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SHIRE EX. 2084
KVK v. SHIRE

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ALARM**

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RX GLAXOSMITHKLINE P. 1447



2%
22 g

Sactroban Ointment®
(mupirocin ointment, 2%)

While every effort has been made to reproduce products faithfully, this section is to be considered a quick reference identification aid. In cases of suspected overdose, etc., chemical analysis of the product should be done.

RX GLAXOSMITHKLINE P. 1448



42 mcg/spray
25 g
180 metered sprays

Becasono AQ® Nasal Spray, 42 mcg
(bedonasthine propionate, 42 mcg hydrochloride)

RX GLAXOSMITHKLINE P. 1450



125 mg/5 mL
100 mL

RX GLAXOSMITHKLINE P. 1449



250 mg/5 mL
50 mL 250 mg/5 mL
100 mL

Ceftin® for Oral Suspension
(cefuroxime axetil powder for oral suspension)

RX GLAXOSMITHKLINE P. 1446



250 mg

500 mg

Ceftin®
(cefuroxime axetil tablets)

RX GLAXOSMITHKLINE P. 1454



RX GLAXOSMITHKLINE P. 1437



3.125 mg Tiltab® 6.25 mg Tiltab®

12.5 mg Tiltab® 25 mg Tiltab®

Coreg®
(carvedilol)

RX GLAXOSMITHKLINE P. 1443



0.05%
15 g

0.05%
60 g

Also available in 30 g

Cutivate® Cream
(fluticasone propionate cream)

RX GLAXOSMITHKLINE P. 1443




0.005%
15 g

0.005%
60 g

Also available in 30 g

Cutivate® Ointment
(fluticasone propionate ointment)

RX GLAXOSMITHKLINE P. 1464



25 mg

Daraprim®
(pyrimethamine)

C-II GLAXOSMITHKLINE P. 1465



15-mg Spansule®

Also available as 5-mg Spansule® and 10-mg Spansule® capsules.



5 mg

Dexedrine®
(dextroamphetamine sulfate)

RX GLAXOSMITHKLINE P. 1466



38 mg

RX GLAXOSMITHKLINE P. 1468



25 mg/37.5 mg

Dyazide®
(hydrochlorothiazide/triamterene)

RX GLAXOSMITHKLINE P. 1470



20 mcg/mL single-dose vial
Adult Dose

RX GLAXOSMITHKLINE P. 1470



20 mcg/mL single-dose, prefilled, disposable Tip-Lok® syringe
Adult Dose



10 mcg/0.5 mL single-dose vial
Pediatric Dose/Adolescent Dose

RX GLAXOSMITHKLINE P. 1470



10 mcg/0.5 mL single-dose, prefilled, disposable Tip-Lok® syringes with 5/8-inch 25-gauge SafetySlide™ needles.

RX GLAXOSMITHKLINE P. 1487



0.5 mg 1.5 mg

Engerix-B®
(Hepatitis B Vaccine (Recombinant))

Because tablets and capsules are shown in this section, do not infer that these are the only dosage forms available. Where a product name is preceded by the symbol †, refer to the description in the Product Information (White Section) for other forms.

RX GLAXOSMITHKLINE P. 1473



150 mg

300 mg

EpiVir®
(lamivudine tablets)

RX GLAXOSMITHKLINE P. 1473



10 mg/mL
240 mL

RX GLAXOSMITHKLINE P. 1477



100 mg

EpiVir-HBV®
(lamivudine)

RX GLAXOSMITHKLINE P. 1477



5 mg/mL
240 mL

EpiVir-HBV® Oral Solution
(lamivudine)

RX GLAXOSMITHKLINE P. 1468



300 mg

Eskalith®
(lithium carbonate)

RX GLAXOSMITHKLINE P. 1485



450 mg

Eskalith CR® Controlled-Release Tablets
(lithium carbonate)

RX GLAXOSMITHKLINE P. 1487



0.5 mg 1.5 mg

Fioan® for Injection
(spirosteno sodium)

RX GLAXOSMITHKLINE P. 1481



50 mcg/spray
16 g
120 metered sprays

Fioan® Nasal Spray, 50 mcg
(fluticasone propionate)

RX GLAXOSMITHKLINE P. 1494



44 mcg/inh
13-g canister
120 metered inhalations
Also available in 7.9-g canister.

RX GLAXOSMITHKLINE P. 1494



110 mcg/inh
13-g canister
120 metered inhalations
Also available in 7.9-g canister.

Fiovent® 110 mcg Inhalation Aerosol
(fluticasone propionate, 110 mcg)

RX GLAXOSMITHKLINE P. 1494



220 mcg/inh
13-g canister
120 metered inhalations
Also available in 7.9-g canister.

Fiovent® 220 mcg Inhalation Aerosol
(fluticasone propionate, 220 mcg)

RX GLAXOSMITHKLINE P. 1500



50 mg/blister

Fiovent® Rotadisk® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

RX GLAXOSMITHKLINE P. 1500



100 mcg/blister

Fiovent® Rotadisk® 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

RX GLAXOSMITHKLINE P. 1500



250 mcg/blister

Fiovent® Rotadisk® 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

Designed to help you identify drugs, this section contains actual size pills and full color reproduction of products selected for inclusion by

Dexedrine —Cont.

