PRODUCT MONOGRAPH

◇C ACT AMPHETAMINE XR

Mixed Salts Amphetamine Extended-Release Capsules

5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg

Central Nervous System Stimulant

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ACTION AND CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of mixed salts amphetamine extended-release capsules have been conducted in healthy adult and pediatric (aged 6-12 years) subjects, and adolescent (aged 13-17 years) and pediatric patients with ADHD. Mixed salts amphetamine extended-release capsules contain dextroamphetamine (*d*-amphetamine) and levoamphetamine (*l*-amphetamine) salts in the ratio of 3:1.

Mixed salts amphetamine extended-release capsules demonstrate linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents aged 13 to 17 years weighing greater than 75 kg/165 lbs, over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs and 5 to 30 mg in children aged 6 to 12 years. There was no unexpected accumulation at steady state.

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of mixed salts amphetamine extended-release capsules in pediatric (aged 6-12 years) and adolescent (aged 13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of *d*-and *l*-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_{∞}) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

<u>Pharmacokinetic Results in Healthy Adult and Pediatric Subjects</u>

Following oral administration of a single dose of mixed salts amphetamine extended-release capsules in healthy adult subjects, peak plasma concentrations (C_{max}) of 28.1 ng/mL and 8.7 ng/mL occurred in about 7 hours for *d*-amphetamine and 8 hours for *l*-amphetamine, respectively. The $AUC_{0\text{-inf}}$ for *d*-amphetamine and *l*-amphetamine were 567ng.hr/mL and 203ng.hr/mL, respectively.

The mean elimination half-life is 1 hour shorter for *d*-amphetamine and 2 hours shorter for *l*-amphetamine in children aged 6 to 12 years compared to that in adults ($t_{1/2}$ is 10 hours for *d*-

amphetamine and 13 hours for *l*-amphetamine in adults, and 9 hours and 11 hours, respectively, for children). Children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of mixed salts amphetamine extended-release capsules, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Pharmacokinetic Results in Children and Adolescents with ADHD

In a 20 mg single dose study in 51 children (aged 6-12 years) with ADHD, the mean T_{max} for *d*-amphetamine was 6.8 hours and the mean C_{max} was 48.8 ng/mL. The corresponding mean T_{max} and C_{max} values for *l*-amphetamine were 6.9 hours and 14.8 ng/mL, respectively. The mean elimination half-life for *d*-amphetamine and *l*-amphetamine was 9.5 and 10.9 hours, respectively. Following dosing of children with ADHD to steady state with mixed salts amphetamine extended-release capsules 10, 20 and 30 mg, the mean *d*-amphetamine C_{max} (ng/mL) in plasma for mixed salts amphetamine extended-release capsules was 28.8 (10 mg), 54.6 (20 mg) and 89.0 (30 mg). For *l*-amphetamine, the mean C_{max} values for the three mixed salts amphetamine extended-release capsules doses were 8.8, 17.2 and 28.1 ng/mL, respectively.

In adolescents aged 13-17 years and weighing less than or equal to 75 kg/165 lbs, the mean elimination half-life for *d*-amphetamine is 11 hours, and 13-14 hours for *l*-amphetamine**.**

Metabolism

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

Excretion

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been

reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased (see **PRECAUTIONS – Drug Interactions**).

Food Effect Study in Healthy Adult Subjects

A single-dose study compared the relative bioavailability of *d*-amphetamine and *l*-amphetamine following administration of a single 30 mg dose of mixed salts amphetamine extended-release capsules fasted, fed (high-fat meal) and sprinkled on food (otherwise fasted) in 21 healthy adult subjects. Food does not affect the extent of absorption of mixed salts amphetamine extended-release capsules, but prolongs T_{max} by 2.5 hours (from 5.2 hours at fasted state to 7.7 hours after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted states.

Renal Impairment

In a pharmacokinetic study of lisdexamfetamine in subjects with normal and impaired renal function, *d*-amphetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2). *D*-amphetamine is not dialyzable. (see **Precautions, Patients with Renal Impairment; Dosage and Administration**).

Clinical Trials

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Fasting Study Title: A Relative Bioavailability Study of Mixed Amphetamine Salts 30 mg Extended-Release Capsules versus ADDERALL XR 30 mg Capsules under Fasted Conditions.

This study assessed the relative bioavailability of ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules) compared to that of ADDERALL XR capsules following a single oral dose (1 x 30 mg XR capsule) in healthy adult subjects when administered under fasted conditions. This was a partial-blind, single-dose, randomized, 2-period, 2-treatment crossover study under fasted conditions.

d-amphetamine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	762.00 773.72 (19.07)	781.31 800.20 (23.91)	97.53	93.65 - 101.56
AUC_I (ng·h/mL)	782.35 794.60 (19.31)	804.01 825.13 (25.16)	97.31	93.30 - 101.48
C_{max} (ng/mL)	41.21 41.71 (16.34)	45.38 46.23 (20.04)	90.82	86.54 - 95.30

d-amphetamine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
T_{max}§ (h)	5.50 (4.00-8.00)	4.50 (3.00-12.00)		
$T_{½}$€ (h)	10.83 (13.85)	10.77 (17.75)		

* ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules)

† Adderall XR Capsules, 30 mg (Shire Canada Inc); purchased in Canada.

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

l-amphetamine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	326.25 333.21 (22.78)	338.57 349.28 (27.70)	96.36	92.40 - 100.49
AUC_I (ng·h/mL)	344.52 352.58 (23.95)	358.21 372.66 (31.90)	96.18	91.84 - 100.72
C_{max} (ng/mL)	15.56 15.76 (16.82)	17.13 17.43 (19.53)	90.87	87.14 - 94.76
T_{max}§ (h)	5.50 (4.00-9.00)	5.00 (2.50-16.00)		
$T_{½}$€ (h)	13.45 (19.93)	13.36 (24.52)		

* ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules)

† Adderall XR Capsules, 30 mg (Shire Canada Inc); purchased in Canada.

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

Fed Study Title: A Relative Bioavailability Study of Mixed Amphetamine Salts 30 mg Extended-Release Capsules versus ADDERALL XR 30 mg Capsules under Fed Conditions.

This study assessed the relative bioavailability of ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules) compared to that of ADDERALL XR capsules following a single oral dose (1 x 30 mg XR capsule) in healthy adult subjects when administered under fed conditions. This was a partial-blind, single-dose, randomized, 2-period, 2-treatment crossover study under fed conditions.

d-amphetamine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T‡ (ng·h/mL)	718.38 726.46 (15.17)	754.19 764.07 (15.89)	95.25	91.89 - 98.74
AUC_I (ng·h/mL)	738.32 746.84 (15.36)	775.11 785.71 (16.22)	95.25	91.72 - 98.92
C_{max} (ng/mL)	35.63 35.94 (13.11)	37.22 38.20 (22.84)	95.73	90.92 - 100.80
T_{max}§ (h)	7.50 (5.00-9.00)	7.00 (4.50-12.00)		
$T_{½}$€ (h)	10.57 (13.76)	10.24 (13.12)		

* ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules)
† Adderall XR Capsules, 30 mg (Shire Canada Inc) ; purchased in Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV%)

l-amphetamine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	300.91 304.75 (16.11)	318.17 322.74 (16.76)	94.57	90.81 - 98.49
AUC_I (ng·h/mL)	317.16 321.67 (16.90)	334.62 340.05 (17.82)	94.78	90.70 - 99.04
C_{max} (ng/mL)	13.44 13.54 (12.53)	14.13 14.46 (21.43)	95.13	90.44 - 100.07
T_{max}§ (h)	7.75 (5.00-9.00)	7.25 (5.05-16.00)		
$T_{½}$€ (h)	12.97 (19.48)	12.43 (15.93)		

*ACT Amphetamine XR, 30 mg (mixed salts amphetamine extended-release capsules)
† Adderall XR Capsules, 30 mg (Shire Canada Inc); purchased in Canada.
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV%)

Children

A double-blind, randomized, placebo-controlled, parallel-group study of 584 children aged 6 to 12 years who met DSM-IV® criteria for ADHD (either combined type or hyperactive-impulsive type) was conducted in a naturalistic setting. Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg/day of mixed salts amphetamine extended-release capsules or placebo. Mixed salts amphetamine extended-release capsules or placebo was taken once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher and parent ratings of attention and hyperactivity, were observed for all mixed salts amphetamine extended-release capsules doses compared to patients who received placebo,

for all three weeks, including the first week of treatment, when all mixed salts amphetamine extended-release capsules subjects were receiving a titration dose of 10 mg/day. Patients who received mixed salts amphetamine extended-release capsules showed behavioral improvements within the first week of treatment ($p<0.001$) and in both morning ($p<0.001$) and afternoon ($p<0.001$) compared to patients on placebo.

A double-blind, randomized, placebo- and active-controlled crossover study of 51 children aged 6 to 12 years with ADHD was conducted in a classroom laboratory setting. In comparison to placebo, mixed salts amphetamine extended-release capsules 10, 20, and 30 mg/day showed rapid improvement and continued significant efficacy ($p<0.05$) up to 12 hours post-dose for all cognitive and behavioral measures.

In these two clinical trials conducted in different settings, mixed salts amphetamine extended-release capsules taken once in the morning demonstrated efficacy in the treatment of ADHD (either combined type or hyperactive-impulsive type) for at least 12 hours.

Adolescents
A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 years (n=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤75kg/165lbs) was randomized to fixed dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg mixed salts amphetamine extended-release capsules or placebo once daily in the morning; patients randomized to doses greater than 10mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75kg/165lbs who were randomized to fixed dose treatment groups receiving final doses of 50 mg and 60 mg mixed salts amphetamine extended-release capsules or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the ADHD-RS-IV total scores for the primary cohort. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (mixed salts amphetamine extended-release capsules 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. Mixed salts amphetamine extended-release capsules at doses of 10-40 mg is effective in the treatment of ADHD in adolescents weighing ≤75kg/165lbs. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adults
A double-blind, randomized, placebo-controlled, parallel-group study of 255 adults who met DSM-IV® criteria for ADHD was conducted. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40 or 60 mg/day of mixed salts amphetamine extended-release capsules or placebo. Mixed salts amphetamine extended-release capsules or placebo was taken once daily in the morning for four weeks. Significant improvements in patient symptoms of inattention and impulsivity/hyperactivity, based upon the 18-item total ADHD symptom score, were observed at endpoint for all mixed salts amphetamine extended-release capsules doses compared to patients who received placebo for all four weeks ($p<0.001$). There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

A long-term, open-label extension of the above-mentioned clinical study was conducted in 223 adult patients. At 12 months, all patients showed continuing symptomatic improvement as measured by the 18-item total ADHD symptom score.

INDICATIONS AND CLINICAL USE

ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

A diagnosis of ADHD (DSM-IV®) implies the presence of hyperactive-impulsive and/or inattentive symptoms that caused impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment (e.g. in social, academic, or occupational functioning), and must be present in two or more settings (e.g. school or work, and at home). The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, "on the go", excessive talking, blurting answers, can't wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program

ACT Amphetamine XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in patients with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of mixed salts amphetamine extended-release capsules for long-term use, i.e., for more than 3 weeks in children aged 6 to 12 years and 4 weeks in adolescents aged 13 to 17 years, and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ACT Amphetamine XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **Dosage and Administration**).

CONTRAINDICATIONS

ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) administration is contraindicated in patients with the following conditions:

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Hyperthyroidism
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Glaucoma
- Agitated states
- History of drug abuse
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result; see **Precautions, Drug Interactions**)
- Allergy to amphetamines or to components of ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) or its container.

WARNINGS

Misuse and Serious Cardiovascular Adverse Events

Amphetamines have a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses that physicians should consider when prescribing this product (see **Precautions, Dependence Liability)**.

The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems and Sudden Death

Children / Adolescents: Sudden death has been reported with sympathomimetic drugs used for ADHD treatment at therapeutic doses in children/adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) generally should not be used in children / adolescents with known serious structural cardiac abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs (see **Contraindications**).

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see **Contraindications**).

Hypertension and other Cardiovascular Conditions
Sympathomimetic medications can cause a modest increase in average blood pressure and average heart rate and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia (see **Warnings**; **Contraindications**). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ACT Amphetamine XR (mixed salts amphetamine extended-release capsules), especially patients with hypertension.

General
Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other sympathomimetic drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Long-Term Suppression of Growth
In a controlled trial of mixed salts amphetamine extended-release capsules in adolescents aged 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was –1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg mixed salts amphetamine extended-release capsules. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

Published data for other stimulants report that in children aged 7-10 years, there is a temporary slowing in growth rate without evidence of growth rebound on treatment. Data are inadequate to determine whether the chronic use of amphetamines, in children may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Pre-existing Psychosis
Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Screening Patients for Bipolar Disorder
Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive

symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children / adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression
Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behavior. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behavior, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behavior should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Seizures
There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment (see **Contraindications**).

PRECAUTIONS

General
The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) should be used with caution in patients who use other sympathomimetic drugs.

Tics
Amphetamines have been reported to exacerbate motor and phonic tics in Tourette's syndrome. Therefore, careful clinical evaluation for tics in Tourette's syndrome in children and their families should precede use of stimulant medications. Mixed salts amphetamine extended-release capsules have been associated with new onset of tics (not necessarily associated with Tourette's syndrome).

Raynaud's Phenomenon
Although rare, a number of instances of a condition resembling Raynaud's phenomenon have been reported. Caution should therefore be observed if patients with Raynaud's disease or thromboangiitis obliterans are to be treated with ACT Amphetamine XR.

Pregnancy / Teratogenic Effect
Amphetamine, in the enantiomer ratio present in ACT Amphetamine XR (*d*- to *l*- ratio of 3:1), had no apparent effect on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50 mg/kg/day (approximately 6 times the maximum recommended human dose of 30 mg/day on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d,l*-), at doses similar to those used clinically in children, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies with mixed salts amphetamine extended-release capsules 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 *d*-amphetamine sulfate with lovastatin during the first trimester of pregnancy.

Pregnancy / Non-teratogenic 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.

Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Use in Geriatrics
Mixed salts amphetamine extended-release capsules have not been studied in the geriatric population.

Use in Pediatrics
ACT Amphetamine XR is indicated for use in children 6 years of age and older. The long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children with ADHD under 6 years of age.

