PDR®
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PHYSICIANS' DESK REFERENCE®

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RX GLAXOSMITHKLINE P. 1447

2%
22 g

Bactroban 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 overdosage, etc., chemical analysis of the product should be done.

RX GLAXOSMITHKLINE P. 1448

42 mcg/spray
25 g
180 metered sprays

Beconase AQ® Nasal Spray, 42 mcg
(beclomethasone dipropionate, monohydrate)

RX GLAXOSMITHKLINE P. 1450

125 mg/5 mL
100 mL

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. 1450

250 mg

500 mg

Ceftin®
(cefuroxime axetil tablets)

RX GLAXOSMITHKLINE P. 1454

RX GLAXOSMITHKLINE P. 1457

3.125 mg Tiltab®
6.25 mg Tiltab®
12.5 mg Tiltab®
25 mg Tiltab®

Coreg®
(carvedilol)

RX GLAXOSMITHKLINE P. 1461

0.05%
15 g

0.05%
60 g
Also available in 30 g

Cutivate® Cream
(fluticasone propionate cream)

RX GLAXOSMITHKLINE P. 1463

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

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

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

10 mcg/0.5 mL single-dose, prefilled, disposable Tip-Lok® syringe
Pediatric/Adolescent Dose

Also available in Pediatric/Adolescent Dose 10 mcg/0.5 mL single-dose, prefilled, disposable Tip-Lok® syringes with 5/8-inch 25-gauge SafetyGlide™ needles.

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. 1485

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

Flolan® for Injection
(epoprostenol sodium)

RX GLAXOSMITHKLINE P. 1481

50 mcg/spray
16 g
120 metered sprays

Flonase® 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.

Flovent® 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.

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

RX GLAXOSMITHKLINE P. 1500

50 mcg/blister

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

RX GLAXOSMITHKLINE P. 1500

100 mcg/blister

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

RX GLAXOSMITHKLINE P. 1500

250 mcg/blister

Flovent® 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

chromosomes analyzed from the bone marrow of with pyrimethamine showed an increased num- structural and numerical aberrations.

Teratogenic Effects: Pregnancy Category C. has been shown to be teratogenic in rats in oral doses 7 times the human dose for che- of malaria or 2.5 times the human dose for of toxoplasmosis. At these doses in rats, there significant increase in abnormalities such as cleft pal- agnathia, oligodactyly, and microphthalmia. Pyri- has also been shown to produce terata such as in hamsters and cleft palate in miniature pigs in oral doses 170 and 5 times the human dose, for chemoprophylaxis of malaria or for treat- toxoplasmosis.

are no adequate and well-controlled studies in preg- DARAPRIM should be used during pregnancy the potential benefit justifies the potential risk to the

administration of folinic acid is strongly recom- when used for the treatment of toxoplasmosis dur-

Pyrimethamine is excreted in human of the potential for serious adverse reactions infants from pyrimethamine and from concur- a sulfonamide with DARAPRIM for treatment of patients with toxoplasmosis, a decision should be whether to discontinue nursing or to discontinue the taking into account the importance of the drug to the WARNINGS and PRECAUTIONS: Pregnancy). Use: See DOSAGE AND ADMINISTRATION

Use: Clinical studies of DARAPRIM did not in- sufficient numbers of subjects aged 65 and over to de- whether they respond differently from younger sub- Other reported clinical experience has not identified in responses between the elderly and younger In general, dose selection for an elderly patient is cautious, usually starting at the low end of the reflecting the greater frequency of decreased or cardiac function, and of concomitant dis- other drug therapy.

SIDE REACTIONS

sensitivity reactions, occasionally severe (such as Johnson syndrome, toxic epidermal necrolysis, ery- multiforme, and anaphylaxis), and hyperphenylala- may occur particularly when pyrimethamine is ad- concomitantly with a sulfonamide. Consult the prescribing information for the relevant sulfon- for sulfonamide-associated adverse events. With pyrimethamine used for the treatment of toxoplas- anorexia and vomiting may occur. Vomiting may be by giving the medication with meals; it usually promptly upon reduction of dosage. Doses used may produce megaloblastic anemia, leuko- thrombocytopenia, pancytopenia, atrophic glossitis, and disorders of cardiac rhythm. Hematologic however, may also occur at low doses in certain in- (see PRECAUTIONS: General).

eosinophilia has been reported rarely.

