DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE**

NOV 9 2000

Tami T. Martin
Vice President
Shire Richwood Inc.
1550 East Gude Drive
Rockville, MD 20850

**RE: NDA #11-522**
Adderall (Mixed salts of a Single-Entity Amphetamine Product) Tablets
MACMIS #9153

Dear Ms. Martin:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a promotional campaign for Adderall (Mixed salts of a Single-Entity Amphetamine Product) Tablets that is misleading and in violation of the Federal Food, Drug, and Cosmetic Act. Specifically, Shire Richwood, Inc. (Shire) has an ongoing promotional campaign focused on comparative superiority claims to methylphenidate that are not substantiated by adequate and well-controlled comparative clinical trials (see for example, journal advertisement #ADD528-JA and sales aid #ADD518). Furthermore, it has come to DDMAC's attention that representatives of Shire are detailing and distributing homemade materials that promote Adderall for the off-label indication of depression.

DDMAC has the following objections to promotional claims for Adderall:

**Unsubstantiated Comparative Claims**

1. Shire's materials contain claims of superiority for Adderall over Ritalin that are not substantiated by adequate and well-controlled studies. Specific misleading claims in the sales aid and journal advertisement include, but are not limited to:

   "On average, Adderall is more effective than Ritalin."
   "Adderall was favored 3 to 1 over Ritalin by clinical staff."
   "Ritalin patients were rated more deviant than Adderall"
   "Adderall showed greater efficacy than Ritalin at midday..."

"Shorter duration of action was noted for methyphenidate..."
"Adderall showed better scores than methylphenidate [for inattentive and hyperactive symptoms]"
"Adderall was superior to MPH ... on CGI-improvement"

Shire references two studies to support these claims: Pelham *et al.,* 1999 (*Pediatrics* Vol. 103 (4): e43) and Pliszka *et al.* (*J. Am. Acad. Child Adolesc. Psychiatry* 39(5): 619-626, 2000). Pelham *et al.,* 1999, is a small pilot study (n=25) that did not use an effective dose range of Ritalin. In addition, the study outcomes demonstrated that, at the lower doses used, there was comparability of Adderall and Ritalin, rather than superiority of Adderall over Ritalin. Furthermore, the study was conducted in an intensive behavioral modification environment that the authors believe may have "differentially influenced dose-response functions" of Adderall versus Ritalin. Pliszka *et al.* (2000) is not adequate because, as the authors point out, the adequacy of the dose of methylphenidate in question.

2. Claims that state or imply that "once-a-day dosing with Adderall is comparable to twice-a-day dosing with methylphenidate" (see sales aid) are misleading because they are not supported by studies that are adequately designed to examine safety or effectiveness in a comparative manner. For example, Swanson *et al.* (Journal of the American Academy of Child & Adolescent Psychiatry Vol. 37(5): 519-526, 1998) was a small study (n=30) that used only one dose of methylphenidate rather than examining a complete dose-response of the drugs being compared. Furthermore, Manos *et al.* (Journal of the American Academy of Child & Adolescent Psychiatry Vol. 38(7): 813-819, 1999) was a small study (n=42) that was neither randomized nor properly blinded (i.e., subjects and their parents were blind to dose, but not to medication).

3. The claim or implication that Adderall is a longer-acting medication than methylphenidate or other ADHD medications is misleading because there are many ADHD medications, including sustained release methylphenidate, that are designed to be long-acting. For example, the claim that "Adderall should be considered for ADHD children when a longer-acting medication is desired" (see sales aid) is misleading.

4. In the sales aid, the claim that "37% of the Adderall sample-responders previously failed treatment with MPH" is misleading because it implies that Adderall has been shown to be effective in treating methylphenidate-resistant patients. However, the study (Manos *et al.*, 1999) cited to support this claim

was not adequately powered or designed to demonstrate that Adderall is effective in patients who previously failed treatment with methylphenidate (also see comment #2). Specifically, in the Manos study, a small subset of the patients receiving Adderall (n=15/42) were identified as having discontinued methylphenidate due to failure to respond or due negative side effects. Two of the seven "resistant" patients also were non-responders in to Adderall. Outcomes regarding negative side effects in the subgroup were not specifically identified.

**Fair Balance**

The journal advertisement #ADD528-JA is lacking in fair balance because the presentation of risk information is not reasonably comparable to the information relating to the effectiveness of Adderall. Specifically, the risk information is presented in small font as a paragraph on the bottom of the page while the effectiveness claims are bolded and bulleted in the center of the page. Furthermore, both the sales aid and the journal ad fail to provide sufficient emphasis of the warnings and contraindications.

**Unapproved Uses**

DDMAC has become aware of a homemade fact sheet, distributed by Shire sales representative(s), which depicts a pie chart of 1999[ ]prescriptions indicating that Adderall has been used to treat ADHD (96%), depression (2%), narcolepsy (1%), and other disorders (2%). Adderall is indicated for the treatment of attention deficit disorder with hyperactivity (ADHD) and narcolepsy. It is not indicated for the treatment of depression. Accordingly, homemade materials and detailing that imply that Adderall is useful in the treatment of depression or disorders other than ADHD and narcolepsy are violative.

To address these objections, DDMAC recommends that Shire do the following:

1. Immediately discontinue materials and promotional activities that have the same or similar issues detailed in this letter.

2. Instruct Shire's representatives to stop promoting Adderall for the treatment of depression or any other off-label indication, and to stop the use of any "homemade" materials.