Patients with Renal Impairment
Due to reduced clearance of *d*-amphetamine in patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73 m^2), observed in a study with lisdexamfetamine, the maximum dose of ACT Amphetamine XR should not exceed 20 mg/day. Further dosage reduction should be considered in patients undergoing dialysis, as *d*-amphetamine is not dialyzable. (see **Action and Clinical Pharmacology; Dosage and Administration).**

Carcinogenesis / Mutagenesis and Impairment of Fertility
No evidence of carcinogenicity was found in studies in which *d,l*-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis.

Amphetamine, in the enantiomer ratio present in mixed salts amphetamine extended-release capsules (*d*- to *l*- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test in vitro. *d,l*-amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in mixed salts amphetamine extended-release capsules (*d*- to *l*- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

Dependence Liability
Amphetamines have been extensively abused (see **Warnings**). Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Careful supervision is therefore recommended during drug withdrawal. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Drug Interactions
Acidifying agents. Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) may 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. As expected by their pharmacologic action, adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents. Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.), may increase absorption of amphetamines. Co-administration of ACT Amphetamine XR and gastrointestinal alkalinizing agents, such as antacids, should be avoided. 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.

Proton Pump Inhibitors. Proton Pump Inhibitors act on proton pumps by blocking acid production thereby reducing gastric acidity. In the presence of a proton pump inhibitor, the median T_{max} of mixed salts amphetamine extended-release capsules was shortened from 5 hours to 2.75 hours. Therefore, co-administration of ACT Amphetamine XR and proton pump inhibitors should be avoided.

Antidepressants, tricyclic. Amphetamines may enhance the activity of tricyclic antidepressant 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. Monoamine oxidase inhibitor 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 some 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.

Serotonergic Drugs
On rare occasions, serotonin syndrome has occurred in association with the use of amphetamines, such as mixed salts amphetamine extended-release capsules, when given in conjunction with serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). It has also been reported in association with overdose of amphetamines, including mixed salts amphetamine extended-release capsules (see **Overdosage**).

As these syndromes may result in potentially life-threatening conditions (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma), treatment with serotonergic drugs should be discontinued if such events occur and supportive symptomatic treatment should be initiated. ACT Amphetamine XR should be used with caution in combination with serotonergic and/or neuroleptic drugs (e.g. triptans, certain tricyclic antidepressants and opiate analgesics, lithium, St. John's Wort, MAOI) due to the risk of serotonergic syndrome (see **Contraindications**).

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

Laboratory Tests
Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

ADVERSE REACTIONS

In a single-dose pharmacokinetic study in 23 adolescents aged 13 to 17 years, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg mixed salts amphetamine extended-release capsules, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

The pre-marketing development program for mixed salts amphetamine extended-release capsules included exposures in a total of 1315 participants in clinical trials (635 pediatric patients aged 6 to 12 years, 350 adolescent patients aged 13-17 years, 248 adult patients, 82 healthy adult subjects).

The 635 pediatric patients were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (n=40). The 248 adult patients were evaluated in one controlled clinical study and one open-label clinical study. The 350 adolescent patients were evaluated in one controlled clinical study and one pharmacokinetic study. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse Events Associated with Discontinuation of Treatment

In two placebo-controlled studies of up to 5 weeks duration in children aged 6 to 12 years with ADHD, 2.4% (10/425) of mixed salts amphetamine extended-release capsules treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of mixed salts amphetamine extended-release capsules in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (n=595) are presented below. Over half of these patients were exposed to mixed salts amphetamine extended-release capsules for 12 months or more.

Table 1: Most Frequent Adverse Events Resulting in Discontinuation (>0.5%)

Adverse Event	**% of Pediatric Patients Discontinuing (n=595)**
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight Loss	1.2
Emotional Lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents aged 13 to 17 years with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among mixed salts amphetamine extended-release capsules-treated patients (n=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.

In one placebo-controlled, 4-week study in adults with ADHD, the most frequent adverse events resulting in discontinuation (>0.5%) in mixed salts amphetamine extended-release capsules treated patients (n=191) were for nervousness including anxiety and irritability (3.1%); for insomnia (2.6%); and for headache, palpitation, and somnolence (1% each). In an open-label extension of the trial (n=223), at 12 months, the only adverse event leading to discontinuation that was reported by at least 2% of patients was depression (4.9%).

Adverse events leading to discontinuations for mixed salts amphetamine extended-release capsules trials in adults were consistent with those reported in mixed salts amphetamine extended-release capsules trials in children and were also consistent with the known side effects for amphetamines.

Adverse Events Occurring in a Controlled Trial
Adverse events reported in a controlled fixed-dose clinical study of pediatric patients treated with mixed salts amphetamine extended-release capsules at doses up to 30 mg/day, or placebo, for up to 3 weeks are presented in the following table.

Table 2: Adverse Events Reported by More than 1% of Children aged 6 to 12 years Receiving Fixed Doses of Mixed Salts Amphetamine Extended-Release Capsules (up to final doses of 10, 20 or 30 mg/day) with an Incidence Greater than Placebo in a Controlled Clinical Study

Body System	**Adverse Event**	**Mixed Salts Amphetamine Extended-Release Capsules (n=374)**	**Placebo (n=210)**
General	Abdominal pain (stomach ache)	14%	10%
	Fever	5%	2%
	Infection	4%	2%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Vomiting	7%	4%
	Nausea	5%	3%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
Nervous System	Insomnia	17%	2%
	Emotional Lability	9%	2%
	Nervousness	6%	2%
	Dizziness	2%	0%
Metabolic/Nutritional	Weight Loss	4%	0%

Adverse events reported in a 4-week clinical trial in adolescents aged 13 to 17 years treated with mixed salts amphetamine extended-release capsules at doses up to 40 mg/day in adolescents weighing ≤75kg/165lbs, or placebo are presented in the following table.

Table 3: Adverse Events Reported by ≥1%* or more of Adolescents Weighing ≤75kg/165lbs Receiving Mixed Salts Amphetamine Extended-Release Capsules with Higher Incidence than Placebo in a Forced Weekly-Dose Titration Study*

Body System	**Adverse Event**	**Mixed Salts Amphetamine Extended-Release Capsules (n=233)**	**Placebo (n=54)**
General	Abdominal pain (stomach ache)	11%	2%
	Asthenia	3%	0%
Cardiovascular	Tachycardia	1%	0%
Digestive	Loss of Appetite [a]	36%	2%
	Dry Mouth	4%	0%
	Dyspepsia	3%	0%

Body System	Adverse Event	Mixed Salts Amphetamine Extended-Release Capsules (n=233)	Placebo (n=54)
	Nausea	3%	0%
	Vomiting	3%	0%
	Diarrhea	2%	0%
Nervous	Insomnia [a]	12%	4%
	Nervousness	6%	6% [b]
	Somnolence	5%	4%
	Emotional Lability	3%	0%
	Depression	1%	0%
	Twitching	1%	0%
Metabolic/Nutritional	Weight Loss [a]	9%	0%
Skin and Appendages	Herpes Simplex	1%	0%
Urogenital	Albuminuria	2%	0%
	Dysmenorrhea	1%	0%

[a] Dose-related adverse events [b] Appears the same due to rounding
* Included doses up to 40mg

Adverse events reported in a controlled fixed dose clinical study of adult patients treated with mixed salts amphetamine extended-release capsules at doses up to 60 mg/day, or placebo, for up to 4 weeks are presented in the following table.