Drug Interactions: **Acidifying agents**—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. Urinary acidifying agents (ammonium chloride, sodium-acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic—Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors—MAO antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines—Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine—Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide—Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate—The stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meprobamate—Amphetamines potentiate the analgesic effect of meprobamate.

Methamphetamine—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine therapy.

Norpinephrine—Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene—In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.

Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of DEXEDRINE have not been performed.

Pregnancy—Teratogenic Effects: Pregnancy Category C. DEXEDRINE has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been 1 report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took dextroamphetamine sulfate with lovasatin during the first trimester of pregnancy. DEXEDRINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: Long-term effects of amphetamines in pediatric patients have not been well established.

Amphetamines are not recommended for use in pediatric patients under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Clinical experience suggests that in psychotic children, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder.

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. Data are inadequate to determine whether chronic administration of amphetamines may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his or her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics, and Tourette's syndrome.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Endocrine: Impotence, changes in libido.

ALLERGIC: Urticaria.

DRUG ABUSE AND DEPENDENCE

Dextroamphetamine sulfate is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended.

Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.

Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE

Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD₅₀ of dextroamphetamine sulfate is 96.8 mg/kg.

Manifestations of acute overdose with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, assaultiveness, hallucinations, panic states.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

TREATMENT

Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdose, administration of intravenous phenolamine (Bedford Laboratories) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

Since much of the SPANSULE capsule medication is coated for gradual release, therapy directed at reversing the effects of the ingested drug and at supporting the patient should be continued for as long as overdose symptoms remain. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

DOSEAGE AND ADMINISTRATION

Amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted.

Late-evening doses—particularly with the SPANSULE capsule form—should be avoided because of insomnia.

Narcology: Usual dose is 5 to 60 mg per day in doses, depending on the individual patient response. Narcology seldom occurs in children under 12 years of age, however, when it does, DEXEDRINE may be used. The initial dose for patients aged 6 to 12 is 5 mg daily dose may be raised in increments of 5 mg at 1-week intervals until an optimal response is obtained. In 12 years of age and older, start with 10 mg daily dose may be raised in increments of 10 mg at 1-week intervals until an optimal response is obtained. If the adverse reactions appear (e.g., insomnia or tachycardia) the dose should be reduced. SPANSULE capsules may be used for once-a-day dosage wherever appropriate. SPANSULE should give first dose on awakening; additional doses at intervals of 4 to 6 hours.

Attention Deficit Disorder with Hyperactivity: Amphetamines are indicated for pediatric patients under 3 years of age with Attention Deficit Disorder with Hyperactivity in pediatric patients from 3 to 5 years of age. The 2.5 mg daily by tablet; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In pediatric patients 6 years of age and older, 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to use a total of 40 mg per day.

SPANSULE capsules may be used for once-a-day dosage wherever appropriate.

With tablets, give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be timed to occur occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

HOW SUPPLIED

DEXEDRINE SPANSULE capsules: Each capsule brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and SP on the brown cap and is imprinted 10 mg — 53 — on the clear body. The 10-mg capsule is imprinted 10 mg — 53 — on the brown cap and is imprinted 15 mg and SE on the clear body. The 15-mg capsule is imprinted 15 mg and SE on the brown cap and is imprinted 15 mg and SE on the clear body. A narrow bar appears above and below 15 mg on the clear body. Available: 5 mg, 10 mg, and 15 mg in bottles of 100. Store at controlled room temperature between 68° and 77°F (see USP).

Dispense in a tight, light-resistant container.

5 mg 100s: NDC 0007-3512-20
10 mg 100s: NDC 0007-3513-20
15 mg 100s: NDC 0007-3514-20

DEXEDRINE SPANSULE capsules are manufactured by Cardinal Health, Winchester, KY 40391.

DEXEDRINE Tablets: Triangular, orange, scored, SRX and K19. Available: 5 mg in bottles of 100, imprinted by Abbott Laboratories, North Chicago, IL. Store between 15° and 30°C (59° and 86°F). Dispense in a tight, light-resistant container.

5 mg 100s: NDC 0007-3512-20
10 mg 100s: NDC 0007-3513-20
15 mg 100s: NDC 0007-3514-20

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Shown in Product Identification Guide, page 10

of distribution in the extracellular space, unlike Fab which distributes in a space only about plasma volume. Ordinarily, following administration of DIGIBIND, improvement in signs and symptoms of digitalis intoxication begins within one-half hour or

affinity of DIGIBIND for digoxin is in the range of 10⁹ M⁻¹, which is greater than the affinity of digoxin for its receptor, potassium ATPase, the presumed receptor for its toxic effects. The affinity of DIGIBIND for digitoxin is about 10⁸ M⁻¹.

DIGIBIND binds molecules of digoxin, making them unavailable for binding at their site of action on cells in the heart. The Fab fragment-digoxin complex accumulates in the urine from which it is excreted by the kidney. The net effect is to shift the equilibrium away from binding of digoxin to its receptors in the body, thereby reversing its effects.

