]) and/or the manufacturer's labeling.

■ **Resistance**—Describes the mechanism of resistance of microorganisms to anti-infective agents. Microbiologic tolerance to these agents also is described. Information on cross-resistance with other anti-infective agents is included. Definition of resistance in terms of in vitro susceptibility test results is described in the Spectrum section. Descriptions of resistant organisms are included in the spectra subsections of Spectrum.

Resistance of cells to antineoplastic agents generally is described in the Pharmacology section. Resistance or tolerance to the pharmacologic and/or therapeutic effects (e.g., tachyphylaxis) of other drugs generally is described in Pharmacology and/or Uses. Tolerance to the pharmacologic effects of some drugs (e.g., opiate agonists) also may be described in the Chronic Toxicity section.

■ **Pharmacokinetics**—Describes absorption, distribution, and elimination (biotransformation and excretion) characteristics of a drug.

The Absorption subsection includes information on extent (bioavailability) and rate of absorption by usual routes of administration and factors (e.g., product formulation) that might influence them. Applicable comparative information on doses, dosage forms, and routes of administration is included. Information on serum concentrations achieved and on the period of time for onset, peak, and duration of pharmacologic and/or therapeutic effect also is included, even when an absorption phase per se does not occur (e.g., following IV administration). Ranges for therapeutic and/or toxic concentrations (e.g., plasma, serum) of the drug are described when established.

The Distribution subsection describes the usual distribution of the drug into body tissue and fluids. Information describing the drug's propensity to cross the blood-brain barrier and placenta and to distribute into milk is included. Protein binding characteristics are presented.

The Elimination subsection describes the biotransformation and excretory characteristics of the drug. Information on elimination half-life and factors influencing it, clearance, site and extent of biotransformation, metabolic products and their activities, and routes of elimination from the body (e.g., urine, feces via bile) and factors affecting them is included. The effect of peritoneal dialysis and hemodialysis on elimination of the drug also is discussed.

■ **Chemistry and Stability**—Includes a brief chemical, structural, and/or pharmacologic description, often compared with other similar drugs, for the purpose of orientation and introduction. Structure-activity relationships are described when applicable. A physical description of drug entities includes physical appearance, taste, odor, and solubility. Solubilities are described according to USP descriptive terms (see the current edition of the *United States Pharmacopeia–National Formulary* [*USP–NF*]) or as appropriate specific solubilities (i.e., amount of solute per volume of solvent).

If the drug is ionizable, the pK_a is given. Other chemical and/or physical constants such as pH and osmolarity/osmolality of commercially available preparations are included. Preservatives and other important excipients in a commercial preparation also are described. Dosage equivalencies (e.g., units per mg of drug, mg of base per mg of salt) are given when the dosage of a drug differs from the commercially available form (e.g., salt, ester). Amounts of important ions (e.g., mg/mEq of potassium, sodium) in commercial preparations also are included.

Applicable stability information such as the effect of pH, autoclaving, heat, light, moisture, air, freezing, and microwave thawing is described. Storage requirements (i.e., recommended environmental storage conditions) also are described. Stability information about reconstituted and/or diluted preparations is provided. Physical and/or chemical compatibility information may be included. Additional detailed compatibility information on injectable drugs is available in the *Handbook on Injectable Drugs* (available from the American Society of Health-System Pharmacists; go to www.ashp.org for details).

■ **Preparations**—Lists commercially available preparations of the drug. Preparations are described under the appropriate heading by USAN or other nonproprietary (generic) name. Combination preparations are described under a separate heading (e.g., Aspirin Combinations) following the appropriate single-entity subsection (e.g., Aspirin); official USP combination names (e.g., Metoprolol Tartrate and Hydrochlorothiazide) are used whenever possible.