Table 4: Adverse Events Reported by ≥1% or More of Adults Receiving Fixed Doses of Mixed Salts Amphetamine Extended-Release Capsules (up to final doses of 20, 40 or 60 mg/day) with an Incidence Greater than Placebo in a Controlled Clinical Trial

Body System	Adverse Event	Mixed Salts Amphetamine Extended-Release Capsules (n=191)	Placebo (n=64)
General	Headache	26%	13%
	Asthenia	6%	5%
	Pain	5%	5% [a]
	Infection	4%	2%
	Photosensitivity Reaction	3%	0%
	Chills	2%	0%
	Fungal Infection	2%	0%
	Neck Pain	2%	0%
Digestive System	Dry Mouth	35%	5%
	Loss of Appetite	33%	3%
	Nausea	8%	3%
	Diarrhea	6%	0%
	Constipation	4%	0%
	Tooth Disorder	3%	2%
	Gastroenteritis	1%	0%
	Thirst	1%	0%

Body System	Adverse Event	Mixed Salts Amphetamine Extended-Release Capsules (n=191)	Placebo (n=64)
	Vomiting	1%	0%
Nervous System	Insomnia	27%	13%
	Nervousness	13%	13% [a]
	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Hyperkinesia	4%	3%
	Libido Decreased	4%	0%
	Emotional Lability	3%	2%
	Somnolence	3%	2%
	Speech Disorder	2%	0%
	Amnesia	1%	0%
	Depersonalization	1%	0%
	Libido Increased	1%	0%
Cardiovascular System	Tachycardia	6%	3%
	Palpitation	4%	0%
	Hypertension	2%	0%
	Vasodilation	1%	0%
Metabolic/Nutritional	Weight Loss	10%	0%
	Bilirubinemia	1%	0%
	SGOT Increased	1%	0%
	SGPT Increased	1%	0%
Musculoskeletal	Twitching	3%	0%
	Myalgia	2%	2% [a]
	Arthralgia	1%	0%
Respiratory	Dyspnea	3%	0%
	Cough Increased	1%	0%
	Sinusitis	1%	0%
Skin and Appendages	Sweating	3%	0%
	Rash	2%	0%
Special Senses	Taste Perversion	2%	0%
Urogenital System	Urinary Tract Infection	5%	0%
	Dysmenorrhea	2%	0%
	Impotence	2%	0%
	Oliguria	1%	0%
	Urinary Tract Disorder	1%	0%
	Urination Impaired	1%	0%

[a] Appears the same due to rounding

The following adverse reactions have also been associated with the use of amphetamine, or mixed salt amphetamine:

Cardiovascular System: elevation of blood pressure, sudden death, myocardial infarction, stroke, palpitations, tachycardia; there have been isolated reports of cardiomyopathy associated with chronic amphetamine use

Digestive System: anorexia, constipation, diarrhea, dryness of the mouth, unpleasant taste, other gastrointestinal disturbances

Eye Disorders: mydriasis, vision blurred

Metabolic and Nutritional: weight loss

Nervous System: aggressive behavior, anger, bruxism, depression, dermatillomania, dizziness, dyskinesia, dysphoria, euphoria, headache, hostility, insomnia, irritability, change in libido, logorrhea, overstimulation, psychotic and manic episodes at recommended doses (e.g., hallucinations, delusional thinking, and mania), paresthesia (including formication), restlessness, tremor, new onset of tics or exacerbation of phonic and motor tics and Tourette's syndrome, seizures

Skin and Appendages: alopecia, hypersensitivity reactions including angioedema and anaphylaxis, urticaria, rash. Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported

Urogenital System: impotence

Vascular Disorders: Raynaud's phenomenon, peripheral coldness

Post-Market Adverse Drug Reactions

Suicidal Behaviour and Ideation:
There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see **Warnings, Suicidal Behaviour and Ideation).**

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

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 nervous system 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: Treatment of overdosage consists of appropriate supportive measures. 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 its recommendation in this regard. *D*-amphetamine is not dialyzable. 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 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.

The prolonged release of mixed salts amphetamine from ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) should be considered when treating patients with overdose.

Animal Toxicology
Acute administration of high doses of amphetamine (*d*- or *d,l*-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Dosing Considerations
ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) is a once-a-day capsule administered orally in the morning. ACT Amphetamine XR capsules dosage should be individualized according to the needs and response of the patient.

ACT Amphetamine XR should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted, to the lowest effective dosage, since individual patient response to ACT Amphetamine XR varies widely.

In patients with severe renal insufficiency (GFR 15 to <30 mL/min/1.73 m^2), the maximum dose should not exceed 20mg/day. Further dosage reduction should be considered in patients undergoing dialysis (see **Action and Clinical Pharmacology; Precautions, Patients with Renal Impairment**).

ACT Amphetamine XR should not be used in patients with symptomatic cardiovascular disease including coronary artery disease in adults and should generally not be used in patients with known serious structural cardiac abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs (see **Contraindications; Warnings**).

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities b) use other

sympathomimetic drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Patients who are considered to need extended treatment with ACT Amphetamine XR should undergo periodic evaluation of their cardiovascular status (see **Warnings**).

ACT Amphetamine XR is a once-a-day capsule for the treatment of ADHD. Capsules may be taken whole in the morning, or the capsule may be opened and the entire contents sprinkled on applesauce. If using the sprinkle administration method, the sprinkled applesauce should be consumed immediately and not stored. Patients should eat the applesauce with the sprinkled capsule contents in its entirety and refrain from chewing. The dose of a single capsule should not be divided - the contents of the entire capsule should be taken. Afternoon doses should be avoided because of the long-acting nature of the drug, including the potential for insomnia.

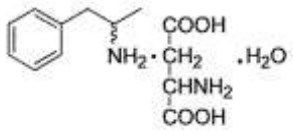
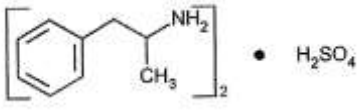
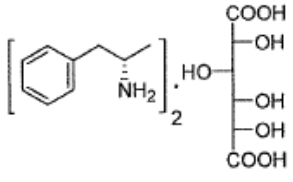
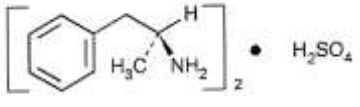
Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Children (6 to 12 years of age)
Amphetamines are not recommended for children under 6 years of age: When in the judgment of the clinician a lower dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The usual starting dose is 10 mg daily. The daily dosage may be adjusted in increments of 5 mg to 10 mg at weekly intervals, as determined by clinical response and tolerability up to the maximum recommended dose of 30 mg per day**.**

Adolescents (13 to 17 years of age) and Adults (over 18 years of age)
In adolescents and adults with ADHD who are either starting treatment for the first time or switching from another stimulant medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 to 10 mg at weekly intervals up to a usual maximum of 20 mg. In some cases, higher doses not to exceed 30 mg/day may be required, as determined by clinical response and tolerability.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names:	Chemical Names:	Structural Formula and Molecular Weights	Description and Solubility
Amphetamine Aspartate Monohydrate	(±)-α-methylphenethylamine-DL-aspartate (l:1) monohydrate	 M.W 286.33 (monohydrate)	White to off-white powder Very soluble in water.
Amphetamine Sulfate USP	(±)-α-methylphenethylamine-sulfate (2:1)	 M.W 368.49	White crystalline powder. Freely soluble in water.
Dextroamphetamine Saccharate	(+)-α-Methylphenethylamine saccharate (2:1)	 M.W 480.56	White to off-white powder. Freely soluble in water.
Dextroamphetamine Sulfate USP	(+)-α-Methylphenethylamine sulfate (2:1)	 M.W 368.49	White crystalline powder. Freely soluble in water.

