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February 21, 2001

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Re: Comment to Docket Nos. 00N-1609 and 00N-1610; Digoxin Products for Oral Use; Revocation of Conditions for Marketing and Reaffirmation of New Drug Status

Dear Sir or Madam:

Bertek Pharmaceuticals Inc. ("Bertek"), in cooperation with Amide Pharmaceutical, Inc. ("Amide"), and by and through counsel, submits these comments to the above-referenced Dockets issued by the Food and Drug Administration ("FDA"), relating to digoxin products for oral use (collectively, the "Digoxin Proposed Rule"). 65 Fed. Reg. 70573 (2000); 65 Fed. Reg. 70538 (2000). Bertek's comments support FDA's position that digoxin products for oral use are new drugs that require approved applications for marketing. Bertek also supports FDA's proposal to revoke the 1974 Digoxin Regulation (21 C.F.R. § 310.500), and to finalize that revocation in a timely fashion. FDA's prompt action in this matter will ensure that the marketplace does not include digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence, formulation and manufacturing changes that have not been reviewed by FDA, and unproven labeling claims. By swiftly removing these tablets from the marketplace, FDA will protect the public health.

Bertek's comments also respond to the December 22, 2000 comments submitted by ReedSmith L.L.P. on behalf of Jerome Stevens Pharmaceuticals, Inc., a manufacturer of digoxin tablets (hereafter, "ReedSmith Comments"). In particular, our comments will clarify the record and correct the misleading and, at times, inaccurate statements in the ReedSmith Comments.

00N-1609

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I. The Existing Market For Digoxin Tablets Presents A Public Health Risk

Bertek supports FDA's proposal to revoke the 1974 Digoxin Regulation, 21 C.F.R. § 310.500, which provides an avenue for marketing digoxin tablets without obtaining FDA approval pursuant to the drug approval requirements set forth in Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355). We agree with FDA that the revocation of this outdated regulation will serve to protect the public health. In today's marketplace, the public health can be safeguarded only by subjecting all digoxin products to the same rigorous standards and bioequivalence testing that is mandated by statute via the post-1984 new drug approval process.[1]

By contrast, the ReedSmith Comments assert that FDA should reconsider its proposal to revoke the 1974 Digoxin Regulation, arguing that FDA failed to identify any threat to public health that has arisen from the operation of the regulation. We strongly disagree and note that the public health risks are numerous and unmistakable, as discussed herein. Additionally, if FDA were to delay the revocation of the 1974 Digoxin Regulation, new companies could enter the digoxin market, and companies that had previously ceased manufacturing could reenter the digoxin market, thereby exacerbating the endangerment to the public health.[2]

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[1] To preserve the administrative record, Bertek notes that its legal counsel has taken the position that, where new drug applications have been approved by FDA, the new drug approval process (i.e., 21 U.S.C. § 355) provides the only legitimate statutory means for the lawful marketing in interstate commerce of digoxin tablets – a legal argument that has been upheld by at least one court and followed by FDA in other instances. See Hoffman-LaRoche v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975); FDA Compliance Policy Guide 7132c.02, 49 Fed. Reg. 38190 (1984) (amended in 1987). As a result, FDA may have no legal authority to reconsider its proposal to revoke the 1974 digoxin regulation.

[2] We note that, in 1988, digoxin tablet marketers included J.J. Balan, Bioline, Burroughs Wellcome, Cooper Drug, Dixon-Shane, Genetco, Gen-King, Glenlawn, Goldline, Harber, Interstate, Kenyon, Lannett, Major, H.L. Moore, Parmed, Pharmaceutical Corp. of America, Purepac, Redi-med, Ruckstuhl, Rugby, Schein, Scrips, Truxton, United Research, Vangard, Veratex, Vita-Rx, Vortech, West-Ward, Williams Generics, and Zenith Goldline. See 1988 Drug Topics® Red Book®, pp. 288-289. By 1991, other market entrants included Aligen, Clinical, Halsey Drug, Medirex, Pioneer Pharmaceuticals, and Qualitest. See 1991 Drug Topics® Red Book®, pp. 246-247. Likewise, Alra, Amide, Glasgow, Jerome Stevens, PD-Rx Pharmaceuticals, Physicians Total Care, Raway, and Southwood were in the market

(Footnote cont'd on next page.)

A. Without An FDA Review For Safety And Effectiveness, The Marketing Of Digoxin Tablets Unnecessarily Risks The Public Health

As FDA has confirmed, GlaxoSmithKline (then, Burroughs Wellcome) initially marketed a digoxin product in the U.S. in 1934. The early marketing of this drug is important to an understanding of FDA's proposed action in 2000 because, in three ways, the law governing drugs has changed fundamentally since 1934. First, in 1934, federal law did not require approval by FDA before a drug could be marketed. That requirement was imposed by Congress in 1938 via the Federal Food, Drug, and Cosmetic Act ("FFDCA"). The 1938 FFDCA required prior FDA approval based solely on a demonstration that the drug was safe for patient use. Second, in 1962, Congress amended the FFDCA to require that FDA must affirmatively approve a drug for its effectiveness, as well as its safety. Third, in 1984, Congress adopted the modern generic drug approval process, by which a generic drug maker can obtain FDA approval of an abbreviated new drug application ("ANDA") upon a demonstration that the generic drug is equivalent to a previously-approved drug. In accordance with the law, GlaxoSmithKline obtained FDA approval for a new drug application ("NDA") for Lanoxin® brand digoxin tablets in 1997. Then, in 1999, Amide obtained FDA approval of its ANDA for digoxin tablets that are therapeutically equivalent to Lanoxin®. Bertek markets and distributes the Amide tablets under the trade name, Digitek®.

Because of digoxin's pre-1938 marketing, digoxin tablets were marketed via regulatory avenues that did not encompass FDA's specific consideration of the safety and effectiveness of each manufacturer's version of digoxin tablets, nor their equivalence to each other. Nor were digoxin tablets determined to be "generally recognized" by scientific experts as safe and effective for their intended use, as FDA declared in the 1974 Digoxin Regulation and reaffirmed in the present Digoxin Proposed Rule.

(Footnote cont'd from previous page.)

in 1996. See 1996 Drug Topics® Red Book®, p. 224. The 2000 Drug Topics® Red Book® provides current digoxin tablet price lists from Alra, American Health, Amide, Bertek, Duramed, Glaxo Wellcome, Jerome Stevens, Major, Medirex, PD-Rx Pharmaceuticals, Pharma Pac, Physicians Total Care, Quality Care, Sky Pharma, Southwood, and Vangard. See 2000 Drug Topics® Red Book®, pp. 287-288.

Instead, FDA implemented a batch certification program for digoxin tablets, involving a review of bioavailability and dissolution testing, and the use of uniform labeling. Unlike the post-1984 new drug approval process that Glaxo and Amide undertook,[3] the batch certification process did not involve FDA's pre-marketing review of the manufacturer's product formulation, standards for purity and quality, active pharmaceutical ingredient specifications and supplier(s), manufacturing facility, manufacturing processes, packaging processes, or stability. As a result, an FDA determination of whether these issues did or could affect the safety or effectiveness of the product was not undertaken. Moreover, after Jerome Stevens submitted its initial batch of digoxin tablets to FDA, the agency rescinded the batch certification program for Jerome Stevens in 1995.[4]

Without a new drug application in place, and with the batch certification tests on hold, FDA's post-marketing supervision of Jerome Stevens' digoxin tablets is severely limited. Under the batch certification process, a manufacturer is not required by law to report all adverse drug experiences ("ADEs") to FDA. As a result, ADEs related to subpotency, superpotency or inconsistent blood levels may exist but not be reported or captured in FDA's database.