3. Respond to this letter, in writing, by November 22, 2000. Shire's response should include a statement of its intent to comply with the above, a list of all promotional materials with the same or similar issues, and Shire's methods for discontinuing these promotional materials. Shire's response should also include its methods for investigating violative behavior among its representatives and the steps that have been taken to ensure that this behavior has ceased.

If you have any questions or comments, please contact Dr. Lisa L. Stockbridge by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 9153 in addition to the NDA number.

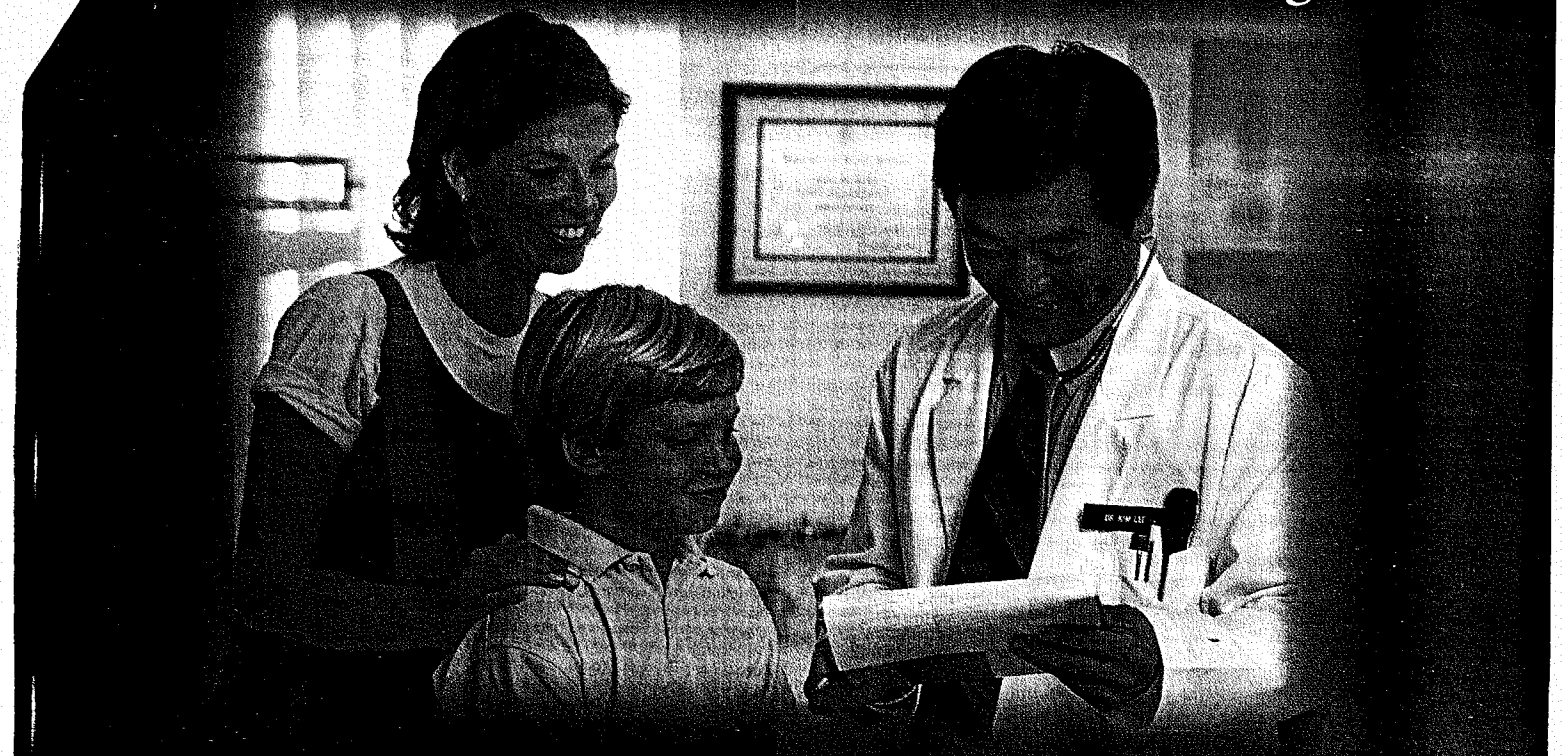
Sincerely,

/S/

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

# SALES AD

# methylphenidate (MPH) seems to be "working fine"...

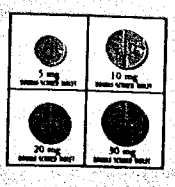


# Why make the switch to ADDERALL®?

- On average, ADDERALL is more effective than Ritalin® ($p<0.001$)[1]
- ADDERALL was favored 3 to 1 over Ritalin by clinical staff for continued medication[1]
- Ritalin patients were rated more deviant than ADDERALL, particularly on lower doses[1]
- ADDERALL scored better than MPH on Clinical Global Impression (CGI) improvement ($p<0.05$)[2]
- There were significantly more responders in the ADDERALL group than the MPH group ($p<0.01$)[2]
- ADDERALL showed better scores than MPH for both inattention and hyperactivity ($p<0.05$)[2]
- Clinical staff clearly preferred ADDERALL over MPH for continuation of treatment[3]
- ADDERALL is dispensed for more ADHD patients than Ritalin[4]
- ADDERALL is safe—low incidence of spontaneously reported adverse events[5]

ADDERALL is generally well tolerated—adverse reactions have seldom been reported (most frequently reported adverse reactions include anorexia, insomnia, stomach pain, headache, irritability, and weight loss). As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exist with ADDERALL treatment and, in rare cases, exacerbations of psychosis have been reported. Since amphetamines may have a high potential for abuse, ADDERALL should only be prescribed as part of an overall multimodal treatment program for ADHD with close physician supervision.





**ADDERALL® XR**

**5 mg, 10 mg, 20 mg & 30 mg TABLETS**
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate, Amphetamine Sulfate
Dextroamphetamine Saccharate, Amphetamine Aspartate

ADD528-JA

*Please see references and brief prescribing information on adjacent page.*



Shire

# JOURNAL AD

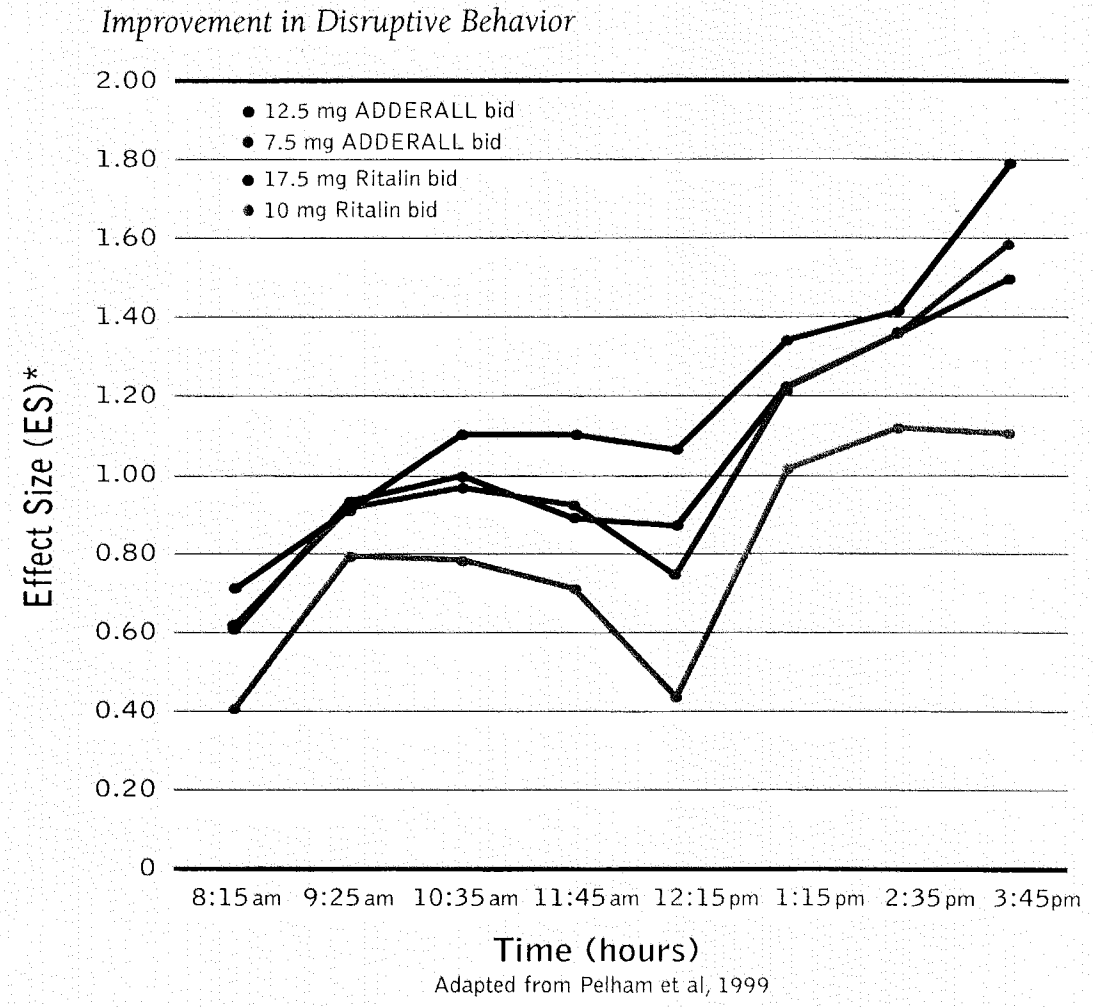
# *By definition,* ADDERALL®

should be your ADHD product of choice

*this back-to-school season...*

# *Achieve well-documented efficacy*[1-3]*— Start this school year with ADDERALL®*

## Staff clinical recommendations for continued medication ***favored ADDERALL 3 to 1*** as compared to Ritalin®[1]




Adapted from Pelham et al, 1999

- **ON AVERAGE, ADDERALL WAS MORE EFFECTIVE THAN RITALIN ($P<0.001$)**[1]
- **ADDERALL** should be considered for ADHD children when a longer-acting medication is desired[1]

*Effect size is a combined overall measure of disruptive behavior that includes recreational and classroom activities. Effect size measures change for each medication relative to placebo. Because the means were expected to decrease with treatment, a positive effect size indicates a beneficial response to treatment.