Composition

ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) is a long-acting, modified-release, amphetamine product designed for once-daily administration combining the neutral sulfate salts of *d*-amphetamine and amphetamine, with the *d*-isomer of amphetamine saccharate and *d,l*-amphetamine aspartate.

Each capsule contains:	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**
Amphetamine Aspartate Monohydrate	1.25	2.5	3.75	5.0	6.25	7.5
Amphetamine Sulfate USP	1.25	2.5	3.75	5.0	6.25	7.5
Dextroamphetamine Saccharate	1.25	2.5	3.75	5.0	6.25	7.5
Dextroamphetamine Sulfate USP	1.25	2.5	3.75	5.0	6.25	7.5
Total amphetamine base equivalence	1.5	3.0	4.5	6.0	7.5	9.0
Total d-amphetamine base equivalent	1.6	3.3	4.9	6.5	8.1	9.8

Inactive Ingredients and Colors: The inactive ingredients in ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) include: gelatin capsules, hydroxypropyl cellulose, ammonio methylacrylate copolymer (type B, powder), ammonio methylacrylate copolymer (type

A, powder), sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, gelatin, and titanium dioxide.

Colorants present in the capsules of different strengths are as follows;

Strength	Colorant used in empty gelatin capsules
5 mg	Red iron oxide, Yellow iron oxide and FD & C Blue # 1
10 mg	D&C Yellow # 10 and FD&C Blue # 1
15 mg	Red iron oxide, Yellow iron oxide and D&C Yellow # 10
20 mg	FD&C Blue # 1
25 mg	D&C Yellow # 10
30 mg	Red iron oxide and Yellow iron oxide

Stability and Storage Recommendations
Dispense in a tight, light-resistant container as defined in the USP. Store between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORMS

5 mg #3 capsules with orange opaque body and light blue opaque cap printed with Purepac logo 'R' and '3062' on both the body and cap in black ink.
Bottles of 100s

10 mg #3 capsules with ivory opaque body and light blue opaque cap printed with Purepac logo 'R' and '3059' on both the body and cap in black ink.
Bottles of 100s

15 mg #2 capsules with orange opaque body and ivory opaque cap printed with Purepac logo 'R' and '3063' on both the body and cap in black ink.
Bottles of 100s

20 mg #2 capsules with light blue opaque body and light blue opaque cap printed with Purepac logo 'R' and '3060' on both the body and cap in black ink.
Bottles of 100s

25 mg #1 capsules with ivory opaque body and ivory opaque cap printed with Purepac logo 'R' and '3064' on both the body and cap in black ink.
Bottles of 100s

30 mg #1 capsules with orange opaque body and orange opaque cap printed with Purepac logo 'R' and '3061' on both the body and cap in black ink.
Bottles of 100s

PHARMACOLOGY

The behavioral manifestations of ADHD are believed to involve an interactive imbalance between dopaminergic and other neurotransmitter systems. However, a fundamental dopaminergic dysfunction appears to have special significance. Amphetamine increases the availability of synaptic dopamine at key sites in the brain by stimulating its release from newly synthesized (cytoplasmic) dopamine pools. Thus, unlike methylphenidate, which increases dopamine availability primarily by blocking reuptake, amphetamine's effect does not appear to be highly dependent on impulse-released dopamine.

This primary mechanism of action of amphetamine is supported by experiments with reserpine and α-methyltyrosine. Pretreatment with reserpine, which is believed to reduce stored vesicular (but not cytoplasmic) dopamine, was ineffective in attenuating responses to amphetamine challenge. In contrast, the depletion of newly synthesized cytoplasmic dopamine through the inhibition of tyrosine hydroxylase (the rate limiting anabolic enzyme) using α-methyltyrosine, did reduce responses following amphetamine challenge.

Systemically administered amphetamine produced stimulation of dopamine release from the nucleus accumbens and dorsal caudate. Administration of a low acute dose of amphetamine produced a region specific decrease in dopamine from the "shell" in comparison to the "core" regions of the nucleus accumbens. Higher acute doses increased extracellular dopamine to the same extent in both regions.

In addition to a dopaminergic mechanism of action, there is experimental evidence to suggest involvement of other neurotransmitter systems in the regulation of behavioral effects (e.g., motor activity). These include interactions between dopaminergic, GABAergic and glutamatergic pathways and possible involvement of cholinergic pathways.

Amphetamine-induced effects are primarily mediated by D1 and D2 receptors. In addition, 5-HT_{2A} and 5-HT_3 receptors, and NMDA receptors are suggested to play a role in amphetamine-induced release of dopamine, and in the regulation of the firing rate and pattern of midbrain dopamine neurons, respectively.

Prenatal exposure to amphetamine was associated with a variety of responses in offspring that included increases in conditioned avoidance, exploratory behavior, and sexual behavior, and decreases in 5-HT content in the medial hypothalamus.

Repeated administration of high concentrations of amphetamine produced striatal, neostriatum, and frontal cortex dopamine nerve fiber degeneration.

Amphetamine interacted with a variety of compounds that included caffeine, cocaine, morphine, diazepam, phencyclidine, clonidine, fluoxetine, lithium, pentobarbital, ethanol, and THC. The mechanism of many of these interactions is currently not known.

Animal Pharmacokinetics

ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) is a once a day product.

Literature studies indicated a stereospecific distribution of the individual dextro (*d*-) and levo (*l*-) enantiomers of amphetamine in the brain and heart of mice. Distribution kinetics in the rat indicated that similar amounts of both enantiomers were excreted in the urine as parent drug and as the hydroxyl metabolite.

Radiolabelled ^{3}H-*d*-amphetamine was distributed in many tissues of pregnant and non-pregnant females and male mice. Amphetamine crossed the placenta and was present in the placenta, whole fetus, and in fetal brain and liver. Fetal tissue concentrations were generally much lower than maternal tissue concentrations.

The metabolism of amphetamine was affected by induction of the CYP450 system with phenobarbital. The direct benzene ring hydroxylation of parent drug was mediated by CYP2D1 in the rat and by the human homologue, CYP2D6, in human microsomes. The deamination of amphetamine was shown to be mediated by the CYP isoform 2C3 from the rabbit, but not the 2C11 and 2C13 isoforms from the rat. N-oxygenation of amphetamine to the hydroxylamine and oxime metabolites was demonstrated *in vitro* with flavin containing monooxygense Form 3 from humans.

The urinary excretion of amphetamine and its major rat metabolite, 4-hydroxyamphetamine, was influenced by strain of rat, significant differences occurring between poor metabolizer versus extensive metabolizer strains.

Human Pharmacokinetics
Pharmacokinetic studies of mixed salts amphetamine extended-release capsules have been conducted in healthy adult and pediatric (aged 6-12 years) subjects, and adolescent (aged 13-17 years) and pediatric patients with ADHD. Mixed salts amphetamine extended-release capsules contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1.

