EF 0.25-0.45	4,543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4,455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III / IV	2,224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF <0.25	2,258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR >0.55	2,346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF >0.45[c]	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

[a] Number of patients with an event during the first 2 years per 1,000 randomized patients.

[b] Relative risk (95% confidence interval).

[c] DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25 to 0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

Heart Failure

LANOXIN is indicated for the treatment of mild to moderate heart failure. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these 3 drugs cannot be specified.

Atrial Fibrillation

LANOXIN is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS

Sinus Node Disease and AV Block

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node

disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome)

After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

Use in Patients With Preserved Left Ventricular Systolic Function

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin. Digoxin should generally be avoided in these patients, although it has been used for ventricular rate control in the subgroup of patients with atrial fibrillation.

PRECAUTIONS

Use in Patients With Impaired Renal Function

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

Use in Patients With Electrolyte Disorders

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

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

Use in Thyroid Disorders and Hypermetabolic States

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

Use in Patients With Acute Myocardial Infarction

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

Use During Electrical Cardioversion

It may be desirable to reduce the dose of digoxin for 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

Use in Patients With Myocarditis

Digoxin can rarely precipitate vasoconstriction and therefore should be avoided in patients with myocarditis.

Use in Patients With Beri Beri Heart Disease

Patients with beri beri heart disease may fail to respond adequately to digoxin if the underlying thiamine deficiency is not treated concomitantly.

Laboratory Test Monitoring

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) 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 *diuretics* are a major contributing factor 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, alprazolam,* and *spironolactone*raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result (see CLINICAL PHARMACOLOGY: Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs,* and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs (e.g., *quinine, penicillamine*) on 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. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block. Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing carvedilol.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when

combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

Drug/Laboratory Test Interactions

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Digoxin showed no genotoxic potential in *in vitro* studies (Ames test and mouse lymphoma). No data are available on the carcinogenic potential of digoxin, nor have studies been conducted to assess its potential to affect fertility..

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 reproductive 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 exposure of a nursing infant to digoxin via breastfeeding 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.

Pediatric Use

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

Geriatric Use

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or

concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

Adults

Cardiac

Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal

Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS

Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other

Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

Table 4 summarizes the incidence of those adverse experiences listed above for patients treated with LANOXIN Tablets or placebo from 2 randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

Table 4. Adverse Experiences In 2 Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
Cardiac		

Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

Infants and Children

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common 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 be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

OVERDOSAGE

Signs and Symptoms

The signs and symptoms of toxicity are generally similar to those described in the ADVERSE REACTIONS section but may be more frequent and can be more severe. Signs and symptoms of digoxin toxicity become more frequent with levels above 2 ng/mL. However, in deciding whether a patient's symptoms are due to digoxin, the clinical state together with serum electrolyte levels and thyroid function are important factors (see DOSAGE AND ADMINISTRATION).

Adults

In adults without heart disease, clinical observation suggests that an overdose of digoxin of 10 to 15 mg was the dose resulting in death of half of the patients. If more than 25 mg of digoxin was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments resulted. Cardiac manifestations are the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects generally occur 3 to 6 hours following overdosage and may persist for the ensuing 24 hours or longer. Digoxin toxicity may result in almost any type of arrhythmia (see ADVERSE REACTIONS). Multiple rhythm disturbances in the same patient are common. Cardiac arrest from asystole or ventricular fibrillation due to digoxin toxicity is usually fatal.

Among the extra-cardiac manifestations, gastrointestinal symptoms (e.g. nausea, vomiting, anorexia) are very common (up to 80% incidence) and precede cardiac manifestations in approximately half of the patients in most literature reports. Neurologic manifestations (e.g. dizziness, various CNS disturbances), fatigue, and malaise are very common. Visual manifestations may also occur with aberration in color vision (predominance of yellow green) the most frequent. Neurological and visual symptoms may persist after other signs of toxicity have resolved. In chronic toxicity, non-specific extra-cardiac symptoms, such as malaise and weakness, may predominate.