Similarly, product reformulations are not reported for FDA's consideration, even though reformulations may affect potency and, thus, bioavailability.[5] In fact, Jerome Stevens' formulation was changed as recently as 1999, when Jerome Stevens changed the color of its 0.125 mg digoxin tablets from white to yellow, apparently as part of an effort to portray the product as interchangeable with the yellow GlaxoSmithKline 0.125 mg tablet. See Attachment 1 (Duramed/Jerome Stevens digoxin package insert, "How Supplied" section, dated 5/99 and 12/99). In other

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3 See 21 U.S.C. § 355(b), (j); 21 C.F.R. §§ 314.50, 314.94.

4 See FDA Quarterly Activities Report, Fourth Quarter, Fiscal Year 1995, at the section on "Human Drugs", http://www.fda.gov/ope/quartly.htm#Human%20Drugs.

5 See, e.g., 62 Fed. Reg. 43535, 43536 (1997) (when describing safety problems with levothyroxine sodium products, FDA explained, "one manufacturer reformulated its levothyroxine sodium product by removing two inactive ingredients and changing the physical form of coloring agents (Ref. 6). The reformulated product increased significantly in potency. . . . This increase in product potency resulted in serious clinical problems.")

cases, FDA has determined that such a color change which involves an addition or deletion of inactive ingredients, may detrimentally affect the product's potency.[6]

Without the pre- and post-marketing review by FDA that is required under the new drug approval process, 21 U.S.C. § 355 and implementing regulations, FDA's regulatory oversight of a marketed drug is minimal. This is true for the digoxin tablets that are marketed under the 1974 Digoxin Regulation. Public health protection necessitates an end to the minimal oversight for these drugs. Moreover, FDA clearly has discretion to end the batch certification program when intervening law provides a more exacting, scientifically-based avenue for marketing drugs.

B. FDA Has Documented Its Safety Concerns With Digoxin Tablets

As the agency detailed in the preamble to the Digoxin Proposed Rule, there have been documented safety concerns with the use of digoxin tablets, both before and after the batch certification process was implemented. In the 1970s, FDA documented bioavailability, potency and dissolution problems, which led to product recalls. 39 Fed. Reg. 2471 (1974). In the 1980s and 1990s, many digoxin makers entered and exited the market (see Footnote 2, herein), in part because of the difficulty in maintaining consistency between product batches. Despite the batch certification program and other safety nets created by the 1974 Digoxin Regulation, FDA continued to document safety issues as late as 1991.[7] As a result of these safety concerns, FDA asked GlaxoSmithKline to submit an NDA demonstrating that its Lanoxin® brand of digoxin tablets met the safety and efficacy standards for post-1984 drug approvals. See 21 U.S.C. § 355(b); 21 C.F.R. § 314.50.

Furthermore, digoxin is a toxic prescription drug used for the treatment of serious heart conditions. This potential for life-threatening digoxin intoxications has caused manufacturers to develop an antidote, Digibind®. There can be no doubt that the use of an unapproved digoxin product carries dangerous health implications. In fact, FDA has recommended additional patient protections for narrow therapeutic

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6 See id. See also, 21 C.F.R. § 314.70(d)(4); 64 Fed. Reg. 34608, 34624 (1999) (Proposed Rule on Supplements and Other Changes).

7 See Digoxin NDA and ANDA Submissions to Resolve Dissolution Problems, F-D-C Reports, Inc., "The Pink Sheet," July 15, 1991, at T&G-5.

range drugs because of the associated public health risks. Specifically, FDA has suggested that "sponsors consider additional testing and/or controls to ensure the quality" of these drugs and "provide increased assurance of interchangeability."[8] While the agency has expressed its confidence that FDA-approved therapeutically equivalent drugs like Lanoxin® and Digitek® can be safely interchanged, FDA has identified concerns about unapproved narrow therapeutic range drugs that have not been proven to be therapeutically equivalent.[9]

These numerous safety concerns establish that FDA's intended actions in the Digoxin Proposed Rule are valid and necessary.

C. The Concurrent Marketing Of Bioequivalent And Potentially Bio*in*equivalent Digoxin Tablets Puts The Public Health At Risk

So long as the digoxin regulation remains in place, digoxin tablets will continue to be marketed under two regulatory systems – the post-1984 new drug approval process and the 1974 Digoxin Regulation's batch certification program. The new drug approval process requires scientific testing for bioequivalence, to prove that an alternative version of digoxin tablets can be safely substituted for the innovator drug, Lanoxin® tablets. But the batch certification process fails to require bioequivalence – the scientific testing that forms the basis for FDA's therapeutic equivalence determination and, hence, safe product substitution. This dual system is unacceptable today – given that two FDA-approved digoxin tablets are on the market, and skyrocketing prescription drug costs continue to trigger patient requests for the generic substitution of their prescriptions.

To summarize, when FDA approved Amide's digoxin tablets, the agency declared that the tablets were therapeutically equivalent, or "AB-rated", to GlaxoSmithKline's tablet. See FDA's Approved Drug Products With Therapeutic Equivalence Evaluations, 20th ed. (2000), at 3-121 (the "Orange Book"). With that

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[8] See FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (Oct. 2000), at 21.

[9] See FDA "Dear Colleague" letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, Center for Drug Evaluation and Research, dated January 28, 1998.

designation, Amide's tablets may be prescribed by physicians and dispensed by pharmacists in place of Lanoxin® tablets, when state law authorizes such "substitution." See id., at Preface, sections 1.2 and 1.7. By contrast, Jerome Stevens' digoxin tablets are not eligible for lawful substitution because they have not been approved by FDA as therapeutically equivalent to Lanoxin®. Consequently, while GlaxoSmithKline's and Amide's digoxin tablets may be safely substituted for each other, FDA and the public do not have scientific data supporting the substitutability of Jerome Stevens' tablets.

The only entity that can provide that data is the manufacturer, Jerome Stevens. Although Jerome Stevens has known since the 1997 Lanoxin® approval that bioequivalence testing would be an important scientific benchmark for all digoxin tablets, the company has failed to publicize any bioequivalence testing that would address the question whether its tablets are bioequivalent to Lanoxin® or, instead, present fluctuating digoxin levels. It is telling that, in the ReedSmith Comments, Jerome Stevens' counsel did not provide bioequivalence data or even allude to bioequivalence testing that the company had conducted or was presently undertaking. Instead, the ReedSmith Comments focused exclusively on "regulatory policy," administrative procedures, and the timeframe involved in complying with the Digoxin Proposed Rule, once it is finalized.

Since bioequivalence data is lacking, any inadvertent substitution of the Jerome Stevens tablets could place a patient at risk. The standardization of digoxin tablet products, as FDA is attempting via the Digoxin Proposed Rule, is imperative for physician/pharmacist confidence and patient safety. Moreover, the risk from inadvertent substitution is heightened for pharmacists and patients since the unapproved tablets cannot be distinguished readily from FDA-approved tablets by their appearance. Data from FDA's Adverse Event Reporting System ("AERS") illustrates this risk. Although Bertek has not completed a systematic review of the AERS database, we note that, from October – December 1999, three adverse drug experiences were reported to FDA due to the "maladministration" of Jerome Stevens' 0.125 mg digoxin tablets.[10]

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[10] The identifying Control numbers and Individual Safety Report numbers for these adverse experiences, as delineated in the AERS database, are as follows: 3394747 / 1001434281; 3395757 / 1001436086; 3408995 / 1001468960.

Because digoxin tablets present a narrow therapeutic range, as described above, the inappropriate substitution of different versions of the tablets raises particular health concerns. The dual regulatory system in place for digoxin tablets heightens that concern, due to the confusion it engenders for those in the health care professions. In particular, physicians, pharmacists, patients and insurance carriers have indicated to Bertek employees that they were unaware that Amide's digoxin tablets are an FDA-approved product that can be legally substituted for Lanoxin®. Bertek customers also failed to understand that Jerome Stevens' digoxin tablets are not AB-rated to Lanoxin® and, thus, cannot be legally substituted. Some suggested to Bertek that all marketed versions of digoxin tablets must be "equally safe," since FDA allows them to remain on the market. Others expressed uncertainty as to appropriate substitution, since the Amide and the Jerome Stevens tablets are both referred to colloquially as "generic" versions of digoxin.[11]

Given all of the above information, it is clear that FDA has a reasoned basis for proposing to revoke the 1974 Digoxin Regulation and calling for the submission of NDAs and ANDAs for the continued marketing of digoxin tablets.