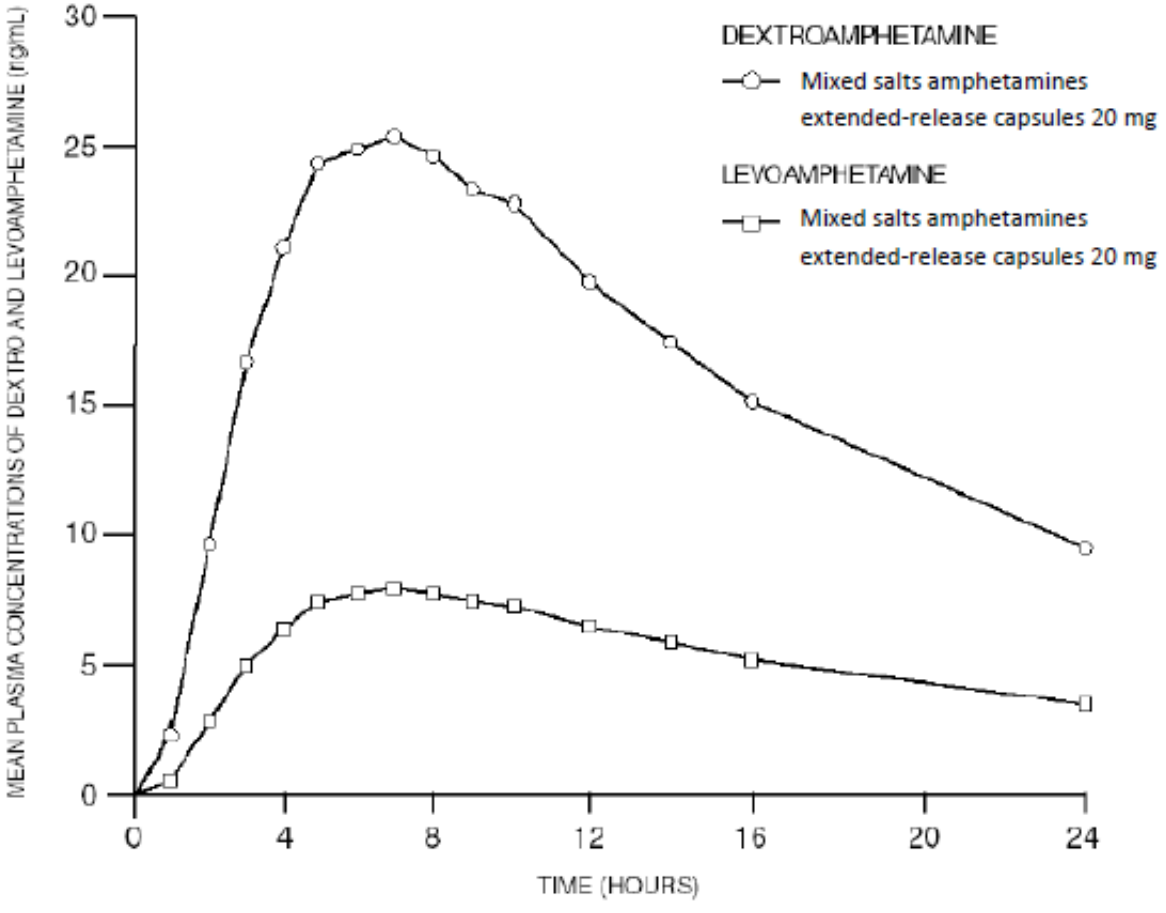
Mixed salts amphetamines extended-release capsules demonstrates linear pharmacokinetics over the dose range of 20 to 60mg in adults and adolescents aged 13 to 17 years weighing greater than 75kg/165lbs, over the dose range of 10 to 40mg in adolescents weighing less than or equal to 75kg/165lbs, and 5 to 30mg in children aged 6 to 12 years. There was no unexpected accumulation at steady state in children.

Pharmacokinetic Results in Healthy Adult and Pediatric Subjects
Following administration of a single dose of mixed salts amphetamine extended-release capsules in healthy adult subjects, the peak plasma concentrations occurred in about 7 hours for *d*-amphetamine and 8 hours for *l*-amphetamine as seen in Table 5.

Table 5: Pharmacokinetic Parameters for Single 20 mg Dose of mixed salts amphetamine extended-release capsules

Treatment	***d*-amphetamine**			***l*-amphetamine**		
	$AUC_{0\text{-}inf}$ (ng·hr/ mL)	**T_{max} (hours)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-}inf}$ (ng·hr/ mL)**	**T_{max} (hours)**	**C_{max} (ng/mL)**
Mixed salts amphetamines extended-release capsules (20 mg, qd)	567	7.0	28.1	203	8.2	8.7

Figure 1: Mean *d*-amphetamine and *l*-amphetamine Plasma Concentrations following a single 20 mg morning administration of mixed salts amphetamines extended-release capsules in the Fed State



The mean elimination half-life is 1 hour shorter for *d*-amphethamine and 2 hours shorter for *l*-amphethamine in children aged 6 to 12 years compared to that in adults ($t_{1/2}$ is 10 hours for *d*-amphetamine and 13 hours for *l*-amphetamine in adults, and 9 hours and 11 hours, respectively, for children).

Pharmacokinetic Results in Children and Adolescents with ADHD

In a 20mg single dose study in 51 children (aged 6-12 years) with ADHD, the mean T_{max} for *d*-amphetamine was 6.8 hours and the mean C_{max} was 48.8ng/mL. The corresponding mean T_{max} and C_{max} values for *l*-amphetamine were 6.9 hours and 14.8ng/mL, respectively. The mean elimination half-life for *d*-amphetamine and *l*-amphetamine was 9.5 and 10.9 hours, respectively. Following dosing of children with ADHD to steady state with mixed salts amphetamines extended-release capsules 10, 20 and 30mg the mean d-amphetamine C_{max} (ng/mL) in plasma for mixed salts amphetamines extended-release capsules was 28.8 (10mg), 54.6 (20mg) and 89.0 (30mg). For *l*-amphetamine, the mean C_{max} values for the three mixed salts amphetamines extended-release capsules doses were 8.8, 17.2 and 28.1ng/mL, respectively.

In adolescents aged 13-17 years and weighing less than or equal to 75kg/165lbs, the mean elimination half-life for *d*-amphetamine is 11 hours, and 13-14 hours for *l*-amphetamine.

Table 6: Mixed salts amphetamines extended-release capsules Pharmacokinetic Parameters at Steady State in Children with ADHD

Treatment	*d*-amphetamine			*l*-amphetamine		
	AUC_{0-24} (ng·hr/ mL)	**T_{max} (hours)**	**C_{max} (ng/mL)**	**AUC_{0-24} (ng·hr /mL)**	**T_{max} (hours)**	**C_{max} (ng/mL)**
Mixed salts amphetamines extended-release capsules (10 mg)	432	6.4	28.8	138	6.4	8.8
Mixed salts amphethamines extended-release capsules (20 mg)	777	5.8	54.6	262	5.7	17.2
Mixed salts amphethamines extended-release capsules (30 mg)	1364	5.5	89.0	444	5.5	28.1

Metabolism

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

Excretion

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow

rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased, (see **Precautions – Drug Interactions**).