Preparations are listed hierarchically by route of administration (alphabetically), dosage form (alphabetically), and strength (in order of increasing strength). When potency is described in terms other than those listed in the drug heading (e.g., potency of cefotaxime sodium is expressed in terms of cefotaxime), the labeled moiety is described parenthetically after the strength [e.g., 1 g (of cefotaxime)]. Although USP has changed its naming conventions to eliminate salt forms in many official monograph titles (active moiety nomenclature concept), the American Society of Health-System Pharmacists continues to oppose this nomenclature change because of resulting confusion and loss of important chemical identity cues, and therefore *AHFS DI®* will continue to include salts in the Preparations headings for clarity.

Route of administration and dosage form listings may be modified (e.g., Injection, for IM use only; Tablets, chewable; Capsules, extended-release). Following each preparation description, the proprietary (trade) names are listed alphabetically and include the corresponding manufacturers. Generally, multiple-source preparations that are available by nonproprietary (generic) name do not include the manufacturers/labelers; these preparations are described as being "available by nonproprietary name."

When established by USP, pharmacy equivalent names (PENs) (e.g., cocareldopa for levodopa and carbidopa) are listed parenthetically alongside the corresponding combination heading. PENs are short and simple names that can be used for convenience by practitioners when it would be impractical to use the complete nonproprietary combination name. PENs are informational rather than official (*USP–NF*), but are offered by USP as standardized terms intended to discourage the proliferation of trivial names and undefined abbreviations for combinations. This abbreviated nomenclature was pioneered by the *British Pharmacopoeia* (*BP*) and subsequently adopted by USP.

Generally, dosage forms used in the Preparations sections are the pharmaceutical dosage forms described in USP. (See the current edition of the *United States Pharmacopeia–National Formulary*.) Several dosage forms (i.e., elixir, extract, fluidextract, spirit, tincture) are used only when the preparation is official (USP or NF). Solution generally is used to describe all liquid preparations of dissolved drug, regardless of solvent; although syrups occasionally are official (USP or NF), these are listed as solutions and syrup is included only as part of the proprietary name.

Applicable legal descriptions (e.g., drugs subject to control under the Federal Controlled Substances Act of 1970, drugs subject to restricted distribution programs) are included.

■ **References**—Includes the bibliography for cited references. Information included in *AHFS DI®* is thoroughly referenced. Although the print version of *AHFS DI®* does not include reference notations, all statements appearing in the publication are documented. Access to referenced statements and the References section of individual drug monographs can be gained through electronic versions (e.g., AHFS® Clinical Drug Information™ [AHFS CDI™], 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®; AHFS DI® Powered by Skyscape) of the publication.

Reference citations currently are accessible for all monographs published originally after March 1984. For monographs originally published prior to that time, bibliographic citations are accessible only for selected revisions occurring since 1984. To determine whether a monograph was published or revised after March 1984, see the copyright notice at the end of the monograph in question. In electronic versions of *AHFS DI®*, approximately 90% of the monographs currently are completely or partially referenced.

For additional information on searching the electronic versions of *AHFS DI®*, contact the eHealth Solutions Division in the Publications and Drug Information Systems Office of ASHP by phone at 301-657-3000 or by FAX at 301-664-8857 or by email at *pdiso@ashp.org*.

■ **Overviews**—Certain monographs in *AHFS DI®* are designated as Overviews. This designation appears in a boldface footnote preceding the Preparations section of the monograph.

Scope

The Overviews are summary descriptions about new molecular entities (NMEs) that include information drawn principally from the manufacturer's labeling (package insert). Pertinent information from other sources such as authoritative therapeutic guidelines, secondary references (e.g., review articles), and a limited number of primary references (e.g., the principal clinical studies) also may be included; however, the overviews are not intended to be comprehensive. When additional information on such drugs is needed before publication of a more detailed (full-length) *AHFS DI®* monograph, the manufacturer's labeling should be consulted.