INDICATIONS AND USAGE

DIGIBIND, Digoxin Immune Fab (Ovine), is indicated for the treatment of potentially life-threatening digoxin intoxication. Although designed specifically to treat life-threatening digoxin overdose, it has also been used successfully to treat life-threatening digoxin overdose. Since human antibody response is limited and the consequences of repeated courses are unknown, DIGIBIND is not indicated for either acute or chronic digitalis toxicity.

Complications of life-threatening toxicity include severe cardiac arrhythmias such as ventricular tachycardia or atrial fibrillation, or progressive bradycardias or severe sinus bradycardia or second or third degree block not responsive to atropine.

Doses of more than 10 mg of digoxin in previously healthy children or adults or 4 mg of digoxin in previously healthy children on ingestion causing steady-state serum concentrations greater than 10 ng/mL, often results in cardiac arrest. This induced progressive elevation of the serum potassium concentration also suggests imminent cardiac arrest.

When the serum potassium concentration exceeds 5 mEq/L in the setting of severe digitalis intoxication, therapy with DIGIBIND is indicated.

CONTRAINDICATIONS

There are no known contraindications to the use of DIGIBIND.

WARNINGS

DIGIBIND ingestion often involves more than one drug; thus, the possibility of other drugs should not be overlooked.

Consider the possibility of anaphylactic, hypersensitivity, or febrile reactions. If an anaphylactoid reaction to the drug infusion should be discontinued and appropriate therapy initiated using aminophylline, oxygen, volume expansion, diphenhydramine, corticosteroids, and airway management as indicated. The need for epinephrine should be balanced against its potential risk in the setting of digitalis toxicity.

The Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose less of an immunologic threat to patients than does an intact immunoglobulin molecule. Patients with known allergies would be particularly at risk, as would individuals who have previously received antibodies or Fab fragments raised in sheep. Papain is used to cleave the whole antibody into Fab fragments, and traces of papain or inactivated papain residues may be present in DIGIBIND. Patients with allergies to papain, chymopapain, or other papaya extracts may be particularly at risk.

Testing for allergy was performed during the clinical development of DIGIBIND. Only one patient developed an allergic reaction at the site of skin testing, with no accompanying systemic reaction; this individual had no adverse reaction to digoxin treatment with DIGIBIND. Since allergy testing is not routinely needed therapy, it is not routinely required before treatment of life-threatening digitalis toxicity with DIGIBIND.

Testing may be appropriate for high risk individuals, especially patients with known allergies or those previously treated with Digoxin Immune Fab (Ovine). The intradermal test can be performed by:

Injecting 0.1 mL of reconstituted DIGIBIND (9.5 mg/mL) in 9.9 mL sterile isotonic saline (1:100 dilution, 9.5 mcg/mL).

Injecting 0.1 mL of the 1:100 dilution (9.5 mcg) intradermally and observing for an urticarial wheal surrounded by a zone of erythema. The test should be read at 20 minutes.

Scratch test procedure is performed by placing one drop of 1:100 dilution of DIGIBIND on the skin and then making a 1-cm scratch through the drop with a sterile needle. The scratch site is inspected at 30 minutes for an urticarial wheal surrounded by erythema.

Scratch testing causes a systemic reaction, a tourniquet test should be applied above the site of testing and measures to prevent anaphylaxis should be instituted. Further administration of DIGIBIND should be avoided unless its use is absolutely essential, in which case the patient should be prepared with corticosteroid and diphenhydramine. The physician should be prepared to treat anaphylaxis.

PRECAUTIONS

General: Standard therapy for digitalis intoxication involves the withdrawal of the drug and correction of factors that contribute to toxicity, such as electrolyte disturbances, hypoxia, acid-base disturbances, and agents such as calcium channel blockers. Also, treatment of arrhythmias may include

DIGIBIND®

(dij - bind)
DIGOXIN IMMUNE FAB (OVINE)

DESCRIPTION

DIGIBIND, Digoxin Immune Fab (Ovine), is a sterilized powder of antigen binding fragments (Fab) from specific antidigoxin antibodies raised in sheep. The production of antibodies specific for digoxin involves conjugating digoxin as a hapten to human albumin. Sheep are immunized with this material to produce antibodies specific for digoxin. The antigenic determinants of the digoxin molecule are then papain-digested and digoxin-specific fragments of the antibody are isolated and purified by ion exchange chromatography. These antibody fragments have a molecular weight of approximately 48,200.

Each vial, which will bind approximately 0.5 mg of digoxin (or digitoxin), contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 76 mg of sorbitol as a stabilizer and 28 mg of sodium chloride. The vial contains no preservatives.

DIGIBIND is administered by intravenous injection after reconstitution with Sterile Water for Injection (4 mL).

CLINICAL PHARMACOLOGY

After intravenous injection of Digoxin Immune Fab (Ovine) in the human, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of about 8 hours. In humans with normal renal function, the half-life appears to be 15 to 20 hours. Experimental studies in animals indicate that these antibody fragments have a

Information will be superseded by supplements and subsequent editions