Food Effect Study in Healthy Adult Subjects

A single dose study compared the relative bioavailability of *d*-amphetamine and *l*-amphetamine following administration of a single 30mg dose of mixed salts amphetamine extended-release capsules fasted, fed (high fat meal) and sprinkled on food (otherwise fasted) in 21 healthy adult subjects. Food does not affect the extent of absorption of mixed salts amphetamine extended-release capsules, but prolongs T_{max} by 2.5 hours by administration with food (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted states.

TOXICOLOGY

Acute Toxicity Studies

The acute LD_{50} amphetamine is as follows:

Species	***LD_{50} (mg/kg)***
Mice (i.v.)	52
Mice (oral)	353
Rat (i.p.)	70
Dog (i.v.)	8.5
Monkey (i.v., oral)	5

Acute toxicity studies conducted in mice, rats, dogs and monkeys showed similar dose-dependent responses. The order for comparative toxicity ranking, based upon the LD_{50} values, was monkey>dog>mouse.

Acute toxicity to dextro (*d*-), and levo (*l*-) amphetamine was age-dependent. Young mice (3-30 days old) tolerated higher doses (up to 180 mg/kg i.p.) than adults. Toxicity increased from 18-days of age onward. Mortality response curves were biphasic for developing mice and polyphasic for adult mice.

Acute toxicity signs noted in mice (25-75 mg/kg i.v.), rats (45-178 mg/kg i.p.), dogs (5-9 mg/kg i.v.) and monkeys (1-6 mg/kg i.v.) included marked to severe hyperactivity, stereotypic behavior, mild to marked clonic and/or tonic convulsions, and (in monkeys) marked increase in respiratory rate, body temperature and pupil size. Death was associated with convulsions and, in dogs, massive endocardial hemorrhages in both ventricles.

Subacute and Subchronic Toxicity Studies

Subacute and subchronic toxicity signs noted in mice (0-2000 ppm of *d,l*-amphetamine in feed) and rats (0-750 ppm of *d,l*-amphetamine in feed) from 14-day and 13-week dietary studies

included hyperactivity, decreased body weight and food consumption. Deaths in the order of 15 to 65% were reported in mice administered with 500-2000 ppm of *d,l*-amphetamine in feed. No treatment-related deaths occurred in the rat study.

Carcinogenicity Studies
No evidence of carcinogenicity was found in studies in which *d,l*-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times respectively the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis.

Reproduction and Teratology Studies
Amphetamine, in the enantiomer ratio present in ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) (*d*- to *l*- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis). Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50 mg/kg/day (approximately 6 times the maximum recommended human dose of 30 mg/day on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- *d*, *l*-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

Mutagenicity Studies
Amphetamine, in the enantiomer ratio present in ACT Amphetamine XR (*d*- to *l*- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. *d,l*-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

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Product Monograph for ADDERALL XR® (mixed salts amphetamine extended-release capsules). Marketed by Shire Canada Inc. Submission Control No.: 185297; Date of Revision: September 18, 2015.

PART III: CONSUMER INFORMATION

ACT Amphetamine XR ®
mixed salts amphetamine
extended-release capsules
5mg, 10mg, 15mg, 20mg, 25mg and 30mg

Read this carefully before you start taking ACT Amphetamine XR. This leaflet is a summary and will not tell you everything about ACT Amphetamine XR. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ACT Amphetamine XR is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (6-12 years), adolescents (13-17 years) and adults.

ACT Amphetamine XR may be a part of your/your child's overall treatment for ADHD. The doctor may also recommend that you/your child have counseling or other therapy.

What it does:
Mixed salts amphetamine, the medicinal ingredient in ACT Amphetamine XR, help increase attention (including the ability to follow directions and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD. ACT Amphetamine XR is an extended release capsule designed to keep improving the symptoms of ADHD throughout the day and into the early evening.

When it should not be used:
Do not take ACT Amphetamine XR if you/your child:

- Are allergic to amphetamines or any of the nonmedicinal ingredients in the formulation or its container (see What the nonmedicinal ingredients are)
- Are sensitive to, allergic to or had a reaction to other stimulant medicines
- Have advanced arteriosclerosis (hardened arteries)
- Have symptomatic heart disease
- Have moderate to severe high blood pressure
- Have agitated states
- Have glaucoma, an eye disease
- Have hyperthyroidism (an overactive thyroid gland)
- Have history of drug abuse
- Are taking or have taken medications from the group called monoamine oxidase inhibitors (MAOI) within the last 14 days.
- Are breastfeeding or plan to breastfeed. ACT Amphetamine XR passes into breast milk.

What the medicinal ingredient is:
Mixed salts amphetamine: *d*-amphetamine Saccharate, Amphetamine Aspartate Monohydrate, *d*-amphetamine Sulfate and Amphetamine Sulfate

What the nonmedicinal ingredients are:
The inactive ingredients in ACT Amphetamine XR (mixed salts amphetamine extended-release capsules) include: gelatin capsules, hydroxypropyl cellulose, ammonio methylacrylate copolymer (type B, powder), ammonio methylacrylate copolymer (type A, powder), sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, gelatin, and titanium dioxide.

Colorants present in the capsules of different strengths are as follows;

Strength	Colorant used in empty gelatin capsules
5 mg	Red iron oxide, Yellow iron oxide and FD & C Blue # 1
10 mg	D&C Yellow # 10 and FD&C Blue # 1
15 mg	Red iron oxide, Yellow iron oxide and D&C Yellow # 10
20 mg	FD&C Blue # 1
25 mg	D&C Yellow # 10
30 mg	Red iron oxide and Yellow iron oxide

What dosage forms it comes in:
Extended-release capsules: 5mg, 10mg, 15mg, 20mg, 25mg and 30mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ACT Amphetamine XR has a potential for abuse, misuse and dependence.
The misuse of ACT Amphetamine XR may cause serious cardiovascular adverse events and sudden death.
(See also **Drug Abuse and Dependence** below**)**

The following have been reported with use of medicines used to treat ADHD such as mixed salts amphetamine extended-release capsules:

1. **Heart-related problems:**
   - **Sudden death in patients who have heart problems or heart defects**
   - **Stroke and heart attack in adults**
   - **Increased blood pressure and heart rate**

Sudden death has been reported with drugs used for ADHD treatment in children/adolescents with structural heart abnormalities or other serious heart problems. Although some serious heart problems alone can carry an increased risk of sudden

death, ACT Amphetamine XR generally should not be used in children, adolescents or adults with known structural heart abnormalities, disease of the heart muscle, serious heart rhythm abnormalities or other serious heart disease or conditions.

Tell your doctor if you or your child has any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor may wish to check you or your child carefully for heart problems before starting ACT Amphetamine XR. Your doctor may wish to check you or your child's blood pressure and heart rate regularly during treatment with ACT Amphetamine XR.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking ACT Amphetamine XR.