The Overviews are intended to provide subscribers to *AHFS DI®* with summaries on new molecular entities that can answer most common questions about these drugs. As such, the Overviews are limited to basic information on the drugs, including brief descriptions (chemical and pharmacologic) of the type of drug, its labeled uses and associated dosages, product availability, selected cautionary information (e.g., warnings and precautions, sensitivity reactions, cautions applicable to specific populations, common adverse effects), drug interactions, and important advice for patients. While selected precautionary information appears in these summaries, the scope of the overview format limits the extent of discussion. As a result, the Overviews do not provide full disclosure about the respective drugs, and therefore it is essential that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Pregnancy Precautions

The pregnancy precautions in the Overviews historically have followed FDA's lettered categories (A, B, C, D, or X), as stated in the manufacturer's labeling. Because of the summary format of the Overviews, only the letter designation usually appears in Overviews. However, as noted previously FDA amended the requirements for pregnancy and lactation labeling in 2014, eliminating these lettered categories and replacing the letters with a narrative structure for pregnancy labeling. Therefore, some *AHFS DI®* Overviews now contain text descriptions of information about use of a drug during pregnancy when the lettered category has not been provided in the labeling.

Following are definitions of the categories FDA previously had designated:

Category A. Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester and there is no evidence of risk in later trimesters. If the drug were used during pregnancy, the possibility of fetal harm appears remote.

Category B. Either animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than on fertility) but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester and there is no evidence of risk in later trimesters. In either case, the drug should be used during pregnancy only when clearly needed.

Category C. Either animal reproduction studies have revealed evidence of an adverse fetal effect and there are no adequate and well-controlled studies in pregnant women or animal reproduction studies have not been performed and it is not known whether the drug can cause fetal harm when administered to pregnant women. In the first case, the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. In the latter case, the drug should be used during pregnancy only when clearly needed.

Category D. There is positive evidence of human fetal risk based on adverse reaction data from investigational or postmarketing experience or studies in humans, but the potential benefits from use of the drug in pregnant women may be acceptable in certain conditions despite the possible risks to the fetus. The drug should be used during pregnancy only in life-threatening situations or severe disease for which safer drugs cannot be used or are ineffective. When the drug is administered during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the fetus.

Category X. The drug may (can) cause fetal toxicity when administered to pregnant women based on animal or human studies demonstrating fetal abnormalities or positive evidence of human fetal risk from adverse reaction data from investigational or postmarketing experience, or both, and the risk of use of the drug during pregnancy clearly outweighs any benefit (e.g., safer drugs or alternative therapies are available). Since the risks clearly outweigh any possible benefits in women who are or may become pregnant, the drug is contraindicated in such women. If the drug is inadvertently administered during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the fetus.

■ **SumMons®**—Certain monographs in *AHFS DI®* are designated as SumMons® (summary monographs). This designation appears in a boldface footnote preceding the Preparations section of the monograph. SumMons® are summary descriptions about the respective drug, which include information that is drawn principally from the manufacturer's labeling (package insert) and/or other pertinent information (such as secondary references [e.g., review articles] and a limited number of primary references [e.g., the principal clinical studies]); however, no attempt is made to be complete, and the information may *not* be evaluative. When additional information on such drugs is needed pending development and publication of a more detailed (full-length) *AHFS DI®* monograph, the manufacturer's labeling should be consulted.

The summaries are intended to provide only basic information on the drugs, and therefore are limited to brief descriptions (chemical and pharmacologic) of the type of drug, its labeled uses and associated dosages, and product availability. While selected precautionary information occasionally may appear in these summaries, no attempt is made to be complete, and therefore it is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications. Some SumMons® have been expanded to include a detailed Cautions section, but it remains *essential* that the labeling be consulted for information on potential drug interactions, laboratory test interferences, and acute toxicity for such expanded descriptions. Some SumMons® also have been expanded to include important "unlabeled/off-label" uses.

■ **Notices**

Other Notices

For other notices of warning, see Notices on p. iii of the master volume issued in January of each year.

4:00 ANTIHISTAMINE DRUGS

§ Omitted from the print version of *AHFS Drug Information* because of space limitations. This monograph is available on the *AHFS Drug Information* web site, http://www.ahfsdruginformation.com. See the Preface for details on accessing this site.