Children

In children aged 1 to 3 years without heart disease, clinical observation suggests that an overdose of digoxin of 6 to 10 mg was the dose resulting in death in half of the patients. If more than 10 mg of digoxin was ingested by a child aged 1 to 3 years without heart disease, the outcome was uniformly fatal when Fab fragment treatment was not given. Most manifestations of toxicity in children occur during or shortly after the loading phase with digoxin. The same arrhythmias or combination of arrhythmias that occur in adults can occur in pediatrics. Sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen less frequently in the pediatric population. Pediatric patients are more likely to present with an AV conduction disturbance or a sinus bradycardia. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal, CNS, and visual. However, nausea and vomiting are not frequent in infants and small children.

In addition to the undesirable effects seen with recommended doses, weight loss in older age groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischemia, drowsiness, and behavioral disturbances including psychotic manifestations have been reported in overdose.

Treatment

In addition to cardiac monitoring, digoxin should be temporarily discontinued until the adverse reaction resolves and may be all that is required to treat the adverse reaction such as in asymptomatic bradycardia or digoxin-related heart block. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances, thyroid function, or concurrent medications) (see WARNINGS and PRECAUTIONS: Drug Interactions). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

When the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with Digoxin Immune Fab (Ovine) [DIGIBIND® or DIGIFAB®] (see Massive Digitalis Overdosage subsection), the use of atropine, or the insertion of a temporary cardiac pacemaker. Digoxin Immune Fab (Ovine) is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see Administration of Potassium subsection) or hypomagnesemia is present. Ventricular arrhythmias may respond to lidocaine or phenytoin.

Administration of Potassium

Before administering potassium in digoxin overdose for hypokalemia, the serum potassium must be known and every effort should be made to maintain the serum potassium concentration between 4 and 5.5 mmol/L. Potassium salts should be avoided as they may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be

administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia.

Massive Digitalis Overdosage

Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart block.

Digoxin Immune Fab (Ovine) should be used to reverse the toxic effects of ingestion of a massive overdose. The decision to administer Digoxin Immune Fab (Ovine) to a patient who has ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity should depend on the likelihood that life-threatening toxicity will occur (see above).

Digoxin is not effectively removed from the body by dialysis due to its large extravascular volume of distribution. 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 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 because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

In cases where a large amount of digoxin has been ingested, hyperkalemia may be present due to release of potassium from skeletal muscle. Hyperkalemia caused by massive digitalis toxicity is best treated with Digoxin Immune Fab (Ovine); initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION

General

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications. In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (i.e., below 1.5 mg/dL).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

Serum Digoxin Concentrations

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL (lower serum trough concentrations of 0.5 to 1 ng/mL may be appropriate in some adult patients, see Maintenance Dosing). However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients

who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. 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.

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

1. Analytical problems in the assay procedure.
2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other than digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.
5. Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

Heart Failure

Adults

Digitalization may be accomplished by either of 2 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. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated 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 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Peak digoxin body stores of 8 to 12 mcg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 mcg/kg) (see PRECAUTIONS).

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 loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial dose of 500 to 750 mcg (0.5 to 0.75 mg) of LANOXIN Tablets 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 mcg (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 LANOXIN Tablets that a 70-kg patient requires to achieve 8 to 12 mcg/kg peak body stores is 750 to 1,250 mcg (0.75 to 1.25 mg).

LANOXIN Injection is frequently used to achieve rapid digitalization, with conversion to LANOXIN Tablets 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 1, CLINICAL PHARMACOLOGY).

Maintenance Dosing

The doses of digoxin used in controlled trials in patients with heart failure have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 mcg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 mcg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 mcg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1,800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in Table 5) the mean (± SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively. There are no rigid guidelines as to the range of serum concentrations that are most efficacious. Several post hoc analyses of heart failure patients in the DIG trial suggest that the optimal trough digoxin serum level may be 0.5 ng/mL to 1 ng/mL.

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:

Maintenance Dose = Peak Body Stores (i.e., Loading Dose) x % Daily Loss/100

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area.)