2. <u>Mental (Psychiatric) problems:</u>

- **New or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, completed suicide)**
- **New or worse bipolar illness, characterized by extreme mood swings, with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness)**
- **New or worse aggressive behavior or hostility**
- **New psychosis (such as hearing voices, believing things that are not true, are suspicious) or new mania (unusually excited, over-active or un-inhibited)**

These new or worse mental problems may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your doctor about any mental problems you or your child have, or about any personal or family history of suicide, bipolar illness, or depression.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time *during* treatment, particularly at the start or during dose changes, and also *after stopping* ACT Amphetamine XR. **Should this happen to you, or to those in your care if you are a caregiver or guardian, talk to your doctor immediately. Close observation by a doctor is necessary in this situation.**

Call your doctor right away if you or your child has any new or worsening mental symptoms while taking ACT Amphetamine XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

BEFORE you/your child uses ACT Amphetamine XR, talk to your doctor, nurse, or pharmacist if you/your child:

- have heart disease or a heart condition, structural heart abnormalities or high blood pressure
- have a family history of sudden death or death related to heart problems
- participate in strenuous exercise or activities
- take other drugs for ADHD
- have mental problems or a family history of mental problems including psychosis, mania, bipolar illness, depression or suicide
- have motion tics (hard to control, repeat twitching of any parts of the body) or verbal tics (hard to control repeating of sounds or words) or Tourette's syndrome
- have relatives with motion tics, verbal tics, or Tourette's syndrome
- have a history of seizures (convulsions, epilepsy) or have had an abnormal brain wave test (EEG)
- are pregnant or plan to become pregnant. Taking ACT Amphetamine XR during pregnancy can cause harm to your baby. If ACT Amphetamine XR is required during pregnancy, the risk to the unborn baby should be weighed against the benefits for the mother. Your doctor can discuss these issues with you
- have symptoms of Raynaud's phenomenon (fingers and toes feeling numb, tingling and changing colour when cold) or thromboangitis obliterans (causes pain in hands and feet)
- have any kidney related problems as your doctor may reduce the dose.

Drug Abuse and Dependence
Amphetamines have the potential for abuse and misuse. Abuse of amphetamines can lead to dependence and possibly serious heart problems and death. Substance abuse may be less likely in patients with ADHD if they are treated with medication. ACT Amphetamine XR should only be given under close medical supervision to patients whose condition has been properly diagnosed (see Serious Warnings and Precautions above).

Growth in Children
Other stimulants have been reported to temporarily slow growth in children, however there is not sufficient evidence to determine if mixed salts amphetamine extended-release capsules in children may cause slower growth (slowed weight gain and/or height). The doctor will be carefully watching your / your child's height and weight. If you / your child is not growing or gaining weight as the doctor expects, the doctor may stop ACT Amphetamine XR treatment.

INTERACTION WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you/your child takes, including drugs prescribed by

other doctors, vitamins, minerals, natural or herbal supplements, or alternative medicines.

The following may interact with ACT Amphetamine XR:

- medicines used to treat depression including monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs)
- medicines that make urine or digestive contents more acidic (e.g., guanethidine, reserpine, ascorbic acid, ammonium chloride, sodium acid phosphate)
- medicines that make urine or digestive contents more alkaline (e.g., sodium bicarbonate, acetazolamide, thiazides)
- medicines used to reduce or increase blood pressure
- cold and allergy medicines
- anti-psychotic medicines (e.g., chlorpromazine, haloperidol)
- lithium
- methenamine therapy
- narcotic pain medicines (e.g., meperidine)
- seizure medicines (e.g., ethosuximide, phenobarbital, phenytoin)
- antacids, ACT Amphetamine XR may interact with a class of medications that reduce the acid produced in the stomach called Proton Pump Inhibitors, commonly known as PPI (e.g., omeprazole). Therefore, do not take antacids at the same time as ACT Amphetamine XR.

While on ACT Amphetamine XR, do not start taking a new medicine or herbal remedy before checking with the doctor.

PROPER USE OF THIS MEDICATION

ACT Amphetamine XR should be taken by mouth, once-a-day early in the morning.

Capsules may be swallowed whole with water or milk. Capsules may be opened and all the contents inside sprinkled on applesauce and taken immediately; do not store for later use. **Do not crush or chew the capsule or the capsule contents before swallowing**.

ACT Amphetamine XR can be taken with or without meals.

In order to receive the most benefit from ACT Amphetamine XR, it is important that ACT Amphetamine XR be taken only as directed by your/ your child's doctor. The doctor may adjust the amount of drug taken by you / your child until it is right for you / your child. From time to time, the doctor may interrupt treatment to check your/ your child's symptoms while you / your child is not taking the drug.

Your doctor may do regular checks of the heart and blood pressure while taking ACT Amphetamine XR. Children should have their height and weight checked often while taking ACT Amphetamine XR. ACT Amphetamine XR treatment may be stopped if a problem is found during these check-ups.

As with all medicines, never share ACT Amphetamine XR with anyone else and take only the number of ACT Amphetamine XR capsules prescribed by your / your child's doctor.

Usual dose:

Children (6 to 12 years of age): The usual starting dose is 10 mg once a day in the morning. The dose may be adjusted up to a maximum dose of 30 mg/day.

Adolescents (13 to 17 years of age) and Adults (18 years of age and over): The usual starting dose is 10 mg once a day in the morning. The dose may be adjusted up to the usual maximum dose of 20 mg/day. In some cases a maximum daily dose of 30 mg/day may be used.

Overdose:

If you think you/your child has taken too much ACT Amphetamine XR contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms

Missed Dose:

If you/your child forget to take your/his or her dose in the morning, wait until the next morning and carry on with the next dose at the usual time. Do not double dose.

Afternoon doses should be avoided because of the long-acting nature of the drug, including the potential for insomnia.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- decrease or loss of appetite
- stomach ache
- difficulty falling asleep
- mood swings
- weight loss
- dry mouth
- headache
- dizziness
- nervousness, anxiety, irritability
- vomiting, nausea, diarrhea

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Common	**Heart palpitations or fast heart beat (see Warnings and Precautions)**		√	
Common	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Common	**New Tics**		√	
Common	**Depression:** feeling sad, loss of interest in usual activities, hopelessness, insomnia or sleeping too much		√	
Uncommon	**Aggressive Behavior, Anger or Hostility**		√	
Uncommon	**High Blood Pressure:** headaches, dizziness, lightheadedness, ringing in the ears, fainting		√	
Uncommon	**Trouble with vision:** eyesight changes or blurred vision		√	
Unknown	**Heart attack:** severe, crushing chest pain that can radiate into the arm and/or jaw, palpitations, shortness of breath, nausea, vomiting, sweating **(see Warnings and Precautions)**			√
Unknown	**New Psychotic or Manic Symptoms:** Paranoia, delusions **-Hallucinations:** Seeing, feeling or hearing things that are not real, **-Mania:** feeling unusually excited, over-active, or uninhibited **(see Warnings and**		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Precautions)			
Unknown	**Suicidal Behavior:** Thoughts or actions about hurting or killing yourself **(see Warnings and Precautions)**			√
Unknown	**Fits (seizures)**			√
Unknown	**Condition Resembling Raynaud's Phenomenon:** discoloration of the hands and feet, pain, sensations of cold and/or numbness		√	
Unknown	**Stroke:** weakness, trouble speaking, vision problems, headache, dizziness			√
Unknown	**Serious Skin Conditions (Steven's Johnson Syndrome, Toxic Epidermal Necrolysis):** Swelling of the skin or serious skin rash seen as severe blisters of the skin and mucous membranes			√

This is not a complete list of side effects. For any unexpected effects while taking ACT Amphetamine XR, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.
Store at room temperature (15-30ºC) in a tight, light-resistant container.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 **(toll-free);**
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited by:

Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

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