* Please see the full AHFS Pharmacologic-Therapeutic Classification© on p. vii. Not all classes are used in the printed edition.

Antihistamines General Statement

■ Antihistamines, which inhibit the effects of histamine at H_1 receptors, have been classified as first generation (i.e., relatively sedating) or second generation (i.e., relatively nonsedating).

Uses

Antihistamines are most often used to provide symptomatic relief of allergic symptoms caused by histamine release. The drugs are not curative and merely provide palliative therapy. Antihistamines are used only as adjunctive therapy to epinephrine and other standard measures in the treatment of anaphylactic reactions and laryngeal edema after the acute manifestations have been controlled. Individual patients vary in their response to antihistamines. A specific antihistamine that provides dramatic relief without adverse effects to one patient may produce intolerable adverse effects in another patient. Trial of various antihistamines may be necessary to determine which drug will provide relief while causing minimal adverse effects.

■ **Nasal Allergies and the Common Cold** Antihistamines are most beneficial in the management of nasal allergies. Seasonal allergic rhinitis (e.g., hay fever) and perennial (nonseasonal) allergic rhinitis are benefited more than perennial nonallergic (vasomotor) rhinitis. Orally administered antihistamines generally provide symptomatic relief of rhinorrhea, sneezing, oronasopharyngeal irritation or itching, lacrimation, and red, irritated, or itching eyes associated with the early response to histamine. The drugs generally are not effective in relieving symptoms of nasal obstruction, which are characteristic of the late allergic reaction, although limited data indicate that cetirizine and levocetirizine may relieve some symptoms of late allergic reactions. Antihistamines (e.g., azelastine) also may be administered intranasally for the symptomatic relief of seasonal allergic rhinitis. (See Uses in Azelastine 52:02.) In comparative studies, intranasal azelastine was more effective than placebo and at least as effective as oral antihistamines (e.g., cetirizine, terfenadine [no longer commercially available in the US]) or intranasal corticosteroids in relieving allergic rhinitis. However, unlike intranasal corticosteroids, azelastine does not appear to exhibit local histologic anti-inflammatory activity; therefore, beneficial effects on nasal obstruction appear to result principally from antihistaminic and/or other activity.

Chronic nasal congestion and headache caused by edema of the paranasal sinus mucosa are often refractory to antihistamine therapy. In the treatment of hay fever, antihistamines are more likely to be beneficial when therapy is initiated at the beginning of the hay fever season when pollen counts are low (e.g., before pollination begins) and if used regularly during the pollen season. Antihistamines are less likely to be effective when pollen counts are high, when pollen exposure is prolonged, and when nasal congestion is prominent.

Although antihistamines frequently are used for symptomatic relief in the common cold, evidence of effectiveness remains to be clearly established. Antihistamines cannot prevent, cure, or shorten the course of the common cold, but may provide some symptomatic relief. Conventional (prototypical, first generation) antihistamines (e.g., those with anticholinergic activity) are considered effective in relieving rhinorrhea and sneezing associated with the common cold, but evidence of efficacy in relieving oronasopharyngeal itching, lacrimation, or itching eyes associated with this condition currently is lacking. Nonsedating (second generation) antihistamines do not appear to be effective in relieving rhinorrhea, suggesting that histamine is not a principal mediator of this manifestation. The extent to which histamine contributes to other manifestations of the common cold currently is unclear, but pathogenesis of the full constellation of symptoms that constitute the common cold appears to be complex, involving a number of mediators and neurologic mechanisms.