Table 5 provides average daily maintenance dose requirements of LANOXIN Tablets for patients with heart failure based upon lean body weight and renal function:

Table 5. Usual Daily Maintenance Dose Requirements (mcg) of LANOXIN for Estimated Peak Body Stores of 10 mcg/kg

Corrected Ccr (mL/min per 70 kg)[a]	Lean Body Weight							Number of Days
	kg	50	60	70	80	90	100	Before Steady
	lb	110	132	154	176	198	220	State Achieved[b]
0		62.5[c]	125	125	125	187.5	187.5	22
10		125	125	125	187.5	187.5	187.5	19
20		125	125	187.5	187.5	187.5	250	16
30		125	187.5	187.5	187.5	250	250	14
40		125	187.5	187.5	250	250	250	13
50		187.5	187.5	250	250	250	250	12
60		187.5	187.5	250	250	250	375	11
70		187.5	250	250	250	250	375	10
80		187.5	250	250	250	375	375	9
90		187.5	250	250	250	375	500	8
100		250	250	250	375	375	500	7

[a] Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body 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.

[b] If no loading dose administered.

[c] 62.5 mcg = 0.0625 mg.

Example: Based on Table 5, 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 dose of 250 mcg (0.25 mg) daily of LANOXIN Tablets, usually taken after the morning meal. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.

Infants and Children

In general, divided daily dosing is recommended for infants and young children (under age 10). 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. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Daily maintenance doses for each age group are given in Table 6 and should provide therapeutic effects with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function:

Table 6. Daily Maintenance Doses in Children With Normal Renal Function

Age	Daily Maintenance Dose (mcg/kg)
2 to 5 Years	10 to 15
5 to 10 Years	7 to 10
Over 10 Years	3 to 5

In children with renal disease, digoxin must be carefully titrated based upon clinical response.

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.

Atrial Fibrillation

Peak digoxin body stores larger than the 8 to 12 mcg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

Dosage Adjustment When Changing Preparations

The difference in bioavailability between LANOXIN Injection or LANOXIN Tablets must be considered when changing patients from one dosage form to the other.

HOW SUPPLIED

LANOXIN (digoxin) Tablets, Scored 125 mcg (0.125 mg): Bottles of 100 with child-resistant cap (NDC 0173-0242-55) and 1,000 (NDC 0173-0242-75); unit dose pack of 100 (NDC 0173-0242-56).

Imprinted with LANOXIN and Y3B (yellow).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

LANOXIN (digoxin) Tablets, Scored 250 mcg (0.25 mg): Bottles of 100 with child-resistant cap (NDC 0173-0249-55), 1,000 (NDC 0173-0249-75), and 5,000 (NDC 0173-0249-80); unit dose pack of 100 (NDC 0173-0249-56). Imprinted with LANOXIN and X3A (white).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature] in a dry place.

LANOXIN and DIGIBIND are registered trademarks of GlaxoSmithKline

DIGIFAB is a registered trademark of Prostherics Inc.

Manufactured for

GlaxoSmithKline

Research Triangle Park, NC 27709

by DSM Pharmaceuticals, Inc.

Greenville, NC 27834 or

GlaxoSmithKline

Research Triangle Park, NC 27709

November 2011

LNT:2PI

Principal Display Panel

NDC 0173-0242-55

LANOXIN®

(digoxin)

Tablets, USP

100 Tablets

Each scored tablet contains

125 mcg (0.125 mg)

R_x only

See prescribing information for dosage information.

Store at 25°C (77°F) in a dry place and protect from light (see insert).

Dispense in tight, light-resistant container as defined in the USP.

Do not use if printed safety seal under cap is broken or missing.

Manufactured by

DSM Pharmaceuticals, Inc.