D. The Existence Of Dual Regulatory Systems Has Resulted In Labeling Inconsistencies For Digoxin Tablets

As FDA explained in the preambles to the Digoxin Proposed Rule, the agency approved GlaxoSmithKline's digoxin tablets on the basis of particular indications for use that were supported by clinical studies – namely, heart failure and atrial fibrillation. What the preambles did not explain is that the digoxin tablets being marketed under the batch certification program had been claiming up to five indications for use: congestive heart failure, atrial fibrillation, atrial flutter,

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[11] Data from Bertek's customer service staff documents the market confusion about the suitability of substituting digoxin tablets. Based on a review of approximately 50 unsolicited inquiries to Bertek, compiled on the company's Medical Information Question reports from March through September 2000, Bertek documented 39 inquiries of confusion about Lanoxin® and Digitek®. In particular, Bertek noted the following: (a) 2 pharmacists, 1 physician, 7 patients, and 1 pharmacy benefit manager called to inquire about the "difference" between Digitek® and Lanoxin®; and (b) 11 pharmacists, 4 physicians, 8 patients, 3 pharmacy benefit managers, 1 wholesale distributor and 1 state board of pharmacy called to inquire whether Digitek® is AB-rated to Lanoxin®.

paroxysmal atrial tachycardia, and cardiogenic shock. 21 C.F.R. § 310.500(e). By permitting digoxin tablets to be marketed under dual regulatory systems, therefore, FDA sanctioned the use of two sets of disparate labeling for the same drug. Such a situation is clearly misleading to physicians, pharmacists and patients, and could have a detrimental affect on the public health. Moreover, by approving only two indications for GlaxoSmithKline's digoxin tablets, FDA implicitly determined that the remaining claims were not supported by substantial evidence of safety and effectiveness.[12] Consequently, we question by what legal authority FDA could permit digoxin tablets with such unproven labeling claims, and thus misbranded labeling,[13] to remain on the market.

II. Given The Public Health Risks, FDA Should Expedite The Revocation Of The 1974 Digoxin Regulation, Not Delay It

As detailed above, there are numerous public health risks inherent in the present situation, where digoxin tablets are marketed under two different regulatory schemes, with two disparate sets of labeling, and where indiscriminate substitution of the tablets cannot be prevented. The potential risks make Jerome Stevens' position all the more difficult to understand. In the ReedSmith Comments, Jerome Stevens argues that FDA should permit the continued marketing of unapproved

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[12] The FFDCA's drug approval provisions require substantial data support for each labeling claim that a drug is safe and effective for a particular indication. 21 U.S.C. § 355(d); 21 C.F.R. § 314.50(d). FDA approves the specific wording of labeling claims, as justified by the scientific data. If insufficient data are presented to justify a particular claim, FDA requires the deletion of the claim from the labeling as a condition of approval. Id. See also, FDA Summary Basis of Approval for NDA 20405, October 26, 1994, Memo from Raymond J. Lipicky, M.D.; Glaxo Lanoxin Label Rewrite Should Await Further CHF Mortality Data, F-D-C Reports, Inc. "The Pink Sheet", May 13, 1996, at 17; Glaxo Wellcome Lanoxin (Digoxin) NDA Approved for Heart Failure, October 6, 1997, at T&G-2.

[13] According to the FFDCA, a drug is misbranded if its labeling makes claims without adequate scientific support. 21 U.S.C. § 352; see e.g., U.S. v. Lanpar Co., 293 F. Supp. 147 (N.D. Tex. 1968) (drug misbranded because of unapproved labeling claims for treatment of obesity); U.S. v. Torigian Laboratories, Inc., 577 F. Supp. 1514 (E.D.N.Y. 194), aff'd without op., 751 F.2d 373 (2d Cir. 1984) (labeling false or misleading because of unsupported sterility claims); U.S. v. General Nutrition, Inc., 638 F. Supp. 556 (W.D.N.Y. 1986) (unapproved drug claims constitute inadequate directions for use in labeling).

digoxin tablets for another two years. We disagree, and applaud FDA's expeditious action to revoke the 1974 Digoxin Regulation within 30 days after issuing the final rule on this matter.

A. FDA's Deadline Delay For Levothyroxine NDAs Is Not A Valid Reason To Delay The Revocation Of The 1974 Digoxin Regulation

Jerome Stevens' claim that FDA has "clear precedent" for delaying the effective date of the finalized Digoxin Proposed Rule, based on the levothyroxine situation, is disingenuous at best. Although the regulatory state of levothyroxine sodium is similar to the digoxin situation in that both are narrow therapeutic range drugs that have been marketed for many years without direct FDA review and approval, the levothyroxine situation can be distinguished from the digoxin situation in three important respects. First, as to levothyroxine, FDA had not made a determination that the products were new drugs before calling for new drug applications in 1997.[14] Nor did the agency declare levothyroxine to be a new drug in the 1997 notice. In fact, in addition to calling for NDAs, FDA specifically permitted the submission of citizen petitions establishing that the product is not subject to the new drug requirements of the FFDCA but, instead, is generally recognized as safe and effective ("GRAS/E") for its intended use. Unlike an NDA, a GRAS/E petition is not covered by user fees – money that assists the agency in reviewing an NDA in a median time of 12 months.[15] Thus, the agency needed to provide an elongated review period so that manufacturers could evaluate and exercise either the NDA or citizen petition option, and the agency could act on a GRAS/E petition outside of the user-fee timeframes. The case of digoxin is much different, since FDA has publicly declared since 1974 that the tablets are new drugs and, thus, the NDA option clearly is the only appropriate review process. Accordingly, an elongated review period is unnecessary for digoxin.

Second, there were no FDA-approved levothyroxine products on the market when FDA called for NDAs for that drug. As a result, FDA provided a three-year effective date, in part, to ensure that there was minimal disruption of the supply of

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14 See 62 Fed. Reg. 43535 (1997).

15 See FDA's FY 1999 Performance Report to Congress for the Prescription Drug User Fee Act of 1992.

this "medically necessary" drug to patients.[16] By contrast, in the digoxin case, there are two FDA-approved digoxin tablets presently on the market, and disruption of supply is not an issue. Third, other unique factors in the administrative processing of the levothyroxine situation resulted in a further delay of FDA's deadline – FDA could not complete a review of one manufacturer's GRAS/E petition before the three-year deadline was to expire (at which time only NDAs would be accepted), and that manufacturer sued FDA over a Freedom of Information Act request for agency documents pertaining to levothyroxine.[17] With all of these distinguishing factors, FDA's three-year timeframe in the levothyroxine case is not an appropriate comparator for protesting the timeframe set forth in FDA's Digoxin Proposed Rule.

B. The Drug Industry Has Been On Notice For Many Years That FDA Wished To Revoke The 1974 Digoxin Regulation And Issue New Drug Approvals For Digoxin Tablet Applications

Jerome Stevens' complaint that FDA's timeframe for revoking the 1974 Digoxin Regulation does not provide Jerome Stevens with enough time to "conduct equivalency testing and prepare premarket applications" for its digoxin tablets is an artificial complaint. The company's implications of unfairness are unfounded. Despite its criticism of the speed with which the Digoxin Proposed Rule was issued by the agency, the reality is that FDA has been working on a regulatory action to withdraw the 1974 Digoxin Regulation for many years, and industry has known it.[18] In fact, Bertek's regulatory counsel, McKenna & Cuneo, L.L.P., has confirmed that the firm has been advising generic drug manufacturers since at least 1993 (upon a review of client files) that FDA was working on a proposed rule to modify or withdraw the 1974 Digoxin Regulation and, thus, reliance on the batch certification program for digoxin tablets would engender a certain amount of regulatory risk.

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16 See 62 Fed. Reg. 43535 (1997).

17 See Jerome Stevens Unithroid Marketing Will Emphasize NDA Approval, F-D-C Reports, Inc., "The Pink Sheet," Aug. 28, 2000, at 4.

18 See Digoxin NDA and ANDA Submissions to Resolve Dissolution Problems, F-D-C Reports, Inc., "The Pink Sheet," July 15, 1991, at T&G-5; Pre-1938 Drugs Will Be Defined as "New Drugs" Requiring Applications, Bioequivalence Studies, CDER Says in Report to Former Edwards Committee, "The Pink Sheet," July 6, 1992, at 7.

Even consumer groups have urged FDA to withdraw pre-1938 unapproved drugs from the market.[19]

Moreover, it was no secret in the mid-1990s that GlaxoSmithKline had submitted an NDA for Lanoxin® tablets to the agency.[20] And in 1997, when FDA approved the NDA for Lanoxin®, Jerome Stevens and the digoxin industry were on notice that the agency may initiate regulatory action to withdraw other digoxin tablets from the market that were not marketed pursuant to approved drug applications. This notice was provided by FDA's Compliance Policy Guide 7132c.02 and by application of the policy to other similarly situated products. To summarize briefly, the CPG explains in relevant part that FDA will initiate enforcement action against "any drug on the market without an approved new drug application" if it is "identical or related to" a drug with an NDA approved after 1962.[21]

Jerome Stevens' statement that it was "not provided the opportunity for any input" into the situation when Bertek sued FDA over the 1974 Digoxin Regulation is also false. The lawsuit against FDA was publicized in numerous news publications.[22] Moreover, court filings are public documents. And Jerome Stevens' own digoxin distributor, Duramed, had knowledge of the suit. In fact, Duramed's legal counsel called Bertek's legal counsel soon after the suit was filed to discuss the fact that

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19 In a May 29, 1996 letter to then-FDA Commissioner David Kessler, the consumer watchdog group, Public Citizen, implored FDA as follows – "We are writing to urge you to expeditiously begin a safety and efficacy review of all pharmaceuticals marketed in the United States prior to 1938, beginning with the most heavily prescribed drugs." The Public Citizen letter then went on to highlight problems with the marketing of the pre-1938 drug, levothyroxine tablets, which were not reviewed by FDA for safety and efficacy under the new drug approval process of 21 U.S.C. § 355.

20 See Glaxo Lanoxin Label Rewrite Should Await Further CHF Mortality Data, F-D-C Reports, Inc., "The Pink Sheet," May 13, 1996, at 17.

21 FDA CPG 7132c.02 (1984, Supp. 1987) at 5; see also, 21 C.F.R. § 314.200(e)(3) (FDA will not find any new drug to be exempt from approval requirements if it is identical, similar or related to an approved drug product).

22 See Firms Sue FDA for Allowing "Unapproved" Digoxin to Remain on Market, Inside Washington's FDA Week, Oct. 6, 2000, at 10; Bertek and Amide Sue FDA to Remove Unapproved Digoxins, F-D-C Reports, Inc., "The Pink Sheet," Oct. 16, 2000, at 7.

Duramed might intervene in the lawsuit. Likewise, Jerome Stevens could have intervened in the lawsuit, if it so chose.

With a reasonable amount of attention to agency policy and knowledge of the digoxin industry, therefore, Jerome Stevens would have had plenty of notice that FDA would seek a revocation of the 1974 Digoxin Regulation. A prudent manufacturer would have been conducting bioequivalence testing and subsequent research and development activities to obtain therapeutic equivalence to Lanoxin® tablets. By asserting its need for more time to conduct these activities – three years after Lanoxin's® FDA approval – Jerome Stevens admits either that it was not paying attention to the regulatory landscape or is having difficulty meeting the requisite bioequivalence specifications. Neither of these excuses is a valid reason for FDA to delay the effective date of the Digoxin Proposed Rule.

C. Jerome Stevens' Call For FDA To Delay Is Hypocritical, When The Company Has Opposed A Delay For Levothyroxine Products

Finally, Jerome Stevens' fixation on the need for FDA to delay any action in revoking the 1974 Digoxin Regulation is directly contradicted by the firm's own declarations made just one month prior to the December 22, 2000 ReedSmith Comments. See ReedSmith comments to FDA re Compliance Date for Approved New Drug Applications for Orally Administered Levothyroxine Sodium Drug Products, dated November 17, 2000, submitted to Docket No. 97N-0314 ("ReedSmith November 17 Comments"). Specifically, Jerome Stevens and its legal counsel, ReedSmith, have taken the completely opposite position in the case of a similarly situated drug, levothyroxine. The difference which necessitates Jerome Stevens' opposite argument is that the company is the only NDA holder for levothyroxine tablets, but is the only non-NDA holder for digoxin tablets.

As a result, we can state our position that FDA should expedite the revocation of the 1974 Digoxin Regulation by quoting ReedSmith's own statements. We have merely replaced the drug, digoxin tablets, for ReedSmith's use of the drug, levothyroxine sodium, and have referred to "NDA/ANDA holders" where ReedSmith referred to Jerome Stevens. Just as we have asserted in Section A above, Jerome Stevens argues in the ReedSmith November 17 Comments that a delay for noncompliant companies to submit NDAs to FDA is not warranted because of the risk to public health, the fact that compliant products are already on the market, and the confusion created by a market that contains both approved and unapproved drug products.

"In light of the concern properly identified by FDA with regard to the potency and stability of [digoxin products], further delay of the deadline would allow potentially unsafe and ineffective products to remain on the market. This situation would create a potential, and unnecessary, risk to public health. With the recent approval of a NDA for [digoxin], there now exists a properly registered and inspected product available to patients in the United States. No medical justification exists to permit unproven products to remain on the market. It would also be unfair to [NDA/ANDA holders], prescribing physicians and consumers to change the rules to which at least one company was required to faithfully comply."[23]

"In light of the availability of [digoxin tablets] with an approved NDA and approved GMP-compliant manufacturing facilities, the basis for extending the deadline again for manufacturers to file and obtain NDA approval no longer applies. There is now available to consumers a [digoxin] product proven safe and effective, with consistent potency and bioavailability – [the NDA/ANDA products]."[24]

"A drug product with NDA approval must now compete with products that have not undergone the same required regulatory review. *FDA should not expand this inequity and risk to public health by extending a delay in NDA approval now that a compliant product is on the market.*"[25]

"In the interest of the public health, [the NDA/ANDA holders] ha[ve] undertaken the effort and expense of complying with FDA's notice by the initial deadline. A number of other manufacturers have not yet done so, but may continue to market their products, despite the potential health risks that FDA has identified. To extend the deadline once again when an NDA-approved product is now available . . . would only perpetuate the risks to

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23 ReedSmith November 17 Comments, at 1-2.

24 ReedSmith November 17 Comments, at 3.

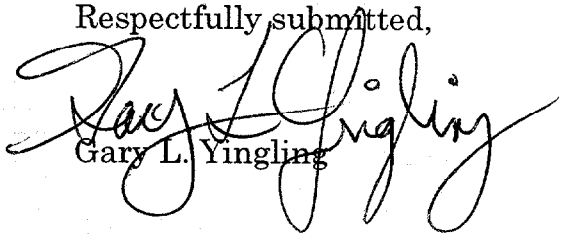
25 ReedSmith November 17 Comments, at 3 (emphasis added).

public health that FDA has identified and be grossly unfair to compliant manufacturers like [the NDA/ANDA holders]."[26]

Clearly, we cannot argue with ReedSmith and Jerome Stevens on these points.

In conclusion, we support FDA's decisions to revoke the 1974 Digoxin Regulation, reaffirm its determination that digoxin products for oral use are new drugs, and declare that manufacturers who wish to market such digoxin products must submit NDA or ANDAs and obtain agency approval of those products.

Respectfully submitted,



Gary L. Yingling

Enclosure(s)
cc: Janet Woodcock, M.D., CDER, FDA
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Linda A. Suydam, Office of the Commissioner
Raymond J. Lipicky, M.D., ODE I, FDA
Gary J. Buehler, OGD, FDA
John M. Taylor, Office of Compliance, FDA
Thomas W. Abrams, DDMAC, FDA

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26 ReedSmith November 17 Comments, at 3.

I00281D0599

DIGOXIN TABLETS

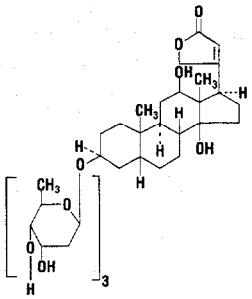
125 µg (0.125 mg)
Scored I.D. Imprint ℔ 914 (white)
250 µg (0.25 mg)
Scored I.D. Imprint ℔ 915 (white)

DESCRIPTION

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin has the molecular formula $C_{41}H_{64}O_{14}$, a molecular weight of 780.95 and melting and decomposition points above 235°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine. Digoxin powder is composed of odorless white crystals.

Digoxin has the chemical name: 3β-[(*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β, 14-dihydroxy-5β-card-20(22)-enolide, and the structure shown:



Digoxin Tablets with 125 µg (0.125 mg) or 250 µg (0.25 mg) digoxin USP are intended for oral use. Each tablet contains the labeled amount of digoxin USP.

Inactive Ingredients:

0.125 mg tablets–corn starch, pregelatinized starch, stearic acid, lactose and magnesium stearate.

0.25 mg tablets–corn starch, pregelatinized starch, stearic acid, lactose and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: The influence of digitalis glycosides on the myocardium is dose related and involves both a direct action on cardiac muscle and the specialized conduction system, and indirect actions on the cardiovascular system mediated by the autonomic nervous system. The indirect actions mediated by the autonomic nervous system involve a vagomimetic action, which is responsible for the effects of digitalis on the sino-atrial (SA) and atrioventricular (AV) nodes; and also a baroreceptor sensitization which results in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: 1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); 2) a slowing of heart rate (negative chronotropic effect); and 3) decreased conduction velocity through the AV node. In higher doses, digitalis increases sympathetic outflow from the central nervous system (CNS) to both cardiac and peripheral sympathetic nerves. This increase in sympathetic activity may be an important factor in digitalis cardiac toxicity. Most of the extracardiac manifestations of digitalis toxicity are also mediated by the CNS.

Pharmacokinetics:

Absorption—Gastrointestinal absorption of digoxin is a passive process. Absorption of digoxin from the Digoxin tablet formulation has been demonstrated to be 60 to 80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability). When digoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparison of the systemic availability and equivalent doses for digoxin preparations are shown in the following table:

PRODUCT	ABSOLUTE BIOAVAILABILITY	EQUIVALENT DOSES (IN MG*)		
Digoxin Tablet	60-80%	0.125	0.25	0.5
Lanoxin Elixir	70-85%	0.125	0.25	0.5
Lanoxin Injection/I.M.	70-85%	0.125	0.25	0.5
Lanoxin Injection/I.V.	100%	0.1	0.2	0.4
Lanoxicaps® Capsules	90-100%	0.1	0.2	0.4

*1 mg = 1000 µg

In some patients, orally administered digoxin is converted to cardioinactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that one in ten patients treated with digoxin tablets will degrade 40% or more of the ingested dose.

Distribution—Following drug administration, a 6 to 8 hour distribution phase is observed. This is followed by a much more gradual serum concentration decline, which is dependent on digoxin elimination from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum levels are in equilibrium with tissue levels and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations are linearly related to maintenance dosage and may be useful in evaluating therapeutic and toxic effects (see Serum Digoxin Concentrations in DOSAGE AND ADMINISTRATION section).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placental barrier. Digoxin is found in breast milk in concentrations similar to the serum level in the mother. Approximately 20 to 25% of plasma digoxin is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (ideal) body weight, not total body weight.

Pharmacologic Response—The approximate times to onset of effect and to peak effect of all the Digoxin preparations are given in the following table:

PRODUCT	TIME TO ONSET OF EFFECT*	TIME TO PEAK EFFECT*
Digoxin Tablets	0.5-2 hours	2-6 hours
Lanoxin Elixir	0.5-2 hours	2-6 hours
Lanoxin Injection/I.M.	0.5-2 hours	2-6 hours
Lanoxin Injection/I.V.	5-30 minutes †	1-4 hours
Lanoxicaps Capsules	0.5-2 hours	2-6 hours

*Documented for ventricular response rate in atrial fibrillation, inotropic effect, and electrocardiographic changes.

†Depending upon rate of infusion.

Excretion—Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to normal subjects, 50 to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 4 to 6 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary by-pass because most of the drug is in tissue rather than circulating in the blood.

INDICATIONS AND USAGE

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea, and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection, or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate), cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

Atrial Fibrillation: Digoxin reduces ventricular rate and thereby improves hemodynamics. Palpitation, precordial distress, or weakness are relieved and concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate.

Atrial Flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a controlled ventricular response. Digoxin treatment should be maintained if atrial fibrillation persists. (Electrical cardioversion is often the treatment of choice for atrial flutter. See discussion of cardioversion in PRECAUTIONS section.)

Paroxysmal Atrial Tachycardia (PAT): Digoxin may convert PAT to sinus rhythm by slowing conduction through the AV node. If heart failure has ensued or paroxysms recur frequently, digoxin should be continued. In infants, digoxin is usually continued for 3 to 6 months after a single episode of PAT to prevent recurrence.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin.

Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS

Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous. Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible. Patients with severe carditis such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, and alprazolam may cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Tetracycline and erythromycin (and possibly other macrolide antibiotics) may metabolites in the gut (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g., hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, and alprazolam* may cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Serum levels of digoxin may be increased by concomitant administration of tetracycline and erythromycin (and possibly other macrolide antibiotics). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine*, certain *anticancer drugs*, and *metoclopramide* may reduce intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since this may impair the excretion of digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS

The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section and Serum Digoxin Concentrations subsection of DOSAGE AND ADMINISTRATION). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (1 to 4% of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g., PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting, and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, and psychosis can occur.

Other—Gynecomastia is occasionally observed. Maculopapular rash or other skin reactions are rarely observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially

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alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

OVERDOSAGE

Treatment of Arrhythmias Produced by Overdosage:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Correction of factors that may contribute to toxicity such as electrolyte disturbances, hypoxia, acid-base disturbances, and removal of aggravating agents such as catecholamines, should also be considered. Potassium salts may be indicated, particularly if hypokalemia is present. Potassium administration may be dangerous in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection below). Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 mL) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, atropine and/or temporary ventricular pacing may be beneficial. Digibind, Digoxin Immune Fab (Ovine), can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within 1/2 hour of Digibind administration. Each 38 mg vial of DIGIBIND will neutralize 0.5 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium. If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second- or third-degree heart block not responsive to atropine. An overdosage of more than 10 mg of digoxin in previously healthy adults or 4 mg in previously healthy children or overdosage resulting in steady-state serum concentrations greater than 10 ng/mL, often results in cardiac arrest.

Severe digitalis intoxication can cause life-threatening elevation in serum potassium concentration by shifting potassium from inside to outside the cell resulting in hyperkalemia. Administration of potassium supplements in the setting of massive intoxication may be hazardous.

Digibind, Digoxin Immune Fab (Ovine), may be used at a dose equimolar to digoxin in the body to reverse the effects of ingestion of a massive overdose. The decision to administer Digibind before the onset of toxic manifestations will depend on the likelihood that life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-toxic arrhythmias.

DOSAGE AND ADMINISTRATION

Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs, or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. Rapid digitalization may be achieved by administering a loading dose based upon projected peak body digoxin stores, then calculating the maintenance dose as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Adults:

Adults—Rapid Digitalization with a Loading Dose. Peak body digoxin stores of 8 to 12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 µg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 µg/kg) [see PRECAUTIONS section].

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6 to 8 hour intervals, **with careful assessment of clinical response before each additional dose.**

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

In previously undigitalized patients, a single initial Digoxin Tablet dose of 500 to 750 µg (0.5 to 0.75 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 125 to 375 µg (0.125 to 0.375 mg) may be given cautiously at 6 to 8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Digoxin Tablets that a 70 kg patient requires to achieve 8 to 15 µg/kg peak body stores is 750 to 1250 µg (0.75 to 1.25 mg).

Although peak body stores are mathematically related to loading doses and are utilized to calculate maintenance doses, they do not correlate with measured serum concentrations. This discrepancy is caused by digoxin distribution within the body during the first 6 to 8 hours following a dose. Serum concentrations drawn during this time are usually not interpretable.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

$$\text{Maintenance Dose} = \text{Peak Body Stores (i.e., Loading Dose)} \times \frac{\%\ \text{Daily Loss}}{100}$$

Where: % Daily Loss = 14 + Ccr/5

surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 - Age)/Scr. For women, this result should be multiplied by 0.85.

Note: This equation cannot be used for estimating creatinine clearance in infants or children.

A common practice involves the use of Lanoxin Injection to achieve rapid digitalization, with conversion to Digoxin Tablets or Lanoxicaps for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see table, CLINICAL PHARMACOLOGY section).

Adults—Gradual Digitalization with a Maintenance Dose: The following table provides average Digoxin Tablet daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function:

Usual Digoxin Daily Maintenance Dose Requirements (µg)
For Estimated Peak Body Stores of 10 µg/kg

		Lean Body Weight (kg/lbs)						
		50/110	60/132	70/154	80/176	90/198	100/220	
	0	63*†	125	125	125	188††	188	22
	10	125	125	125	188	188	188	19
	20	125	125	188	188	188	250	16
Corrected	30	125	188	188	188	250	250	14 Number of
Ccr	40	125	188	188	250	250	250	13 Days
(mL/min	50	188	188	250	250	250	250	12 Before
per 70 kg)	60	188	188	250	250	250	375	11 Steady-State
	70	188	250	250	250	250	375	10 Achieved
	80	188	250	250	250	375	375	9
	90	188	250	250	250	375	500	8
	100	250	250	250	375	375	500	7

*63 µg = 0.063 mg
† 1/2 of 125 µg tablet or 125 µg every other day
‡ 1 1/2 of 125 µg tablet.

Example—based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 mL/min, should be given a 250 µg (0.25 mg) Digoxin Tablet each day, usually taken after the morning meal. Steady-state serum concentrations should not be anticipated before 11 days.

Infants and Children: Digitalization must be individualized. Divided daily dosing is recommended for infants and young children. Children over 10 years of age require adult dosages in proportion to their body weight.

Usual Digitalizing and Maintenance Dosages for Digoxin Tablets in Children **with Normal Renal Function Based on Lean Body Weight**

Age	Digitalizing* Dose (µg/kg)	Daily† Maintenance Dose (µg/kg)
2 to 5 Years	30 to 40	25 to 35% of *oral* loading dose‡
5 to 10 Years	20 to 35	
Over 10 years	10 to 15	

* I.V. digitalizing doses are 80% of oral digitalizing doses.
† Divided daily dosing is recommended for children under 10 years of age.
‡ Projected or actual digitalizing dose providing clinical response.

In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area.

Lanoxin Injection Pediatric can be used to achieve rapid digitalization, with conversion to an oral digoxin formulation for maintenance therapy. If patients are switched from intravenous to oral digoxin tablets or elixir, allowances must be made for differences in bioavailability when calculating maintenance dosages (see bioavailability table in CLINICAL PHARMACOLOGY section and dosing table above).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Digitalizing and daily maintenance doses for each age group are given above and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger doses are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation.

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6 to 8 hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

[See third table above.]

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

Serum Digoxin Concentrations: Measurement of serum digoxin concentrations can be helpful to the clinician in determining the state of digitalization and in assigning certain probabilities to the likelihood of digoxin intoxication. Studies in adults considered adequately digitalized (without evidence of toxicity) show that about two-thirds of such patients have serum digoxin levels ranging from 0.8 to 2.0 ng/mL. Patients with atrial fibrillation or atrial flutter require and appear to tolerate higher levels than do patients with other indications. On the other hand, in adult patients with clinical evidence of digoxin toxicity, about two-thirds will have serum digoxin levels greater than 2.0 ng/mL. Thus, whereas levels less than 0.8 ng/mL are infrequently associated with toxicity, levels greater than 2.0 ng/mL are often associated with toxicity. Values in between are not very helpful in deciding whether a certain sign or symptom is more likely caused by digoxin toxicity or by something else. There are rare patients who are unable to tolerate digoxin even at serum concentrations below 0.8 ng/mL. Some researchers suggest that infants and young children tolerate slightly higher serum concentrations than do adults.

To allow adequate time for equilibration of digoxin between serum and tissue, **sampling of serum concentrations for clinical use should be at least 6 to 8 hours after the last dose,** regardless of the route of administration or formulation used. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations if the sampling is done at 8 or 12 hours after a dose. After a single daily dose, the concentration will be 10 to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. Ideally, sampling for assessment of steady-state concentrations should be done just before the next dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other than digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS sections) causing an alteration in the sensitivity of the patient to digoxin.
5. The patient falls outside the norm in his response to or handling of digoxin. This decision should only be reached after exclusion of the other possibilities and generally should be confirmed by additional correlations of clinical observations with serum digoxin concentrations.

The serum concentration data should always be interpreted in the overall clinical context and an isolated serum concentration value should not be used alone as a basis for increasing or decreasing digoxin dosage.

Adjustment of Maintenance Dosage in Previously Digitalized Patients:

Digoxin Tablet maintenance doses in individual patients on steady-state digoxin can be adjusted upward or downward in proportion to the ratio of the desired versus the measured serum concentration. For example, a patient at steady-state on 125 µg (0.125 mg) of Digoxin Tablets per day with a measured serum concentration of 0.7 ng/mL, should have the dose increased to 250 µg (0.25 mg) per day to achieve a steady-state serum concentration of 1.4 ng/mL, **assuming the serum digoxin concentration measurement is correct, renal function remains stable during this time, and the needed adjustment is not the result of a problem with compliance.**

Dosage Adjustment When Changing Preparations: The difference in bioavailability between injectable Lanoxin or Lanoxicaps and Lanoxin Elixir Pediatric or Digoxin Tablets must be considered when changing patients from one dosage form to another.

Lanoxin Injection and Lanoxicaps doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) are approximately equivalent to 125 µg (0.125 mg) and 250 µg (0.25 mg) doses of Digoxin Tablets and Lanoxin Elixir Pediatric (see table of CLINICAL PHARMACOLOGY section). Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Store at 15° to 25° C (59° to 77° F) in a dry place and protect from light.

HOW SUPPLIED

DIGOXIN TABLETS, Scored 125 µg (0.125mg): Bottles of 100 (NDC 51285-914-02), 1000 (NDC 51285-914-05), imprinted ℞ 914 (white).
DIGOXIN TABLETS, Scored 250 µg (0.25mg): Bottles of 100 (NDC 51285-915-02), 1000 (NDC 51285-915-05), imprinted ℞ 915 (white).

℞ only

Mfd for: DURAMED PHARMACEUTICALS, INC.
Cincinnati, OH 45213 USA
By: JEROME STEVENS PHARMACEUTICALS, INC.
Bohemia, NY 11716 USA

I00281D **REV. 05/99**

I00281E1299

DIGOXIN TABLETS

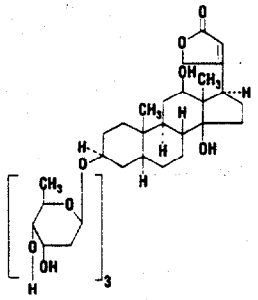
125 µg (0.125 mg)
Scored I D. Imprint ⊕ 914 (yellow)
250 µg (0.25 mg)
Scored I D. Imprint ⊕ 915 (white)

DESCRIPTION

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group. The glycosides are composed of two portions, a sugar and a cardenolide (hence "glycosides").

Digoxin has the molecular formula $C_{41}H_{64}O_{14}$, a molecular weight of 780.95 and melting and decomposition points above 235°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine. Digoxin powder is composed of odorless white crystals.

Digoxin has the chemical name: 3β-[(*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-0-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12β, 14-dihydroxy-5β-card-20(22)-enolide, and the structure shown:



Digoxin Tablets with 125 µg (0.125 mg) or 250 µg (0.25 mg) digoxin USP are intended for oral use. Each tablet contains the labeled amount of digoxin USP.

Inactive ingredients:
0.125 mg tablets–corn starch, pregelatinized starch, stearic acid, lactose, magnesium stearate, and D&C yellow #10.
0.25 mg tablets–corn starch, pregelatinized starch, stearic acid, lactose and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: The influence of digitalis glycosides on the myocardium is dose related and involves both a direct action on cardiac muscle and the specialized conduction system, and indirect actions on the cardiovascular system mediated by the autonomic nervous system. The indirect actions mediated by the autonomic nervous system involve a vagomimetic action, which is responsible for the effects of digitalis on the sino-atrial (SA) and atrioventricular (AV) nodes; and also a baroreceptor sensitization which results in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: 1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); 2) a slowing of heart rate (negative chronotropic effect); and 3) decreased conduction velocity through the AV node. In higher doses, digitalis increases sympathetic outflow from the central nervous system (CNS) to both cardiac and peripheral sympathetic nerves. This increase in sympathetic activity may be an important factor in digitalis cardiac toxicity. Most of the extracardiac manifestations of digitalis toxicity are also mediated by the CNS.

Pharmacokinetics:

Absorption—Gastrointestinal absorption of digoxin is a passive process. Absorption of digoxin from the Digoxin tablet formulation has been demonstrated to be 60 to 80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability). When digoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparison of the systemic availability and equivalent doses for digoxin preparations are shown in the following table:

PRODUCT	ABSOLUTE BIOAVAILABILITY	EQUIVALENT DOSES (IN MG*)		
Digoxin Tablet	60-80%	0.125	0.25	0.5
Lanoxin Elixir	70-85%	0.125	0.25	0.5
Lanoxin Injection/I.M.	70-85%	0.125	0.25	0.5
Lanoxin Injection/I.V.	100%	0.1	0.2	0.4
Lanoxicaps® Capsules	90-100%	0.1	0.2	0.4

*1 mg = 1000 µg

In some patients, orally administered digoxin is converted to cardioinactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that one in ten patients treated with digoxin tablets will degrade 40% or more of the ingested dose.

Distribution—Following drug administration, a 6 to 8 hour distribution phase is observed. This is followed by a much more gradual serum concentration decline, which is dependent on digoxin elimination from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum levels are in equilibrium with tissue levels and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations are linearly related to maintenance dosage and may be useful in evaluating therapeutic and toxic effects (see Serum Digoxin Concentrations in DOSAGE AND ADMINISTRATION section).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier [illegible] altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (ideal) body weight, not total body weight.

Pharmacologic Response—The approximate times to onset of effect and to peak effect of all the Digoxin preparations are given in the following table:

PRODUCT	TIME TO ONSET OF EFFECT*	TIME TO PEAK EFFECT*
Digoxin Tablets	0.5-2 hours	2-6 hours
Lanoxin Elixir	0.5-2 hours	2-6 hours
Lanoxin Injection/I.M.	0.5-2 hours	2-6 hours
Lanoxin Injection/I.V.	5-30 minutes †	1-4 hours
Lanoxicaps Capsules	0.5-2 hours	2-6 hours

*Documented for ventricular response rate in atrial fibrillation, inotropic effect, and electrocardiographic changes.
†Depending upon rate of infusion.

Excretion—Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to normal subjects, 50 to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 4 to 6 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary by-pass because most of the drug is in tissue rather than circulating in the blood.

INDICATIONS AND USAGE

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea, and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection, or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate), cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

Atrial Fibrillation: Digoxin reduces ventricular rate and thereby improves hemodynamics. Palpitation, precordial distress, or weakness are relieved and concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate.

Atrial Flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a controlled ventricular response. Digoxin treatment should be maintained if atrial fibrillation persists. (Electrical cardioversion is often the treatment of choice for atrial flutter. See discussion of cardioversion in PRECAUTIONS section.)

Paroxysmal Atrial Tachycardia (PAT): Digoxin may convert PAT to sinus rhythm by slowing conduction through the AV node. If heart failure has ensued or paroxysms recur frequently, digoxin should be continued. In infants, digoxin is usually continued for 3 to 6 months after a single episode of PAT to prevent recurrence.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS

Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous. Anorexia, nausea, vomiting, and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible. Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, and alprazolam may cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Tetracycline and erythromycin (and possibly other macrolide antibiotics) may [illegible] gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation and may be as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g., hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, and alprazolam* may cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Serum levels of digoxin may be increased by concomitant administration of tetracycline and erythromycin (and possibly other macrolide antibiotics). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine*, certain *anticancer drugs*, and *metoclopramide* may reduce intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since this may impair the excretion of digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS

The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section and Serum Digoxin Concentrations subsection of DOSAGE AND ADMINISTRATION). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (1 to 4% of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm, and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g., PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting, and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, and psychosis can occur.

Other—Gynecomastia is occasionally observed. Maculopapular rash or other skin reactions are rarely observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea, and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially

DIGOXIN TABLETS

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DIGOXIN TABLETS

OVERDOSAGE

Treatment of Arrhythmias Produced by Overdosage:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Correction of factors that may contribute to toxicity such as electrolyte disturbances, hypoxia, acid-base disturbances, and removal of aggravating agents such as catecholamines, should also be considered. Potassium salts may be indicated, particularly if hypokalemia is present. Potassium administration may be dangerous in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection below). Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 mL) may be given at a rate not exceeding 20 mEq per hour or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol, and phenytoin, although use of the latter must be considered experimental. In advanced heart block, atropine and/or temporary ventricular pacing may be beneficial. Digibind, Digoxin Immune Fab (Ovine), can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within 1/2 hour of Digibind administration. Each 38 mg vial of DIGIBIND will neutralize 0.5 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium. If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second- or third-degree heart block not responsive to atropine. An overdosage of more than 10 mg of digoxin in previously healthy adults or 4 mg in previously healthy children or overdosage resulting in steady-state serum concentrations greater than 10 ng/mL, often results in cardiac arrest.

Severe digitalis intoxication can cause life-threatening elevation in serum potassium concentration by shifting potassium from inside to outside the cell resulting in hyperkalemia. Administration of potassium supplements in the setting of massive intoxication may be hazardous.

Digibind, Digoxin Immune Fab (Ovine), may be used at a dose equimolar to digoxin in the body to reverse the effects of ingestion of a massive overdose. The decision to administer Digibind before the onset of toxic manifestations will depend on the likelihood that life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-toxic arrhythmias.

DOSAGE AND ADMINISTRATION

Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs, or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. Rapid digitalization may be achieved by administering a loading dose based upon projected peak body digoxin stores, then calculating the maintenance dose as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Adults:

Adults—Rapid Digitalization with a Loading Dose. Peak body digoxin stores of 8 to 12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger stores (10 to 15 µg/kg) are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 µg/kg) (see PRECAUTIONS section).

The loading dose should be based on the projected peak body stores and administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6 to 8 hour intervals, **with careful assessment of clinical response before each additional dose.**

If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

In previously undigitalized patients, a single initial Digoxin Tablet dose of 500 to 750 µg (0.5 to 0.75 mg) usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 125 to 375 µg (0.125 to 0.375 mg) may be given cautiously at 6 to 8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Digoxin Tablets that a 70 kg patient requires to achieve 8 to 15 µg/kg peak body stores is 750 to 1250 µg (0.75 to 1.25 mg).

Although peak body stores are mathematically related to loading doses and are utilized to calculate maintenance doses, they do not correlate with measured serum concentrations. This discrepancy is caused by digoxin distribution within the body during the first 6 to 8 hours following a dose. Serum concentrations drawn during this time are usually not interpretable.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

$$\text{Maintenance Dose} = \text{Peak Body Stores (i.e., Loading Dose)} \times \frac{\%\ \text{Daily Loss}}{100}$$

Where: % Daily Loss = 14 + Ccr/5

(140 - Age)/Scr. For women, this result should be multiplied by 0.85.

Note: This equation cannot be used for estimating creatinine clearance in infants or children.

A common practice involves the use of Lanoxin Injection to achieve rapid digitalization, with conversion to Digoxin Tablets or Lanoxicaps for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see table, CLINICAL PHARMACOLOGY section).

Adults—Gradual Digitalization with a Maintenance Dose: The following table provides average Digoxin Tablet daily maintenance dose requirements for patients with heart failure based upon lean body weight and renal function.

Usual Digoxin Daily Maintenance Dose Requirements (µg)
For Estimated Peak Body Stores of 10 µg/kg

	Lean Body Weight (kg/lbs)							
	50/110	60/132	70/154	80/176	90/198	100/220		
Corrected Ccr (mL/min per 70 kg)	0 63*†	125	125	125	188‡†	188	22	Number of Days Before Steady-State Achieved
	10 125	125	125	188	188	188	19	
	20 125	125	188	188	188	250	16	
	30 125	188	188	188	250	250	14	
	40 125	188	188	250	250	250	13	
	50 188	188	250	250	250	250	12	
	60 188	188	250	250	250	375	11	
	70 188	250	250	250	250	375	10	
	80 188	250	250	250	375	375	9	
	90 188	250	250	250	375	500	8	
	100 250	250	250	375	375	500	7	

*63 µg = 0.063 mg
† 1/2 of 125 µg tablet or 125 µg every other day
‡ 1 1/2 of 125 µg tablet

Example—based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 mL/min, should be given a 250 µg (0.25 mg) Digoxin Tablet each day, usually taken after the morning meal. Steady-state serum concentrations should not be anticipated before 11 days.

Infants and Children: Digitalization must be individualized. Divided daily dosing is recommended for infants and young children. Children over 10 years of age require adult dosages in proportion to their body weight.

Usual Digitalizing and Maintenance Dosages for Digoxin Tablets in Children **with Normal Renal Function Based on Lean Body Weight**

Age	Digitalizing* Dose (µg/kg)	Daily† Maintenance Dose (µg/kg)
2 to 5 Years	30 to 40	25 to 35% of *oral* loading dose‡
5 to 10 Years	20 to 35	
Over 10 years	10 to 15	

* I.V. digitalizing doses are 80% of oral digitalizing doses.
† Divided daily dosing is recommended for children under 10 years of age.
‡ Projected or actual digitalizing dose providing clinical response.

In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area.

Lanoxin Injection Pediatric can be used to achieve rapid digitalization, with conversion to an oral digoxin formulation for maintenance therapy. If patients are switched from intravenous to oral digoxin tablets or elixir, allowances must be made for differences in bioavailability when calculating maintenance dosages (see bioavailability table in CLINICAL PHARMACOLOGY section and dosing table above).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Digitalizing and daily maintenance doses for each age group are given above and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Larger doses are often required for adequate control of ventricular rate in patients with atrial flutter or fibrillation.

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6 to 8 hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

[See third table above.]

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided above can be used in calculating this dose for patients with normal renal function. In children with renal disease, digoxin dosing must be carefully titrated based upon clinical response.

Long-term use of digoxin is indicated in many children who have been digitalized for acute heart failure, unless the cause is transient. Children with severe congenital heart disease, even after surgery, may require digoxin for prolonged periods.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

Serum Digoxin Concentrations: Measurement of serum digoxin concentrations can be helpful to the clinician in determining the state of digitalization and in assigning certain probabilities to the likelihood of digoxin intoxication. Studies in adults considered adequately digitalized (without evidence of toxicity) show that about two-thirds of such patients have serum digoxin levels ranging from 0.8 to 2.0 ng/mL. Patients with atrial fibrillation or atrial flutter require and appear to tolerate higher levels than do patients with other indications. On the other hand, in adult patients with clinical evidence of digoxin toxicity, about two-thirds will have serum digoxin levels greater than 2.0 ng/mL. Thus, whereas levels less than 0.8 ng/mL are infrequently associated with toxicity, levels greater than 2.0 ng/mL are often associated with toxicity. Values in between are not very helpful in deciding whether a certain sign or symptom is more likely caused by digoxin toxicity or by something else. There are rare patients who are unable to tolerate digoxin even at serum concentrations below 0.8 ng/mL. Some researchers suggest that infants and young children tolerate slightly higher serum concentrations than do adults.

To allow adequate time for equilibration of digoxin between serum and tissue, **sampling of serum concentrations for clinical use should be at least 6 to 8 hours after the last dose,** regardless of the route of administration or formulation used. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose. After a single daily dose, the concentration will be 10 to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. Ideally, sampling for assessment of steady-state concentrations should be done just before the next dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

3. Administration of a digitalis glycoside other than digoxin.
4. Conditions described in **WARNINGS** and **PRECAUTIONS** sections causing an alteration in the sensitivity of the patient to digoxin.
5. The patient falls outside the norm in his response to or handling of digoxin. This decision should only be reached after exclusion of the other possibilities and generally should be confirmed by additional correlations of clinical observations with serum digoxin concentrations.

The serum concentration data should always be interpreted in the overall clinical context and an isolated serum concentration value should not be used alone as a basis for increasing or decreasing digoxin dosage.

Adjustment of Maintenance Dosage in Previously Digitalized Patients:

Digoxin Tablet maintenance doses in individual patients on steady-state digoxin can be adjusted upward or downward in proportion to the ratio of the desired versus the measured serum concentration. For example, a patient at steady-state on 125 µg (0.125 mg) of Digoxin Tablets per day with a measured serum concentration of 0.7 ng/mL, should have the dose increased to 250 µg (0.25 mg) per day to achieve a steady-state serum concentration of 1.4 ng/mL. **assuming the serum digoxin concentration measurement is correct, renal function remains stable during this time, and the needed adjustment is not the result of a problem with compliance.**

Dosage Adjustment When Changing Preparations: The difference in bioavailability between injectable Lanoxin or Lanoxicaps and Lanoxin Elixir Pediatric or Digoxin Tablets must be considered when changing patients from one dosage form to another.

Lanoxin Injection and Lanoxicaps doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) are approximately equivalent to 125 µg (0.125 mg) and 250 µg (0.25 mg) doses of Digoxin Tablets and Lanoxin Elixir Pediatric (see table of CLINICAL PHARMACOLOGY section). Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Store at 15° to 25° C (59° to 77° F) in a dry place and protect from light.

HOW SUPPLIED

DIGOXIN TABLETS, Scored 125 µg (0.125mg). Bottles of 100 (NDC 51285-916-02), 1000 (NDC 51285-916-05), imprinted ℞ 914 (yellow).

DIGOXIN TABLETS, Scored 250 µg (0.25mg). Bottles of 100 (NDC 51285-915-02), 1000 (NDC 51285-915-05), imprinted ℞ 915 (white).

℞ only

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