Routine, prolonged administration of fixed combinations containing antihistamines, nasal decongestants, anticholinergics, analgesic-antipyretics, caffeine, antitussives, and/or expectorants has been questioned. Single-ingredient products generally are safer than combination products, while also facilitating dosage adjustment. There is no evidence that combinations containing 2 or more antihistamines are more effective than one antihistamine or that combinations of subtherapeutic doses of 2 or more antihistamines are more effective than therapeutic doses of one antihistamine. Oral antihistamine combinations containing an analgesic-antipyretic and/or nasal decongestant; an antitussive and nasal decongestant; an analgesic-antipyretic, antitussive, and nasal decongestant; or an antitussive may be rational if each ingredient has demonstrated clinical effectiveness and is present in therapeutic dosage. Selective use of such combinations can provide a convenient and rational approach for relief of concurrent symptoms (e.g., rhinorrhea, nasal congestion, cough), which often are present in allergic rhinitis and other conditions (e.g., common cold), by allowing the patient to use a single combination rather than multiple single-entity preparations. Combination preparations generally should be used only when symptoms amenable to each ingredient are present concurrently. Combinations containing an antihistamine and an expectorant, anticholinergic agent, or bronchodilator are *not* considered rational.

Although cough and cold preparations that contain antihistamines, nasal decongestants, cough suppressants, and/or expectorants commonly were used in pediatric patients younger than 2 years of age, systematic reviews of controlled trials have concluded that nonprescription (over-the-counter, OTC) cough and cold preparations are *no* more effective than placebo in reducing acute cough and other symptoms of upper respiratory tract infection in these patients. Furthermore, adverse events, including deaths, have been (and continue to be) reported in pediatric patients younger than 2 years of age receiving these preparations. (See Cautions: Pediatric Precautions.)

■ **Other Allergic Conditions** Antihistamines are often effective in the treatment of allergic dermatoses and other dermatoses associated with histamine release, but effectiveness varies with the causative agent and symptoms may return when the drug is stopped. Antihistamines have been used in the symptomatic treatment of chronic idiopathic urticaria; occasionally, patients

who do not experience adequate relief with an antihistamine (H_1-receptor antagonist) alone may benefit from the addition of an H_2-receptor antagonist. However, in one study, the addition of an H_2-receptor antagonist did not provide a substantial increase in response (as determined by reduction in whealing). Some antihistamines also may symptomatically relieve pruritus accompanying atopic dermatitis, contact dermatitis, pruritus ani or vulvae, and insect bites. Some evidence suggests that first generation antihistamines such as hydroxyzine and diphenhydramine may be more effective than second generation antihistamines (e.g., terfenadine [no longer commercially available in the US], loratadine) for the relief of pruritus associated with certain allergic dermatoses (e.g., atopic dermatitis), but additional study is needed to elucidate further the relative efficacy of these drugs as antipruritics. Antihistamines also may be used in the treatment of dermatographism. Patients with dermatographism or other urticarial conditions who do not experience adequate relief with an antihistamine (H_1-receptor antagonist) alone may benefit from the addition of an H_2-receptor antagonist to enhance relief of pruritus and wheal formation.

Antihistamines are useful in the management of allergic conjunctivitis caused by foods or inhaled allergens. Allergic or hypersensitivity reactions to penicillin, streptomycin, sulfonamides, and other drugs may be amenable to antihistamine therapy. Pruritus and urticaria accompanying these conditions usually are temporarily relieved; edema is more resistant and serum sickness is not benefited.

Symptoms of mild transfusion reactions not caused by ABO incompatibility or pyrogens may be alleviated by antihistamines. The drugs should *not* be added to blood being transfused. Antihistamines may be administered prophylactically to patients with a history of transfusion reactions, but the drugs should not be given routinely to patients receiving blood. Antihistamines also may be useful to prevent sequelae following desensitization procedures and allergic reactions to radiographic contrast media. It must be kept in mind that prophylactic use of antihistamines may mask incipient signs of allergic reactions, and the patient's hypersensitivity may not be recognized until a serious reaction occurs.

Although epinephrine is the initial drug of choice for patients with anaphylactic or anaphylactoid reactions, antihistamines are useful in the ancillary treatment of pruritus, urticaria, angioedema, and bronchospasm associated with these reactions. Concurrent use of H_1- and H_2-receptor antagonists appears to reduce the adverse effects of histamine on the peripheral vasculature and myocardium during anaphylaxis.

■ **Asthma** Antihistamines may provide some benefit in certain asthmatic patients, but the drugs usually are not effective in treating bronchial asthma per se and should *not* be used in the treatment of severe acute asthma attacks. In addition, antihistamines are not included in the usual recommended regimens for the management of asthma, including long-term control of the disease. Antihistamine and decongestant combinations may provide symptomatic relief (e.g., of rhinitis) in patients with chronic rhinitis and persistent asthma, but the drugs have not been shown to have a protective effect on lower airways; other agents (e.g., inhaled corticosteroids) are for protective effects on lower airways. In general, patients with predictable seasonal asthma should receive long-term anti-inflammatory therapy (e.g., inhaled corticosteroids, mast-cell stabilizers), initiated prior to the anticipated onset of exposure to allergens and continued throughout the season. The drugs may be used with caution to treat hay fever or other airway disorder with a histamine-mediated component in patients with such disorders and asthma. Although some clinicians believe that the anticholinergic effects (e.g., reduction of nasal secretions) of some of these drugs may cause thickening of bronchial secretions resulting in further airway obstruction in asthmatics, especially those with status asthmaticus, most experts consider complete avoidance of currently available antihistamines in asthmatics unjustified. (See Cautions: Precautions and Contraindications.)

■ **Motion Sickness and Vertigo** Some antihistamines (e.g., dimenhydrinate, diphenhydramine, meclizine, promethazine) are useful for the prevention and treatment of nausea, vomiting, and/or vertigo associated with motion sickness and they are considered the drugs of choice for the management of this condition. For additional information on the use of antihistamines for the management of motion sickness, see Dimenhydrinate and see Meclizine Hydrochloride in 56:22.08. Dimenhydrinate and meclizine have also been used in the symptomatic treatment of vertigo associated with diseases affecting the vestibular system (e.g., labyrinthitis, Ménière's disease). Nonphenothiazine antihistamines are less effective than the phenothiazines in controlling nausea and vomiting not related to vestibular stimulation.

■ **Chemotherapy-induced Nausea and Vomiting** Some antihistamines (e.g., diphenhydramine) may be useful as adjunctive antiemetic agents to prevent chemotherapy-induced nausea and vomiting†; however, the American Society of Clinical Oncology currently does not recommend that antihistamines be used alone as antiemetic agents in patients receiving chemotherapy.

■ **Insomnia** Some antihistamines, especially the ethanolamines such as diphenhydramine and doxylamine, are used for their sedative effects as nighttime sleep aids. The US Food and Drug Administration (FDA) states that diphenhydramine currently is the only antihistamine commercially available in the US that has been shown to be both safe and effective for *self-medication* as a nighttime sleep aid. In individuals who experience occasional sleeplessness or those who have difficulty falling asleep, diphenhydramine (administered as either the citrate or hydrochloride salt) is more effective than placebo in reducing sleep onset (i.e., time to fall asleep) and increasing the depth and quality of sleep. Although the safety and efficacy of doxylamine as a nighttime sleep aid have not been fully established, the FDA states that, pending further accumulation of data, doxylamine-containing nighttime sleep aids that have been approved for this use may continue to be marketed in the US. Some proprietary sleep aids also may continue to contain pyrilamine despite a lack of substantial evidence of safety and efficacy for use of this antihistamine as a nighttime sleep aid; however, many such preparations have been or are likely to be reformulated with other antihistamines (e.g., diphenhydramine).

■ **Other Systemic Uses** Some antihistamines such as diphenhydramine have been used effectively as antitussives. Diphenhydramine also may be useful in the management of tremor early in the course of parkinsonian syndrome and in the management of drug-induced extrapyramidal reactions.

■ **Topical and Other Local Uses** Diphenhydramine and tripelennamine (no longer commercially available in the US; extemporaneous formulation would be necessary) are used topically for temporary relief of pruritus and pain associated with various skin conditions including minor burns, sunburn, minor cuts or scrapes, insect bites, or minor skin irritations. The drugs may provide effective localized antipruritic activity when applied topically if pruritus and discomfort are histamine mediated; the weak local anesthetic action of the drugs also may contribute to the overall effect. However, many clinicians suggest that topical diphenhydramine not be used on large areas of the body or more often than directed, since increased percutaneous absorption of the drug may occur that can result in systemic adverse effects and toxicity. (See Acute Toxicity: Manifestations.) Topical diphenhydramine also should not be used for *self-medication* in the management of varicella (chickenpox) or measles without first consulting a clinician.

Some antihistamines also have been used for their topical or local anesthetic effects in ophthalmic, urologic, proctologic, gastroscopic, otolaryngologic, and dental procedures. However, topical use of antihistamines generally is discouraged because sensitivity reactions (e.g., sensitization, hypersensitivity) may result. (See Cautions: Sensitivity Reactions.) In addition, use of certain antihistamines (e.g., diphenhydramine) for local anesthesia via local infiltration also is discouraged because of the risk of local tissue necrosis. If the drugs are used topically as antipruritics, therapy generally should be short-term (i.e., for no longer than 7 days) because of the increasing risk of sensitivity reactions from prolonged or repeated use. Antihistamines are more effective, especially if pruritus is generalized, and are less likely to cause sensitivity reactions when the drugs are administered systemically rather than applied topically.

Dosage and Administration

■ **Administration** Antihistamines usually are administered orally. Although some of these drugs may be given IV, IM, or subcutaneously, most antihistamines are not administered parenterally because they frequently cause local irritation. Some antihistamines also may be administered topically or intranasally. Topical use of antihistamines generally is discouraged since sensitivity reactions (e.g., sensitization, hypersensitivity) may result. In addition, topical preparations containing diphenhydramine should not be used more often than directed for any condition, applied on large areas of the body, or used concomitantly with other preparations containing diphenhydramine, including those used orally, since increased serum concentrations of diphenhydramine may occur that can result in CNS toxicity. (See Acute Toxicity: Manifestations.) Topical diphenhydramine also should not be used for *self-medication* in the management of varicella (chickenpox) or measles without first consulting a clinician.

■ **Dosage** Dosage of antihistamines should be individualized according to the patient's response and tolerance.

Cautions

Adverse effects, which vary in incidence and severity with the individual drug, are caused by all antihistamines, although serious toxicity rarely occurs. Individual patients vary in their susceptibility to the adverse effects of these drugs, and such effects may disappear despite continued therapy. Geriatric patients may be particularly susceptible to dizziness, sedation, and hypotension. Most mild reactions may be relieved by a reduction in dosage or changing to another antihistamine.

Severe cardiovascular effects, including prolongation of the QT interval, arrhythmias, cardiac effects, hypotension, palpitations, syncope, dizziness and/or death have been reported in patients receiving astemizole (no longer commercially available in the US) or terfenadine (no longer commercially available in the US). These cardiotoxic effects usually were associated with higher than recommended dosages and/or increased plasma concentrations of the drugs and their active metabolites.

■ **CNS Effects** CNS depression is common with usual dosage of antihistamines, especially with the ethanolamine derivatives. Sedation, ranging from mild drowsiness to deep sleep, occurs most frequently; however, in the treatment of allergies, this effect may be therapeutically useful. Dizziness, lassitude, disturbed coordination, and muscular weakness may also occur. In some patients, the sedative effects disappear spontaneously after the antihistamine has been administered for 2–3 days. Individuals who perform potentially hazardous tasks requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) should be warned about possible drowsiness, dizziness, or weakness. Patients also should be warned to avoid consuming alcoholic beverages while taking antihistamines, since alcohol may potentiate these CNS effects. In addition, patients already receiving other CNS depressants (e.g., sedatives, tranquilizers) should be warned not to undertake *self-medication* with an antihistamine without first consulting their clinician. Patients using diphenhydramine or doxylamine for *self-medication* should be warned that the drugs may cause *marked* drowsiness. Acrivastine, desloratadine, fexofenadine, loratadine,