OVERDOSAGE

the ingestion of 300 mg or more of pyrimeth- gastrointestinal and/or central nervous system signs present, including convulsions. The initial symp- are usually gastrointestinal and may include abdomi- nausea, severe and repeated vomiting, possibly in- hematemesis. Central nervous system toxicity may by initial excitability, generalized and pro- convulsions which may be followed by respiratory failure, circulatory collapse, and death within a few Neurological symptoms appear rapidly (30 minutes hours after drug ingestion), suggesting that in gross pyrimethamine has a direct toxic effect on the nervous system.

fatal dose is variable, with the smallest reported fatal being 375 mg. There are, however, reports of pe- patients who have recovered after taking 375 to

no specific antidote to acute pyrimethamine poison- the event of overdosage, symptomatic and supportive should be employed. Gastric lavage is recom- and is effective if carried out very soon after drug Parenteral diazepam may be used to control con- Folinic acid should also be administered within 2 of drug ingestion to be most effective in counteracting on the hematopoietic system (see WARNINGS). the long half-life of pyrimethamine, daily monitoring blood counts is recommended for up to several after the overdose until normal hematologic values

DOSAGE AND ADMINISTRATION

Treatment of Toxoplasmosis: The dosage of for the treatment of toxoplasmosis must be adjusted so as to provide maximum therapeutic ef- a minimum of side effects. At the dosage required, is a marked variation in the tolerance to the drug. patients may tolerate higher doses than older indi- Concurrent administration of folinic acid is recommended in all patients.

starting dose is 50 to 75 mg of the drug daily, to- 1 to 4 g daily of a sulfonamide of the sulfapyri- e.g., sulfadoxine. This dosage is ordinarily con- tinued for 1 to 3 weeks, depending on the response of the patient and tolerance to therapy. The dosage may then be reduced to about one-half that previously given for each drug and continued for an additional 4 to 5 weeks.

The pediatric dosage of DARAPRIM is 1 mg/kg/day divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one half and continued for approximately 1 month. The usual pediatric sulfonamide dosage is used in conjunction with DARAPRIM.

For Treatment of Acute Malaria: DARAPRIM is NOT recommended alone in the treatment of acute malaria. Fast-acting schizonticides, such as chloroquine or quinine, are indicated for treatment of acute malaria. However, DARAPRIM at a dosage of 25 mg daily for 2 days with a sulfonamide will initiate transmission control and suppression of non-falciparum malaria. DARAPRIM is only recommended for patients infected in areas where susceptible plasmodia exist. Should circumstances arise wherein DARAPRIM must be used alone in semi-immune persons, the adult dosage for acute malaria is 50 mg for 2 days; children 4 through 10 years old may be given 25 mg daily for 2 days. In any event, clinical cure should be followed by the once-weekly regimen described below for chemoprophylaxis. Regimens which include suppression should be extended through any characteristic periods of early recrudescence and late relapse, i.e., for at least 10 weeks in each case.

For Chemoprophylaxis of Malaria:

Adults and pediatric patients over 10 years — 25 mg (1 tablet) once weekly

Children 4 through 10 years — 12.5 mg (½ tablet) once weekly

Infants and children under 4 years — 6.25 mg (¼ tablet) once weekly

HOW SUPPLIED

White, scored tablets containing 25 mg pyrimethamine, imprinted with "DARAPRIM" and "A3A" in bottles of 100 (NDC 0173-0201-55).

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

REFERENCES

1. Eyles DE, Coleman N. Synergistic effect of sulfadiazine and Daraprim against experimental toxoplasmosis in the mouse. *Antibiot Chemother.* 1953;3:483-490.
2. Jacobs L, Melton ML, Kaufman HE. Treatment of experimental ocular toxoplasmosis. *Arch Ophthalmol.* 1964;71: 111-118.
3. Jim RTS, Elizaga FV. Development of chronic granulocytic leukemia in a patient treated with pyrimethamine. *Hawaii Med J.* 1977;36:173-176.
4. Sadoff L. Antimalarial drugs and Burkitt's lymphoma. *Lancet.* 1973;2:1262-1263.
5. Bahna L. Pyrimethamine. *LARC Monogr Eval Carcinog Risk Chem.* 1977;13:233-242.
6. Clive D, Johnson KO, Spector JKS, et al. Validation and characterization of the L5178Y/TK +/- mouse lymphoma mutagen assay system. *Mut Res.* 1979;59:61-108.

Manufactured by DSM Pharmaceuticals, Inc.
Greenville, NC 27834 for
GlaxoSmithKline, Research Triangle Park, NC 27709

March 2003/RL-1179

Shown in Product Identification Guide, page 315

DEXEDRINE®

[*dex 'ə-drēn*]

(dextroamphetamine sulfate)

SPANSULE®

sustained release capsules and Tablets

℞

WARNING

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION

DEXEDRINE (dextroamphetamine sulfate) is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is *d*-alpha-methylphenethylamine, and is present in all forms of DEXEDRINE as the neutral sulfate.