Greenville, NC 27834 for

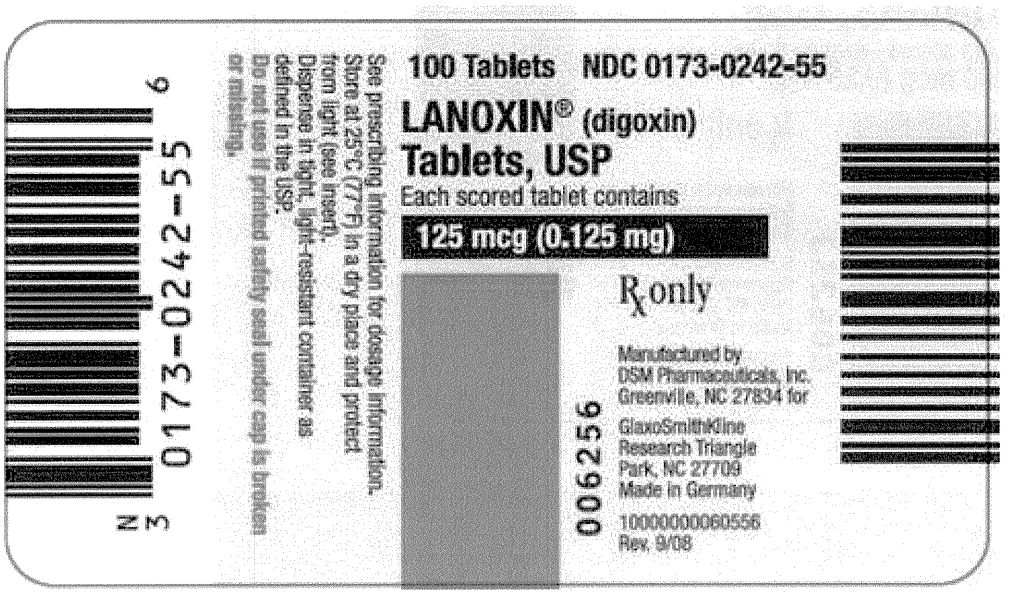
GlaxoSmithKline

Research Triangle Park, NC 27709

Made in Germany

10000000060556

Rev. 9/08



Principal Display Panel

NDC 0173-0249-55

LANOXIN®

(digoxin)

Tablets, USP

100 Tablets

Each scored tablet contains

250 mcg (0.25 mg)

R_x only

See prescribing information for dosage information.

Store at 25°C (77°F) in a dry place (see insert).

Dispense in tight container as defined in the USP.

Do not use if printed safety seal under cap is broken or missing.

Manufactured by

DSM Pharmaceuticals, Inc.

Greenville, NC 27834 for

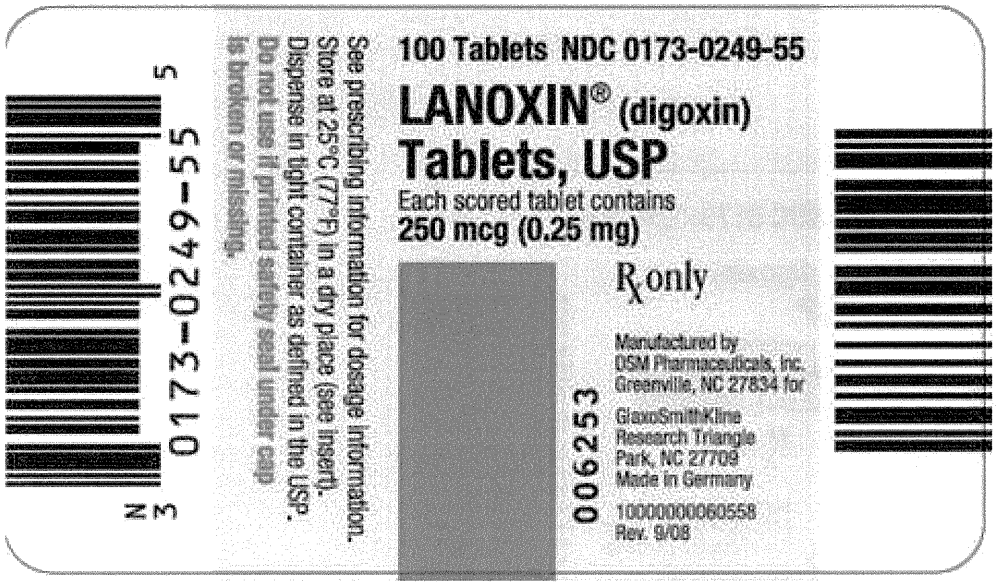
GlaxoSmithKline

Research Triangle Park, NC 27709

Made in Germany

10000000060558

Rev. 9/08



LANOXIN

digoxin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0173-0242
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIGOXIN (DIGOXIN)	DIGOXIN	125 ug