*Please see references and full prescribing information on inside back page.*

## *Pelham et al, on ADDERALL efficacy[1]:*

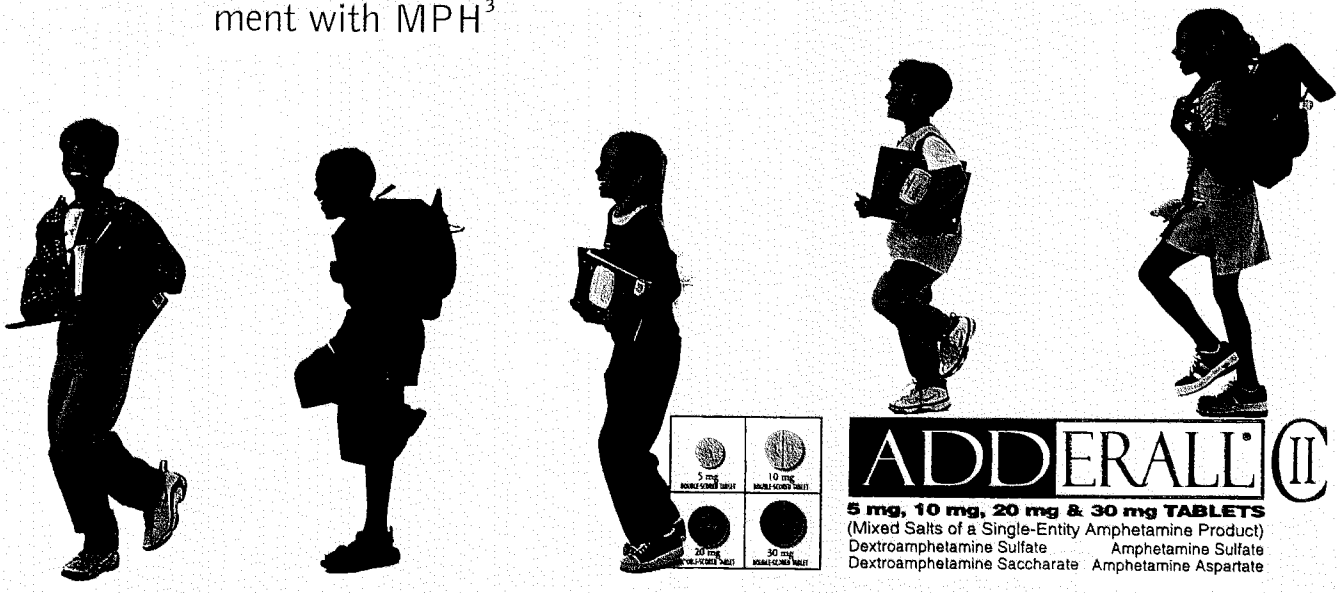
- On average, **ADDERALL** was more effective than Ritalin ($P<0.001$)[1]
- **ADDERALL** showed greater efficacy than Ritalin at midday and at day's end across numerous behavioral measures in both recreational and classroom activities[1]

## *Pliszka et al, on ADDERALL efficacy[2]:*

- Both medications were superior to placebo at reducing inattentive and hyperactive symptoms[2]
- **ADDERALL** showed better scores than methylphenidate (MPH) for both measures ($P<0.05$)[2]
- Clinical Global Impression (CGI)-improvement and index indicated both medications were greatly superior to placebo[2]
- **ADDERALL** was superior to MPH ($P<0.05$) on CGI-improvement[2]

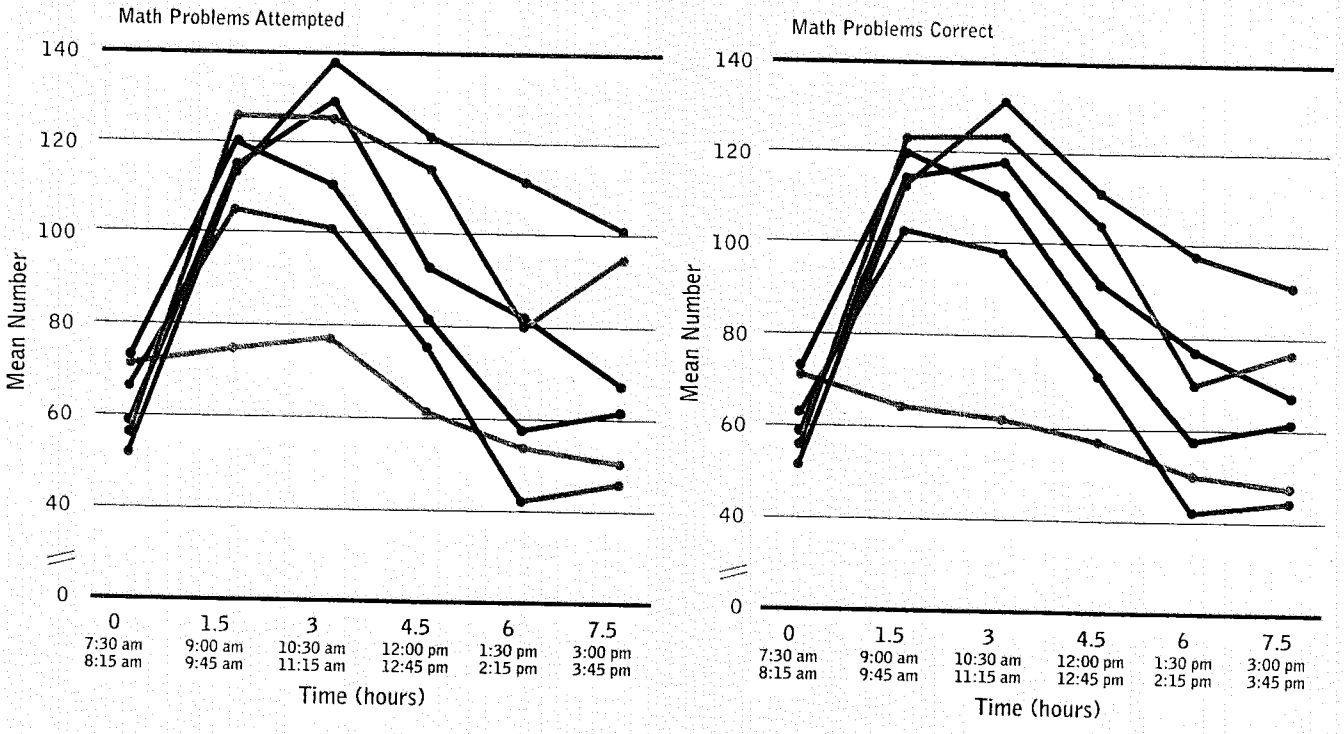
## *Manos et al, on ADDERALL efficacy[3]:*

- Single-dose treatments of **ADDERALL** appear to be as effective as twice-daily dosing of MPH, which increases the possibility of avoiding in-school dosing[3]
- 37% of the **ADDERALL** sample-responders previously failed treatment with MPH[3]



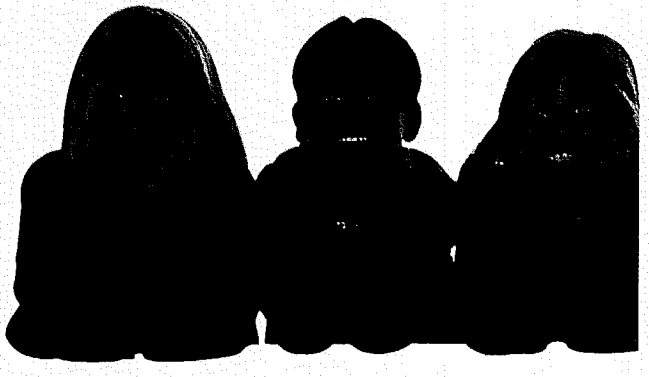
# *Achieve long duration of action[1,3,4]— Start this school year with ADDERALL®*

**ADDERALL** produced a statistically significant, dose-related increase in objective measures of behavior compared to placebo* ($P<.0001$)[4]




- The duration of action of a single dose of **ADDERALL** is up to twice as long as that of a single dose of Ritalin, depending on the dose administered[1]

*Age-appropriate math problems attempted and math problems correct.



ADDERALL is a registered trademark of Shire Richwood Inc.
Ritalin is a registered trademark of Novartis Pharmaceuticals Corp.

*Please see references and full prescribing information on inside back page.*

## *Swanson et al on ADDERALL duration of action[4]:*

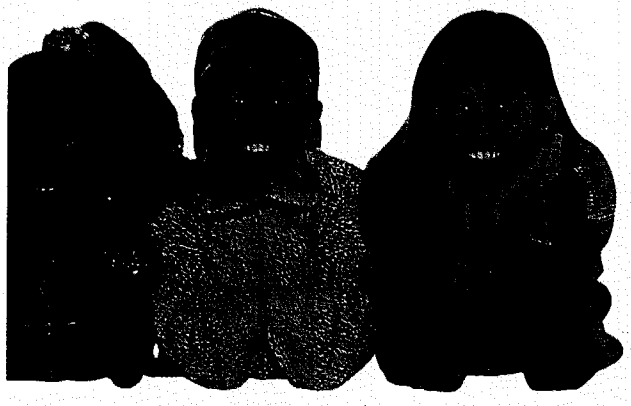
- Duration of action increased with dose of ADDERALL[4]

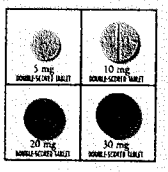
## *Pelham et al on ADDERALL duration of action[1]:*

- Shorter duration of action was noted for the methylphenidate (MPH) condition than for most of the **ADDERALL** conditions[1]

## *Manos et al on ADDERALL duration of action[3]:*

- Once-a-day dosing with **ADDERALL** was comparable to twice-a-day dosing with methylphenidate in reducing behavioral symptoms during the school day[3]
- Single-dose treatments of **ADDERALL** (average 10.6 mg per day) appear to be as effective as twice-daily dosing of MPH (average 19.5 mg per day)[3]
- Both parent and teacher ratings reported less symptomatic behavior during the "best dose week" than the placebo week—with no differences emerging between **ADDERALL** and MPH[3]






ADDERALL® XR

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(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

# *Avoid in-school dosing—*[1,3,4,5] *Start this school year with ADDERALL®*

| *Study* | *Potential to avoid in-school dosing* |
|---|---|
| Swanson et al[4] | ADDERALL has a longer half-life than Ritalin, which may enable a single dose to cover most of a child's school day, a goal of long-acting stimulants[4] |
| Greevich et al[5] | Compared to ADDERALL, children initially treated with methylphenidate (MPH) are more likely to require in-school dosing[5] |
| Pelham et al[1] | ADDERALL produced consistently strong effects at all time points evaluated—especially midday and late afternoon/evening[1] |
| Manos et al[3] | Single-dose treatments of ADDERALL (average 10.6 mg per day) appear to be as effective as twice-daily dosing of MPH (average 19.5 mg per day) which increases the possibility of avoiding in-school dosing[3] |

- **ADDERALL** may provide the ability to manage the medical regimen of a child outside the parameters of the school—which appears to be quite beneficial to the child in terms of privacy and to the school in terms of time savings[3]

- Given that low total lifetime dose is a goal with psychoactive medications, routinely reducing or possibly eliminating the midday dose of stimulants with a product like **ADDERALL** may be a beneficial strategy for ADHD children[1]

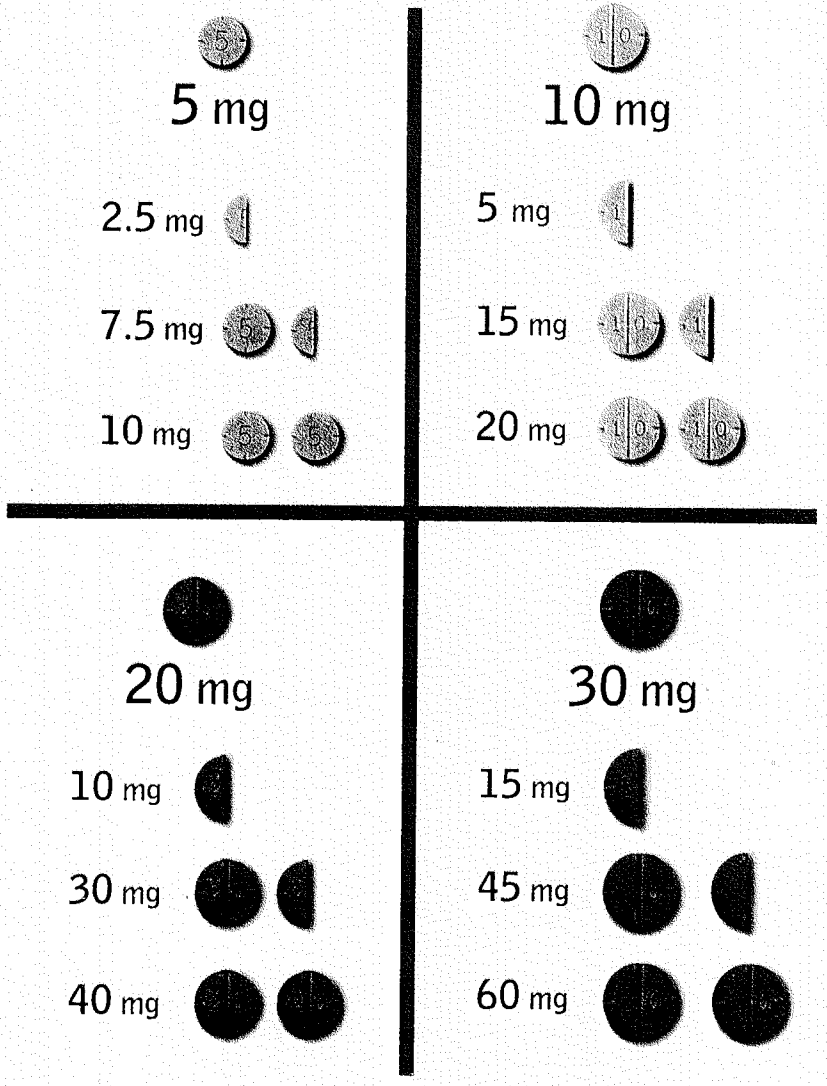
ADDERALL is a registered trademark of Shire Richwood Inc.
Ritalin is a registered trademark of Novartis Pharmaceuticals Corp.

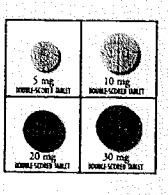
*Please see references and full prescribing information on inside back page.*

# *Choose convenience—*
# *Start this school year with ADDERALL*

It's easy to find the ADDERALL dose that may help improve behavior and academic performance without the need for an in-school dose

*ADDERALL **double-scored** tablets offer **easy titration**—*
*achieve precise, individualized dosage with a single prescription*



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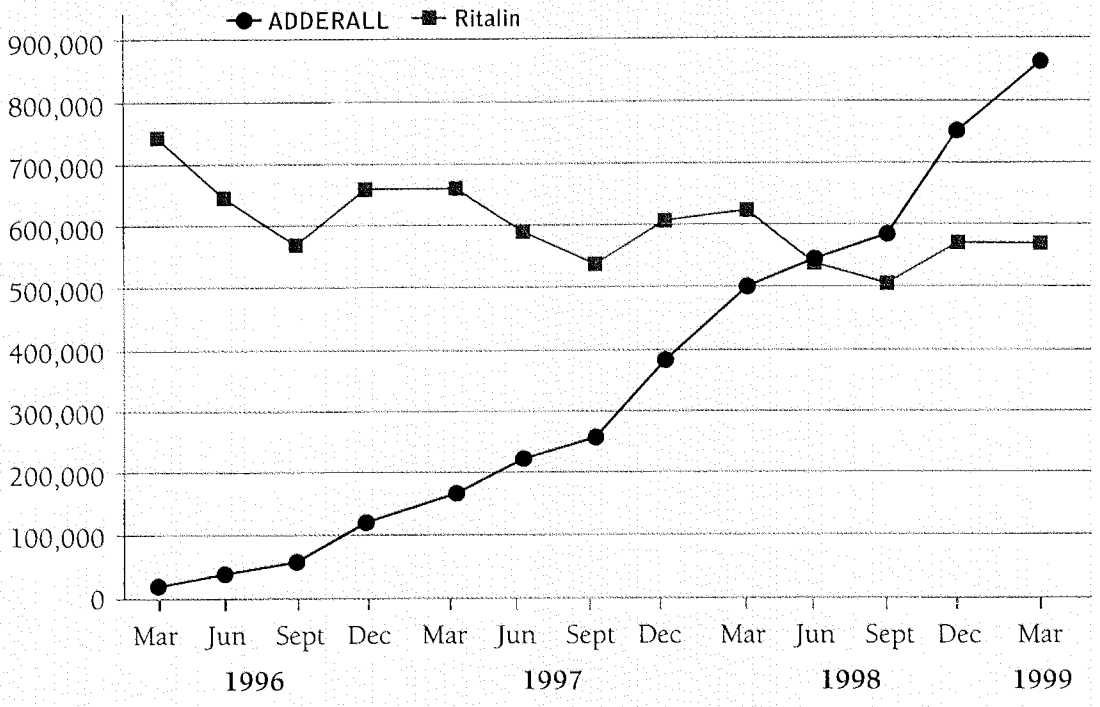
# *Acknowledge preference—Start this school year with ADDERALL®*

ADDERALL, the fastest-growing ADHD product, is now dispensed for more ADHD patients than Ritalin[6]

*Total prescriptions by quarter for ADDERALL vs Ritalin—1996 through March 1999[6]*




Staff clinical recommendations for continued medication favored ADDERALL 3 to 1 as compared to Ritalin[1]

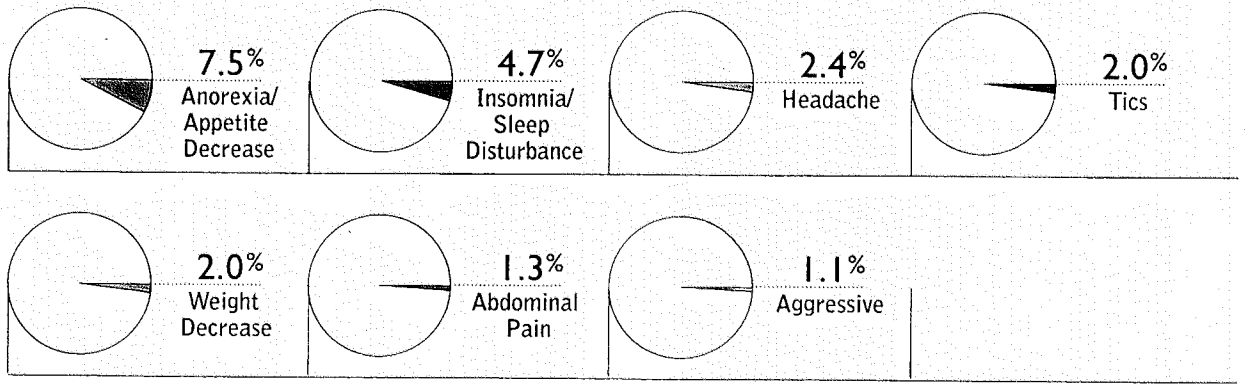
Compared to ADDERALL, children initially treated with methylphenidate are more likely to have their medication changed within the first 6 months ($P<0.001$)[5]

ADDERALL is a registered trademark of Shire Richwood Inc.
Ritalin is a registered trademark of Novartis Pharmaceuticals Corp.

*Please see references and full prescribing information on inside back page.*

# *Achieve efficacy[1-3] and duration of action[1,3,4] without compromising safety—Start this school year with ADDERALL*

*Open Safety Investigation of ADDERALL in Eligible Patients With ADHD: Most frequently reported adverse events (n=611) (>1%)[7*]*

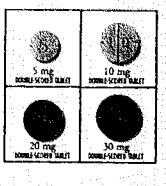



—Usage data were collected from 611 children, 3-12 years of age[7*]
—The children had at least three office visits during the 1-year usage period[7*]

*Thirty-four patients receiving greater than 40 mg were excluded from this analysis.

The ADDERALL risk profile demonstrated a very low incidence of spontaneously reported adverse events following more than 2.3 million prescriptions in 1998[8]

| *Study* | *Side effect findings[1-4]* |
|---|---|
| Manos et al[3] | No significant or main interaction effects for dosage level, medication type, or dosage level by medication type interaction were noted[3] |
| Pelham et al[5] | Both drugs produced low and comparable levels of clinically significant side effects |
| Swanson et al[4] | No serious or unusual side effects were noted—measures of side effects were no more frequent or severe in most medication conditions than in the placebo condition[4] |
| Tuszka et al[6] | Side effects were no different from placebo |



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*Safety/Preference*

**ADDERALL®** is generally well tolerated—adverse reactions have seldom been reported (most frequently reported adverse reactions include anorexia, insomnia, stomach pain, headache, irritability, and weight loss).

As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exists with **ADDERALL** treatment and, in rare cases, exacerbations of psychosis have been reported.

Since amphetamines have a high potential for abuse, **ADDERALL** should only be prescribed as part of an overall multimodal treatment program for ADHD with close physician supervision.

*References/PI*

**References:** 1. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics* [serial online]. 1999;103:e43. 2. Pliszka S, Browne RG, Wynne SK, et al. Comparing Adderall and methylphenidate in ADHD. APA Annual Meeting, May 15-20, 1999, Washington DC. Abstract. 3. Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall® in school-age youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 1999;38:7. In press. 4. Swanson J, Wigal S, Greenhill L, et al. Analog classroom assessment of Adderall® in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 1998;37(5):519-525. 5. Grcevich S, Rowane WA, Marcellino B, et al. Assessing the clinical practice of prescribing Adderall vs. methylphenidate to children with attention-deficit hyperactivity disorder. APA Annual Meeting, May 15-20, 1999. Washington DC. Abstract. 6. IMS, National Prescription Audit, January 1996-January 1999. 7. Data on file, Shire Richwood Inc. Analysis of open-label data collected from March 1995 through February 1996. 8. Data on file, Shire Richwood Inc.

*Please see references above and full prescribing information on inside back page.*

# ADDERALL® TABLETS

**Rx ONLY**

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:** A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate.

**CLINICAL PHARMACOLOGY:** Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

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

**INDICATIONS: Attention Deficit Disorder with Hyperactivity:** Adderall is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with 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.

In **Narcolepsy**

**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).

**WARNINGS:** Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

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

**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 one time in order to minimize the possibility of overdosage.

**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.

**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 receptors, 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 receptors, thus inhibiting the central stimulant effects of amphetamines.

*Lithium carbonate* -

The anorectic and 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 amphetamine, have not been performed.

**Pregnancy - Teratogenic Effects:** Pregnancy Category C. Amphetamine 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 one 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. Amphetamines 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.

**Pediatric Use:** Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

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.

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/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 when amphetamines are used for other than the anorectic effect.

**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.

**Symptoms:** Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.

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 (Regitine®, Novartis) 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.

**DOSAGE AND ADMINISTRATION:** Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

**Attention Deficit Disorder with Hyperactivity:** Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 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 exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

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

**Narcolepsy:** Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

**HOW SUPPLIED:**

ADDERALL® 5 mg: Blue double-scored tablet, debossed "AD" on one side and "5" on the other side (NDC 58521-031-01)
ADDERALL® 10 mg: Blue double-scored tablet, debossed "AD" on one side and "10" on the other side (NDC 58521-032-01)
ADDERALL® 20 mg: Orange double-scored tablet, debossed "AD" on one side and "20" on the other side (NDC 58521-033-01)
ADDERALL® 30 mg: Orange double-scored tablet, debossed "AD" on one side and "30" on the other side (NDC 58521-034-01)

In bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

MG #10185

Revised: July 1998

**Shire Richwood Inc.**

Florence, KY 41042
1-800-536-7878

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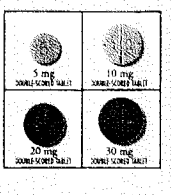



ADDERALL® II

**5 mg, 10 mg, 20 mg & 30 mg TABLETS**

(Mixed Salts of a Single-Entity Amphetamine Product)

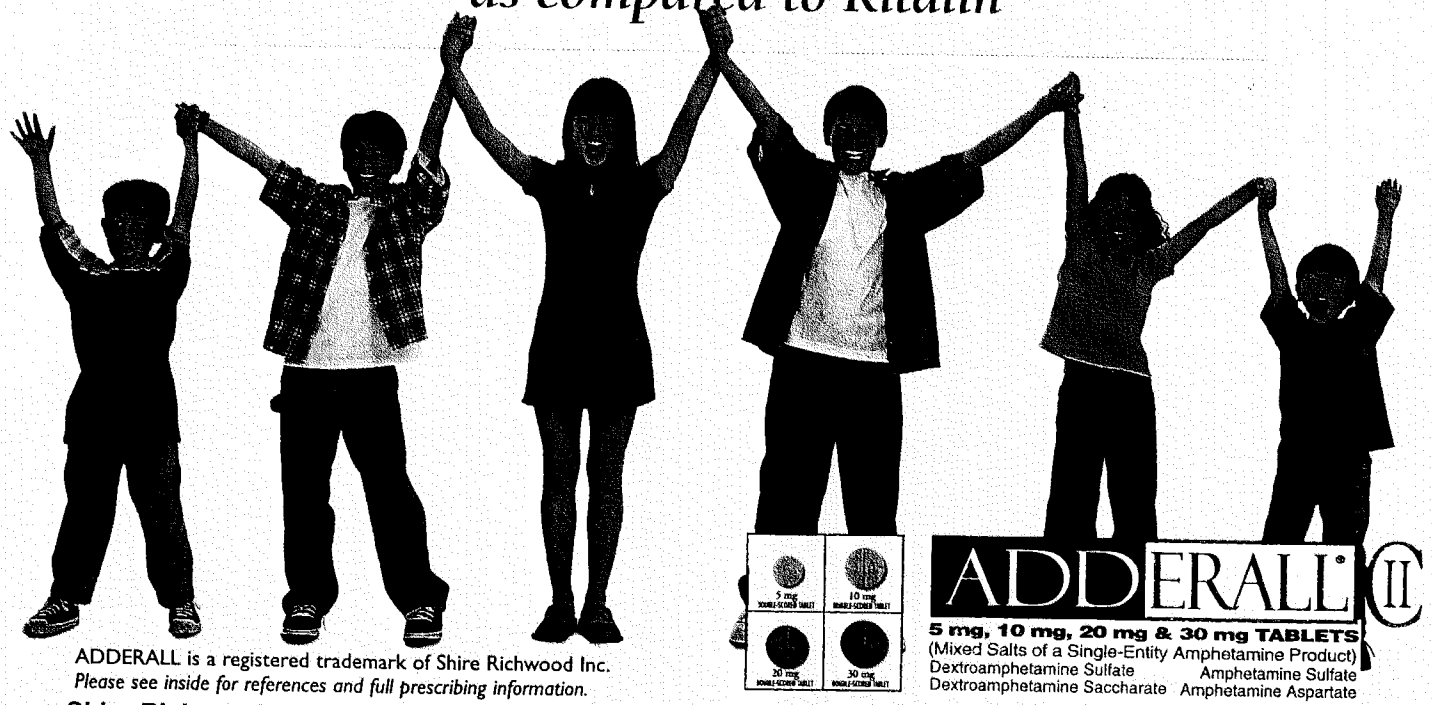
Dextroamphetamine Sulfate — Amphetamine Sulfate
Dextroamphetamine Saccharate — Amphetamine Aspartate

References/PI

# *By definition, ADDERALL® should be your ADHD product of choice this back-to-school season:*

- **ADDERALL** provides well-documented efficacy[1-3]
- **ADDERALL** was superior to MPH on CGI-improvement ($P<0.05$)[2]
- Duration of action increases with dose of **ADDERALL**[4]
- Compared to **ADDERALL**, children initially treated with MPH are more likely to require in-school dosing[5]
- **ADDERALL** is safe—low incidence of spontaneously reported adverse events[1-4,8]

## *Staff clinical recommendations for continued medication **favored ADDERALL 3 to 1** as compared to Ritalin[1]*

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*Please see inside for references and full prescribing information.*

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