SPANSULE capsules: Each SPANSULE sustained-release capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period.

Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10-mg capsule is imprinted 10 mg — 3513 — on the brown cap and is imprinted 10 mg — SB — on the clear body. The 15-mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Product reformulation in 1996 has caused a minor change in the color of the time-released pellets within each capsule. Inactive ingredients now consist of cetyl alcohol, D&C Yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C Blue No. 1, FD&C Blue No. 1 aluminum lake, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hypromellose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.

Tablets: Each triangular, orange, scored tablet is debossed SKF and E19 and contains dextroamphetamine sulfate, 5 mg. Inactive ingredients consist of calcium sulfate, FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6, gelatin, lactose, mineral oil, starch, stearic acid, sucrose, talc, and trace amounts of other inactive ingredients.

CLINICAL PHARMACOLOGY

Amphetamines are noncatecholamine, sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevations of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence that clearly establishes the mechanism whereby amphetamines produce mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

DEXEDRINE SPANSULE capsules are formulated to release the active drug substance in vivo in a more gradual fashion than the standard formulation, as demonstrated by blood levels. The formulation has not been shown superior in effectiveness over the same dosage of the standard, noncontrolled-release formulations given in divided doses.

Pharmacokinetics: The pharmacokinetics of the tablet and sustained-release capsule were compared in 12 healthy subjects. The extent of bioavailability of the sustained-release capsule was similar compared to the immediate-release tablet. Following administration of three 5-mg tablets, average maximal dextroamphetamine plasma concentrations (C_{max}) of 36.6 ng/mL were achieved at approximately 3 hours. Following administration of one 15-mg sustained-release capsule, maximal dextroamphetamine plasma concentrations were obtained approximately 8 hours after dosing. The average C_{max} was 23.5 ng/mL. The average plasma $T_{½}$ was similar for both the tablet and sustained-release capsule and was approximately 12 hours.

In 12 healthy subjects, the rate and extent of dextroamphetamine absorption were similar following administration of the sustained-release capsule formulation in the fed (58 to 75 gm fat) and fasted state.

INDICATIONS AND USAGE

DEXEDRINE is indicated:

1. In Narcolepsy.

2. In Attention Deficit Disorder with Hyperactivity, as an integral part of a total treatment program that typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in pediatric patients (ages 3 years to 16 years) with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: Moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

PRECAUTIONS

General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at 1 time in order to minimize the possibility of overdosage.

The tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Continued on next page

Product information on these pages is effective as of August 2004. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

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—MAOI 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.

Meperidine—Amphetamines potentiate the analgesic effect of meperidine.

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

Norepinephrine—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 overdosage, 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 lovastatin 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.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

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 LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Manifestations of acute overdosage 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 overdosage, administration of intravenous phentolamine (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 overdosage symptoms remain. Saline cathartics are useful for hastening the evacuation of pellets that have not already released medication.

DOSAGE AND ADMINISTRATION

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

Late evening doses—particularly with the [illegible] capsule form—should be avoided because of the [illegible] insomnia.

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

Attention Deficit Disorder with Hyperactivity: [illegible] mended for pediatric patients under 3 years of age.

In pediatric patients from 3 to 5 years of age, the [illegible] 2.5 mg daily, by tablet; daily dosage may be [illegible] ments of 2.5 mg at weekly intervals until optimal [illegible] is obtained.

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

SPANSULE capsules may be used for once-a-[illegible] wherever appropriate.

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

Where possible, drug administration should be [illegible] occasionally to determine if there is a recurrence [illegible] ional symptoms sufficient to require continued [illegible]

HOW SUPPLIED

DEXEDRINE SPANSULE capsules: Each capsule has a brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and SB on the brown cap and is imprinted 5 mg and SB on the [illegible]. The 10-mg capsule is imprinted 10 mg — 3512 on the brown cap and is imprinted 10 mg — SB — 5[illegible] body. The 15-mg capsule is imprinted 15 mg and SB on the brown cap and is imprinted 15 mg and SB on the [illegible]. A narrow bar appears above and below 15 mg on the [illegible]. Available: 5 mg, 10 mg, and 15 mg in bottles of [illegible].

Store at controlled room temperature between 15° and 30°C (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, [illegible] SKF and E19. Available: 5 mg in bottles of 100, [illegible] tured by Abbott Laboratories, North Chicago, IL [illegible].

Store between 15° and 30°C (59° and 86°F). Dispense in a tight, light-resistant container.

5 mg 100s: NDC 0007-3519-20

GlaxoSmithKline, Research Triangle Park, NC 27[illegible]

September 2003/DX:L53

Shown in Product Identification Guide, page [illegible]

DIGIBIND®

[dij '-bind]

DIGOXIN IMMUNE FAB (OVINE)

DESCRIPTION

DIGIBIND, Digoxin Immune Fab (Ovine), is a sterile, lyophilized powder of antigen binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. [illegible] tion of antibodies specific for digoxin involves conjugation of digoxin as a hapten to human albumin. Sheep are immunized with this material to produce antibodies against the antigenic determinants of the digoxin molecule. The antibody is then papain-digested and digoxin-specific Fab fragments of the antibody are isolated and purified by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,200.

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 75 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 per vial).

CLINICAL PHARMACOLOGY

After intravenous injection of Digoxin Immune Fab [illegible] in the baboon, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of about 9 [illegible] hours.[1] In humans with normal renal function, the half-life appears to be 15 to 20 hours.[2] Experimental studies [illegible] mals indicate that these antibody fragments have a [illegible] of distribution in the extracellular space, unlike antibody which distributes in a space only about plasma volume.[1] Ordinarily, following administration of DIGIBIND, improvement in signs and symptoms of digoxin intoxication begins within one-half hour or [illegible]

[illegible] ity of DIGIBIND for digoxin is in the range of 10^9 [illegible] M^{-1}, which is greater than the affinity of digoxin for [illegible], potassium) ATPase, the presumed receptor for its [illegible]. The affinity of DIGIBIND for digitoxin is about [illegible] M^{-1}.

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

[illegible]CATIONS AND USAGE

[illegible]GIBIND, Digoxin Immune Fab (Ovine), is indicated for [illegible] of potentially life-threatening digoxin intoxication. [illegible] though designed specifically to treat life-threatening [illegible] digoxin overdose, it has also been used successfully to [illegible] life-threatening digitoxin overdose.[3] Since human [illegible] is limited and the consequences of repeated [illegible] are unknown, DIGIBIND is not indicated for milder [illegible] digitalis toxicity.

[illegible] of life-threatening toxicity include severe [illegible] arrhythmias such as ventricular tachycardia or [illegible] fibrillation, or progressive bradyarrhythmias [illegible] severe sinus bradycardia or second or third degree [illegible] block not responsive to atropine.

[illegible] of more than 10 mg of digoxin in previously [illegible] adults or 4 mg of digoxin in previously healthy children [illegible] ingestion causing steady-state serum concentrations [illegible] greater than 10 ng/mL, often results in cardiac arrest. [illegible]-induced progressive elevation of the serum potassium [illegible] concentration also suggests imminent cardiac arrest. [illegible] potassium concentration exceeds 5 mEq/L in the setting [illegible] of severe digitalis intoxication, therapy with [illegible]GIBIND is indicated.

[illegible]NTRAINDICATIONS

[illegible]re are no known contraindications to the use of [illegible]GIBIND.

[illegible]NINGS

[illegible] ingestion often involves more than one drug; thus, [illegible] from other drugs should not be overlooked.

[illegible]ld consider the possibility of anaphylactic, hypersensitivity, or febrile reactions. If an anaphylactoid reaction [illegible] 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 must be balanced against its potential risk in the setting of digitalis toxicity.

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

[illegible] testing for allergy was performed during the clinical [illegible]stration of DIGIBIND. Only one patient developed erythema at the site of skin testing, with no accompanying [illegible] reaction; this individual had no adverse reaction to [illegible] treatment with DIGIBIND. Since allergy testing may delay urgently needed therapy, it is not routinely required before treatment of life-threatening digitalis toxicity with DIGIBIND.

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

[illegible]luting 0.1 mL of reconstituted DIGIBIND (9.5 mg/mL) [illegible] to 9.9 mL sterile isotonic saline (1:100 dilution, 95 mcg/mL).

[illegible]jecting 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.

[illegible]cratch test procedure is performed by placing one drop of 1:100 dilution of DIGIBIND on the skin and then making a ¼-inch scratch through the drop with a sterile needle. The scratch site is inspected at 20 minutes for an urticarial wheal surrounded by erythema.

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

[illegible]CAUTIONS

[illegible]eral: Standard therapy for digitalis intoxication includes withdrawal of the drug and correction of factors that may contribute to toxicity, such as electrolyte disturbances, hypoxia, acid-base disturbances, and agents such as catecholamines. Also, treatment of arrhythmias may include