Inactive Ingredients	
Ingredient Name	**Strength**
STARCH, CORN	
STARCH, POTATO	
LACTOSE	
MAGNESIUM STEARATE	
D&C YELLOW NO. 10	
FD&C YELLOW NO. 6	

Product Characteristics

Color	YELLOW	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	LANOXIN;Y3B
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0173-0242-56	100 in 1 BLISTER PACK		
2	NDC:0173-0242-75	1000 in 1 BOTTLE		
3	NDC:0173-0242-55	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020405	09/14/1984	09/30/2015

LANOXIN

digoxin tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0173-0249
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DIGOXIN (DIGOXIN)	DIGOXIN	250 ug

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN	
STARCH, POTATO	
LACTOSE	
MAGNESIUM STEARATE	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	LANOXIN;X3A
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0173-0249-56	100 in 1 BLISTER PACK		
2	NDC:0173-0249-80	5000 in 1 BOTTLE		
3	NDC:0173-0249-75	1000 in 1 BOTTLE		
4	NDC:0173-0249-55	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020405	07/02/1984	09/30/2015

Labeler - GlaxoSmithKline LLC (167380711)

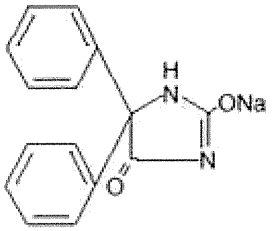
Revised: 11/2011 GlaxoSmithKline LLC

DILANTIN- phenytoin sodium capsule, extended release
Parke-Davis Div of Pfizer Inc

Dilantin®
(extended phenytoin sodium capsules, USP)

DESCRIPTION

Phenytoin sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2, 4-imidazolidinedione, having the following structural formula:



Each 30 mg Dilantin- (*extended phenytoin sodium capsule*, USP)-contains 30 mg phenytoin sodium, USP. Also contains lactose monohydrate, NF; confectioner's sugar, NF; talc, USP; and magnesium stearate, NF. The capsule shell cap and body components contain titanium dioxide (cap and body); gelatin (cap and body); D&C yellow No. 10 (cap); FD&C red No. 3 (cap). Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted to *Prompt Phenytoin Sodium Capsules*, USP with a rapid rate of absorption with peak blood concentration expected in 1½ to 3 hours.

Each 100 mg Dilantin- *100 mg (extended phenytoin sodium capsule, USP)* -contains 100 mg phenytoin sodium. Also contains lactose monohydrate, NF; confectioner's sugar, NF; talc, USP; and magnesium stearate, NF. The capsule body contains titanium dioxide, USP and gelatin, NF. The capsule cap contains FD&C red No. 28; FD&C yellow No. 6; and gelatin NF. Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted to *Prompt Phenytoin Sodium Capsules*, USP with a rapid rate of absorption with peak blood concentration expected in 1½ to 3 hours.

CLINICAL PHARMACOLOGY

Mechanism of Action

Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the *motor cortex* where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to *stabilize* the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation at synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

Pharmacokinetics and Drug Metabolism

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7

to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

When serum level determinations are necessary, they should be obtained at least 5–7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Dilantin capsules, peak serum levels occur 4 to 12 hours after administration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Patients with Renal or Hepatic Disease

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations.

Age

Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20–30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

Gender and Race

Gender and race have no significant impact on phenytoin pharmacokinetics.

Pediatrics

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day).

INDICATIONS AND USAGE

Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections).

CONTRAINDICATIONS

Phenytoin is contraindicated in those patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins.

Coadministration of Dilantin is contraindicated with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

WARNINGS

Effects of Abrupt Withdrawal

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. In the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Dilantin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Dilantin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. Dilantin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see **DRESS/Multiorgan hypersensitivity** below).

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Dilantin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents