Mixed Amphetamine Salts Extended-Release in the Treatment of Adult ADHD: A Randomized, Controlled Trial

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ABSTRACT

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a serious neurobehavioral disorder of childhood onset that often persists into adolescence and adulthood. Functional impairments, underachievement, and difficult interpersonal relationships illustrate the need for effective treatment of ADHD through adulthood.

Method:This prospective, multisite, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study was conducted to assess the efficacy, safety, and duration of action of mixed amphetamine salts extended-release (MAS XR) in adults with ADHD, combined type. Adults ≥18 years of age were given placebo or MAS XR 20, 40, or 60 mg/day for 4 weeks.The main outcome measures were the ADHD Rating Scale and Conners' Adult ADHD Rating Scale Short Version Self-Report (CAARS-S-S).

FOCUS POINTS

- Attention-deficit/hyperactivity disorder (ADHD) is a serious neurobehavioral disorder of childhood onset that often persists into adulthood.
- Stimulants have been studied extensively in children with ADHD and have a well-established safety and efficacy profile.
- Stimulants are indirect agonists of catecholaminergic transmission in the central nervous system and increase the amount of dopamine and norepinephrine available presynaptically.
- In this study, mixed amphetamine salts extended-release (MAS XR) 20-60 mg/day were safe and effective in adults with ADHD.
- Treatment response to MAS XR was related to ADHD symptom severity and a trend toward dose response for efficacy was observed for adults with higher baseline symptom severity.
- MAS XR seems to have an acceptable cardiovascular safety profile in adults with ADHD.

Results: Two hundred fifty-five subjects were randomly assigned to treatment with MAS XR or placebo. MAS XR treatment was associated with

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statistically and clinically significant ADHD symptom reduction at endpoint; mean ADHD Rating Scale scores were 18.5 for the 20-mg group (P=.OO1), 18.4 for the 40-mg group (P<.001), and 18.5 for the 60-mg group (Pc.001). Adults with severe symptoms (ADHD Rating Scale score ≥32 at baseline) had significantly greater symptom reduction with the highest MAS XR dose (60 mg/day), however, this dose-response relationship was determined by post-hoc analysis.The mean MAS XR effect size was 0.8. Statistically significant (Pc.05) improvements in CAARS-S-S ADHD index scores occurred at 4- and 12-hours postdose for all MAS XR groups, indicating a 12-hour duration of effect. Symptoms improved within the first treatment week. Most adverse events reported were mild or moderate in intensity, and the most commonly reported adverse events were consistent with the known profile of stimulant medications. Vital signs and electrocardiograms showed no clinically significant cardiovascular changes.

Conclusion: These results suggest that MAS XR is safe and effective in adults with ADHD and controlled ADHD symptoms for up to 12 hours.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a serious neurobehavioral disorder of childhood onset that often persists into adolescence and adulthood. Estimates of the prevalence and persistence of ADHD vary depending on the diagnostic criteria used and definitions of persistence.[1] Based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria,[2] -10% of school-aged youth worldwide are affected by ADHD[3-5] and 4.4% of adults in the United States have ADHD.[6] With 209 million adults ≥18 years of age and a 4.4% prevalence rate, >9 million adults in the US may have ADHD.[7]

Faraone and colleagues[8] surveyed primary care and psychiatry practices to determine whether patterns of diagnosis and treatment of adult ADHD differ. Only 25% of the patients with ADHD were first diagnosed in childhood or adolescence. Although ADHD is a chronic disorder, many individuals are able to compensate until the challenges of family and career become overwhelming. In the Faraone and colleagues[8] study, >90% of adults with undiagnosed ADHD were self-referred, both in primary care and psychiatric settings, and common symptoms that motivated self-referral were general disorganization, problems with time management, a tendency to leave projects incomplete, and difficulty functioning at work. Greater than 50% of previously undiagnosed adults had complained about ADHD symptoms to other healthcare professionals in the past. Unlike the standard of care in pediatrics, adults are not routinely screened for ADHD in primary care. Lack of training and uncertainty about the diagnosis likely contribute to the underrecognition of the disorder in adults.

Clinical, family, psychopharmacologic, neurobiologic, neuropsychological, and outcome studies support the validity of adult ADHD.[9] Neuroimaging studies[10,11] indicate a profile of prefrontal dopaminergic hypoactivity in both adult and childhood ADHD. The core symptoms of ADHD —inattentiveness, impulsivity, and hyperactivity —are well documented in adult ADHD, although hyperactivity symptoms tend to diminish with age.[12,13] Similar functional impairments, such as educational or occupational underachievement and difficult interpersonal relationships, affect both children and adults with ADHD.[14-16] Compared with age- and gender-matched individuals, teenagers and young adults with ADHD are >4 times as likely to have automobile accidents.[17] Significantly fewer adults with ADHD had attended college, twice as many had been divorced, and half as many were completely satisfied with their professional lives and career tracks.[16] These life impairments illustrate the need for effective treatment of ADHD throughout the lifespan.

Stimulant medications have been studied extensively in children with ADHD and have a well-established safety and efficacy profile. Research suggests that adults with ADHD respond well to stimulants when adequate doses are used.[18,19] A number of once-daily extended-release (XR) stimulant formulations have been developed recently and are likely to increase

treatment compliance,[20] particularly in a population that tends to be forgetful and disorganized. Additionally, XR formulations may reduce the abuse potential compared with immediate-release (IR) formulations.[2122]

Mixed amphetamine salts XR (MAS XR) capsules contain a 1:1 ratio of immediate-to-delayed-release MAS pellets.The pharmacokinetic profile of one MAS XR 20-mg capsule is equivalent to that of two MAS IR 10-mg tablets dosed 4-6 hours apart.[23]The safety profile and rapid onset of action of MAS XR are similar to those of the IR tablets, but the long-acting formulation provides a persistent 12-hour therapeutic effect with once-daily dosing.[2425] A linear pharmacokinetic profile for MAS XR 20 mg, 40 mg, and 60 mg/day has been demonstrated in healthy adults.[26]This randomized, double-blind, placebo-controlled, forced-dose-escalation study was designed to assess the efficacy and safety of MAS XR 20, 40, and 60 mg/day in adults with ADHD. We hypothesized that MAS XR would reduce ADHD symptoms significantly in adults and that higher doses would lead to greater symptom improvement.

METHODS

Subjects and Eligibility Criteria

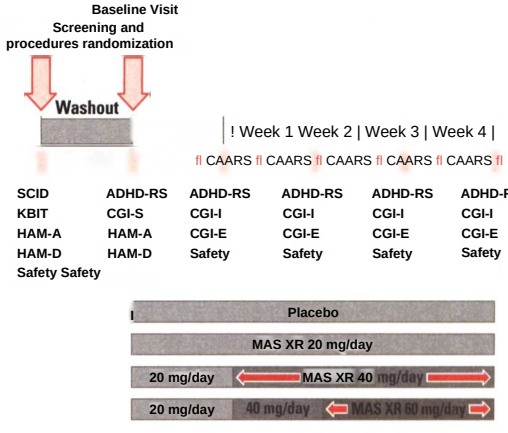
Subjects were outpatients ≥18 years of age who were referred by clinics and had a primary diagnosis of ADHD established by psychiatric evaluation using DSM-IV-TR criteria.[2] Diagnosis required identification of at least six of nine symptoms for hyperactive/impulsive and inattentive subtype criteria and ADHD onset by 7 years of age. Subjects were in good physical health, with normal vital signs and 12-lead electrocardiogram (ECG) measurements.This study complied with institutional review board regulations and the Declaration of Helsinki, 2000 revision. Each subject provided written, informed consent after study procedures and objectives were disclosed.

Subjects incapable of following study instructions or having an intelligence quotient <80 (Kaufman Brief Intelligence Test) were excluded from the study. Several comorbid psychiatric diagnoses were excluded: psychosis, bipolar illness, pervasive developmental disorder, severe obsessive-compulsive disorder, and severe depressive (17-item Hamilton Rating Scale for Depression score >19) and anxiety disorders (14-item Hamilton Rating Scale for Anxiety score >17). Subjects were excluded for a positive drug screen or substance abuse history (or living with someone with a substance abuse disorder); glaucoma; hyperthyroidism; seizure, tic disorder, orTourette syndrome; and pregnancy or lactation. Also excluded were subjects who were taking within 30 days of the screening visit any anticonvulsant drugs, clonidine, guanfacine, systemic steroids, medications that affect blood pressure (BP) or the heart or have central nervous system effects, pemoline, or investigational drugs.

Study Design

This was a multisite, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of three doses of MAS XR in adults with ADHD. The study was conducted between February 6, 2002, and May 24, 2002. Eligible subjects were randomly assigned (3 active:1 placebo) to a daily morning dose of MAS XR 20 mg, 40 mg, or 60 mg for 4 weeks (Figure 1).This was a forced-dose-escalation design and dosage modification was not permitted; subjects were excluded if sustained drug intolerance occurred.

FIGURE 1.
Study design



CAARS=Conners' Adult ADHD Rating Scale; SCID=Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; KBIT=Kaufman Brief Intelligence Test; CGI-S=Clinical Global Impressions-Severity; CGI-I=Clinical Global Impressions-Improvement; HAM-A=Hamilton Rating Scale for Anxiety; CGI-E=Global Impressions-Efficacy; HAM-D=Hamilton Rating Scale for Depression; MAS XR=mixed amphetamine salts extended-release.

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Measurements

Primary Efficacy Assessments

Investigators completed the ADHD Rating Scale to assess the 18 individual symptom criteria of ADHD in DSM-IV-TR at baseline and at each clinic visit. The ADHD Rating Scale is composed of two subscales, inattentive and hyperactive/impulsive; all items were scored on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms).

Secondary Efficacy Assessments

Conners' Adult ADHD Rating Scale-Short Version-Self-Report (CAARS-S-S) was used to determine the duration of MAS XR action. Each item was scored on a 4-point scale, from 0 (not at all, never) to 3 (very much, very frequently). The five CAARS-S-S subscales include the 12-item ADHD index and 4-factor-derived, 5-item scales. The CAARS-S-S ADHD index measures the overall level of ADHD-related symptoms using items that capture daily symptomatology, such as "I have a short fuse/hot temper," "I am always on the go," "I feel restless even when sitting still," and "Things I hear or see distract me from what I'm doing." Using an interactive voice-response system, subjects completed the CAARS-S-S at 4- and 12-hours postdose 3 days/week during the washout week and each of the 4 treatment weeks.

The Clinical Global Impressions-Severity (CGI-S), -Improvement (CGI-I), and -Efficacy (CGI-E) scales were used to determine overall improvement over time. The CGI-S is a cross-sectional assessment of the severity of illness using a 7-point scale and was assessed at baseline and end point.The CGI-I (also a 7-point scale) provides a longitudinal assessment of overall symptom improvement relative to baseline and was measured weekly during the 4 treatment weeks. Investigators also completed the CGI-E weekly. The CGI-E consists of two items (Therapeutic Effects and Side Effects), each of which is a 4-point scale intended specifically to capture medication effects.

Safety Assessments

Safety was assessed through physical examination, neurologic evaluation, vital sign measurements, and clinical laboratory test results. A 12-lead ECG, performed at baseline and 2-week intervals, was evaluated for safety by the investigator but was analyzed for ECG measures by a central laboratory. Spontaneously reported adverse events (AEs) were recorded weekly using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)[27] terminology.

Statistical Analysis

Determination of Sample Size

An enrollment of 200 subjects was required to detect a standardized treatment difference of 0.60 between any MAS XR group and the placebo group at 80% power (type I error=.05) using a 2-sided t-test.

Randomization

Eligible subjects were randomly assigned to one of the four double-blind treatment groups (MAS XR 20, 40, or 60 mg/day or placebo) in a 1:1:1:1 ratio using a block randomization schedule. Each site initially received treatment kits in two complete blocks (eg, eight pre-numbered drug kits); additional kits were provided in complete blocks as needed.The clinical study coordinator at each site assigned eligible subjects the next available randomization number in ascending order. Statistical tests were completed to determine whether the counts (Cochran-Mantel-Haenszel [CMH] test) and means (F test) for demographic and baseline characteristics were similar across treatment groups.

Analyses were performed using SAS statistical software, version 6.12 or higher.[28] Efficacy results were analyzed on the intent-to-treat (ITT) sample (all subjects assigned to treatment with at least one valid post-baseline ADHD Rating Scale total score). Safety results were analyzed for all subjects assigned to treatment. For all measures, the endpoint was defined as the last valid postbaseline observation (numerically equivalent to a last observation-carried forward analysis).

Primary Efficacy Analysis

For the ADHD Rating Scale total score at endpoint, an analysis of covariance (ANCOVA) was performed, with treatment and site as fixed effects and the baseline score as a covariate. Dunnett's test was used to compare each active treatment group with placebo if an overall treatment effect was detected.This model was also applied to ADHD Rating Scale total scores at each treatment week and the ADHD Rating Scale subscale scores at endpoint. Effect size for the ADHD Rating Scale total score at endpoint was calculated as the mean treatment difference for MAS XR versus placebo divided by the pooled standard deviation.

Secondary Efficacy Analyses

Endpoint CAARS-S-S ADHD index scores were analyzed using an ANCOVA model, with treatment and site as fixed effects and the average baseline ADHD index score as a covariate. For significant overall treatment effects, pairwise comparisons were performed using a closed-testing procedure: a t-test between the least-squares means of the MAS XR 60-mg and placebo groups was performed first; if a significant difference was detected, the same test was performed for the 40-mg and 20-mg groups. To determine the treatment effect at 4- and 12-hours postdose, a similar analysis was performed for both postdose ADHD index scores at endpoint.

A dichotomized variable was created for the CGI-I: the "improved" category included subjects "very much improved" and "much improved"; the "not improved" category included all other ratings. For placebo and active treatment pairs, the dichotomized CGI-I at endpoint was analyzed for differences using a CMH test adjusted for site.The CGI-S and CGI-E results were summarized as categorical variables (n, % for each rating).

Post-Hoc Efficacy Analyses

To further investigate the dose-response relationship between ADHD Rating Scale scores and actual final dose (adjusted for final dose duration and baseline severity), a 1-way ANCOVA was performed. Actual dose was the effect, and baseline ADHD Rating Scale total score was a covariate.The difference in ADHD Rating Scale change from baseline among the active doses was assessed for each treatment week. Actual dose refers to the final dose achieved, which in some cases was less than the dose assigned by randomization. Because this was a forced-dose-escalation design, subjects assigned to higher doses did not achieve their final assigned dose until midway through the study. Some subjects may have withdrawn from the study before reaching the assigned dose. The model included the placebo dose to address the issue of minimum effective dose. Analyses were performed on ITT subjects segregated by the median baseline ADHD Rating Scale score: <32 (mild) and ≥32 (severe). The median baseline score was chosen to provide similar sample sizes for this analysis.

The linear association between final MAS XR dose at each treatment week and the proportion of subjects rated "very much improved" or "much improved" on the CGI-I scale was analyzed using the Mantel-Haenszel x^2 test.

Safety Analyses

Treatment-emergent AEs were summarized by body system, preferred term, and treatment group. Because the same subject may have reported the same AE when receiving different doses of MAS XR in this forced-dose-escalation design, the counts (and percentages) of AEs by treatment group are not independent observations.This lack of independence could affect the variability and would invalidate a test that assumes independence of the proportions. Because there is no methodology for a statistical test for linear trends in proportions where the proportions are dependent, no statistical test for a dose relationship for AEs was conducted. An ANCOVA model with treatment as a fixed effect and baseline as a covariate was fitted to the laboratory, vital sign, and ECG interval data for each visit. For statistically significant treatment effects, Dunnett's test assessed which active-treatment groups differed significantly from the placebo group. ECGs included interval measurements (RR interval, PR, QRS, QT, QTcB [Bazett correction], heart rate) and tracing interpretations (rhythm, conduction, morphology, myocardial infarction, ST segments,T waves, U waves).

Post-Hoc Safety Analyses

Outlier analyses of safety measures, including AE reports, vital signs, and ECGs (including QTcF [Fridericia correction]) were completed to further investigate the dose-response relationship for safety measures. Individual BP measurements ≥140 mmHg for systolic or ≥90 mmHg for diastolic on two consecutive visits were considered clinically significant.[28] A predefined limit of ≥110 beats per minute was considered clinically significant for individual pulse measurements. Individual changes in QT or QTcF intervals >60 milliseconds relative to baseline values were considered clinically noteworthy.[30]

RESULTS

Study Sample

Eighteen study sites screened 339 adults, and 259 subjects entered the washout phase of the study; 255 were randomly assigned to treatment, and 248 were included in the ITT sample (Figure 2).

Treatment groups were similar with respect to demographic and baseline symptom severity data (Table 1).The only statistically significant group difference observed in demographic or baseline characteristics occurred for previousstimulant exposure, whereby the placebo group had a significantly lower overall exposure than the three active-treatment groups.

Subjects, predominantly white males, ranged in age from 18-76 years.The mean time since ADHD diagnosis was 5.5 years. Mean baseline ADHD Rating Scale total scores ranged from 31-33. The mean CAARS-S-S ADHD index scores ranged from 20-23. Greater than 75% of subjects were stimulant naive.

TABLE 1.
Demographic Characteristics and Baseline Symptom Severity of the ITT Sample*

	MAS XR Assigned Dose				
	Placebo (n=60)	20 mg/day In=64)	40 mg/day In=64)	60 mg/day (n=60)	V-value
Aae Group, n 1%)					.89'
18-29	14(23)	18(28)	15(23)	12(20)	
30-39	17(28)	14(22)	20 (31)	21 (35)	
40-49	17(28)	20(31)	17(27)	13(22)	
a50	17(20)	12(19)	12(19)	14(23)	
Mean age (range)	39.3(18-59)	38.8(19-65)	38.9 (20-68)	39.9(18-76)	.93*
Sex. n 1%)					.16*
Male	41 (68)	41 (64)	38 (59)	29 (48)	
Race. n(%)					.66'
White	54 (90)	56 (87)	58 (91)	53 (88)	
Black	3(5)	3(5)	2(3)	0	
Hispanic	2(3)	4(6)	2(3)	5(8)	
Other	1 (2)	1 (2)	2(3)	2(3)	
Years since diaanosis. mean±SD	5.0±7.2	4.6±6.8	4.9±8.6	7.1±10.2	.31'
Previous stimulant exoosure. n (%)	8(13)	15(23)	17(27)	15(25)	.04'
CGI-S. n (%!					.89'
Mild	1 (2)	4(6)	3(5)	3(5)	
Moderate	33 (55)	36 (56)	41 (64)	33 (55)	
Marked	23 (38)	20(31)	18(28)	22(37)	
Severe	3(5)	4(6)	2(3)	2(3)	
ADHD-RS. mean±SD					
Total score	33.0±8.8	31.1±9.6	31.3±8.1	32.9±9.8	.45'
Inattentive score	18.9±4.8	17.8±5.4	18.0±5.0	18.2±6 1	.57'
Hyperactive/impulsive score	14.1±6.2	13.4±6.0	13.3±5.3	14.7±5.5	.43'
CAARS-S-S ADHD Index score, mean±SD	22.4±5.7	21.6±5.8	20.2±5.4	22.6±5.4	.12*

* Some of the percentages may not equal 100 due to rounding.
t Based on the Cochran-Mantel-Haenszel statistic, with adjustment for center.
t Based on the F test, using a model that included center and treatment group.

ITT=intent-to-treat; MAS XR=mixed amphetamine salts extended-release; CG I-S=Clinical Global Impressions-Severity; ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; CAARS-S-S=Conners' Adult ADHD Rating Scale Short Version Self-Report.

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Efficacy

Primary Efficacy

ADHD Rating Scale Total Scores

A 2-way analysis of variance (ANOVA) showed no difference in baseline scores across treatment groups <$F_{3,}$ 227=-87; P=.456). All MAS XR groups had improved ADHD Rating Scale total scores at endpoint (F_{32}26=$^{7-.61}$; P<-001; ANOVA for a treatment effect). However, the active-treatment groups improved nearly two fold compared with placebo (Table 2).The MAS XR 60-mg group had the greatest improvement in mean ADHD Rating Scale total scores. Mean ADHD Rating Scale inattentive subscale scores showed a statistically significant treatment effect (F_{32}26=G-89, P<.001). Dunnett's test detected significantly improved inattentive subscale scores for each MAS XR group compared with placebo. However, there was no dose-response effect (Table 2). Likewise, there was a statistically significant treatment effect

TABLE 2.
Efficacy Outcomes

	MAS XR Assigned Dose			ANOVA'		
Measure	**20 mg/day (n=64)**	**40 mg/day (n=64)**	**60 mg/day (n=60)**	**F**	**df**	**P-va/ue**
ADHD-RS Total Score				7.61	3, 226	<001
Endpoint mean+SD	18.5±12.5	18.4±11.5	18.5±11.7			
Placebo-adjusted difference (95% CI)	-6.6 (-11.Oto -2.3)	-7.2 (-11.5 to -2.8)	-7.8 (-12.2 to -3.4)			
P-value	.001	<.001	<.001			
ADHD-RS Inattentive Score				6.89	3, 226	<.001
Endpoint mean±SD	10.7±7.4	10.3±7.3	10.0±7.3			
Placebo-adjusted difference (95% CI)	-3.5 (-6.1 to -0.9)	-4.1 (-6.7 to -1.5)	-4.5 (-7.2 to -1.9)			
P-value	.005	.001	<001			
ADHD-RS HyDeractive/Inwulsive Score				6.23	3, 226	<.001
Endpoint mean±SD	7.8±6	8.0±5.3	8.5±5.3			
Placebo-adjusted difference (95% CI)	-3.1 (-5.2 to -1.0)	-3.0 (-5.1 to -0.9)	-3.3 (-5.4 to -1.3)			
P-value	.001	.002	.001			
CAARS-S-S ADHD Index Score 4 (ranae: 2-6) Hours Postdose				5.04	3,198	.002
Endpoint mean±SD	14.9±7.2	14.6±6.8	14.7±6.7			
Placebo-adjusted difference (95% CI)	-3.4 (-5.7 to -1.2)	-2.7 (-5.1 to -0.4)	-4.4 (-6.7 to -2.1)			
P-value	.004	.021	<.001			
CAARS-S-S ADHD Index Score 12 (ranae; 10-14) Hours Postdose				6.34	3,194	<001
Endpoint mean±SD	15.3±7.2	14.3±6.8	14.3±6.5			
Placebo-adjusted difference (95% CI)	-3.3 (-5.6 to -ID.	-3.2 (-5.4 to -0.9)	-4.9 (-7.1 to -2.6)			
P-value	.004	.006	<.001			

*Last observation carried forward for the ITT sample.

tDunnett's method for multiple comparisons used for the construction of 95% Cis and P-values.

MAS XR=mixed amphetamine salts extended-release; ANOVA=analysis of variance; ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; CAARS-S-S=Conners'Adult ADHD Rating Scale Short Version Self-Report; ITT=intentto treat.

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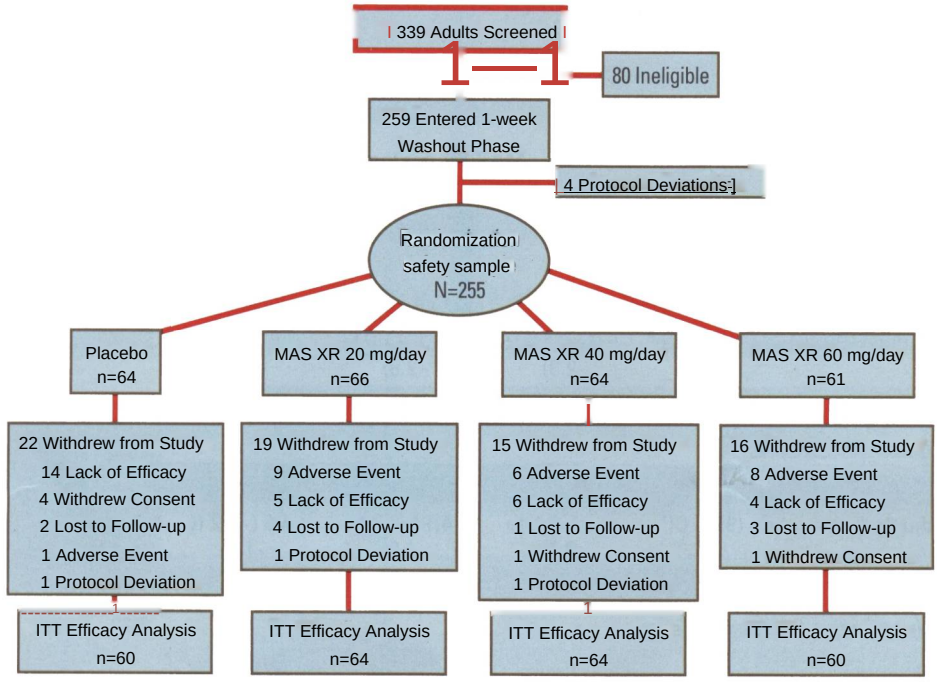
for mean ADHD Rating Scale hyperactive/impulsive subscale scores ($F_{3,226}$=6.23; P<.001), and Dunnett's test detected significantly improved scores for each MAS XR group compared with placebo, but a dose-response effect was not noted (Table 2).

Post-Hoc Analysis by Baseline Severity

Of the subjects with severe baseline symptoms (ADHD Rating Scale total score ≥32), those receiving MAS XR 60 mg/day improved significantly compared with the placebo group

FIGURE 2.

Subject flow chart: all subjects with at least 1 valid postbaseline primary efficacy assessment



MAS XFUmixed amphetamine salts extended-release; ITT-intent-to-treat.

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TABLE 3.

Summary and Analysis of Dichotomized CGI-I at Endpoint*

Dichotomized CGI-I Category	Placebo (n=60)	MAS XR 20 mg/day hi=64)	MAS XR 40 mg/day (n=64)	MAS XR 60 mg/day (n=60)	P-value'
Improved	16(27%)	32 (50%)	36 (56%)	35 (58%)	<.001
Not improved	44 (73%)	32 (50%)	28 (44%)	25 (42%)	
Difference*	N/A	23%	30%	32%	
P-value (CMH)[5]	N/A	.012	<.001	<.001	

* Last observation carried forward for the ITT sample.

t Based on the nonzero correlation CMH statistic with adjustment for center.

t Difference in the percentage of MAS XR subjects who were improved compared with placebo subjects.

§ With adjustment for center, comparing the percentage of subjects categorized as improved for each MAS XR group with the placebo group.

CGI-I=Clinical Global Impressions-Improvement; MAS XR=mixed amphetamine salts extended-release; N/A=not applicable; CMH=Cochran-Mantel-Haenszel; ITT=intent to treat.

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(mean point difference: -11.1; P=.0007) and the 20-mg group (-8.2; P=.001); improvement approached statistical significance compared with the 40-mg group (-5.2; P=.1O), suggesting a trend toward a linear dose-response relationship (Figure 3). For subjects with severe symptoms who were receiving MAS XR 40 mg/day, the change in mean ADHD Rating Scale scores at week 4 approached statistical significance compared with the placebo group (-5.9; P=.O6) but not the 20-mg group (-3.0; P=.34).The change in ADHD Rating Scale scores for subjects with severe symptoms who were receiving MAS XR 20 mg/day was not statistically different from the change for subjects receiving placebo (-2.9; P=.36).

Clinical improvement, defined as at least a 30% reduction in ADHD Rating Scale total scores, was substantially higher in the subjects receiving active treatment than in those receiving placebo. Of those who completed the study, 61% receiving placebo achieved at least a 30% reduction in ADHD Rating Scale total scores compared with 74%, 80%, and 82% of subjects receiving MAS XR 20, 40, and 60 mg/day, respectively.

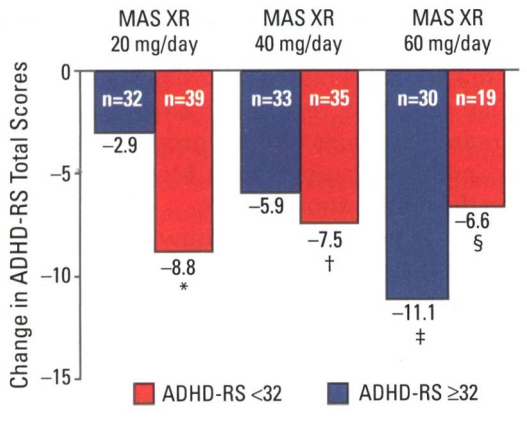
Secondary Efficacy

CAARS-S-S ADHD Index

ANOVA indicated a statistically significant treatment effect for the 4-hour postdose CAARS-S-S ADHD index ($F_{3,198}$=5.04; P=.OO2) and the 12-hour postdose CAARS-S-S ADHD index ($F_{3,194}$=6.34; Pc.001) (Table 2). The endpoint CAARS-S-S ADHD index scores were similar (14-15 unit points for all MAS XR groups) at 4- and 12-hours postdose, suggesting that MAS XR has a 12-hour duration of effect in adults with ADHD, although this should be considered a preliminary finding since the CAARS-S-S ADHD index is not a validated measure of diurnal symptom change. At both 4- and 12-hours postdose, all MAS XR groups were statistically significantly improved compared with placebo on the CAARS-S-S ADHD index, but dose-response relationships did not occur at either time point (Table 2).

FIGURE 3.

Least-squares mean differences in ADHD-RS total scores for MAS XR compared with placebo at week 4 (actual dose) by baseline ADHD symptom severity. This analysis indicates a dose-response effect for subjects with more severe ADHD



* Pc.0001 vs placebo.

t P<.0005 vs placebo.

t P=.0007 vs placebo

§ P=.O101 vs placebo.

ADHD-RS=Attention-Deficit/Hyperactivity Rating Scale; MAS XR=mixed amphetamine salts extended-release.

Weisler RH, Biederman J, Spencer TJ, Wilens TE, Faraone SV, Chrisman AK, Read SC, Tulloch SJ. CNS Spectr. Vol 11, No 8. 2006.

TABLE 4.

AEs Reported by at Least 10% of Subjects in Any Treatment Group"

	MAS XR Assigned Dose			
AE (COSTART Term), n (%)	Placebo (n=64)	20 mg/day (n=66)	40 mg/day (n=64)	60 mg/day (n=61)
Dry mouth	3(5)	16(24)	28(44)	23 (38)
Anorexia	2(3)	13(20)	27 (42)	23 (38)
Insomnia	8(13)	14(21)	19(30)	16(26)
Headache	8(13)	9(14)	19(30)	16(26)
Nervousness	8(13)	7(11)	10(16)	7(12)
Weight loss	0	3(5)	10(16)	7(12)
Nausea	1 (2)	5(8)	5(8)	6(10)
Agitation	3(5)	5(8)	4(6)	6(10)
Anxiety	2(3)	4(6)	4(6)	6(10)

*AEs considered possibly or probably related to study medication for all subjects who received at least one dose of study medication. Because this was a forced-dose-escalation design over a 4-week period, subjects may have reported the same AE more than once and at more than one MAS XR dose.

MAS XR=mixed amphetamine salts extended-release; AEs=adverse events; COSTART=Coding Symbols for a Thesaurus of Adverse Reaction Terms.

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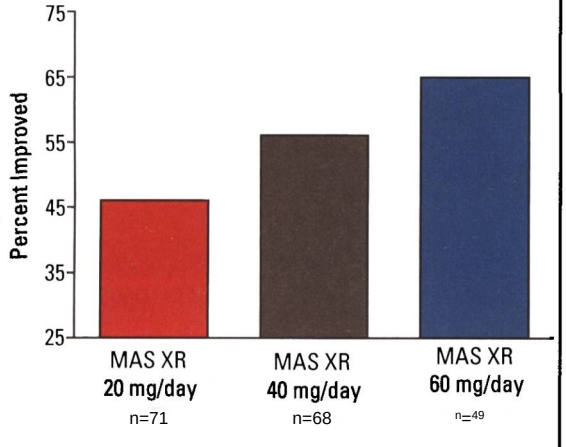
Clinical Global Impressions

Only 27% of placebo subjects experienced robust improvement (endpoint CGI-I score of 1 or 2 ["very much improved" or "much improved"]) compared with 55% of subjects receiving MAS XR (103/188). The nonzero correlation CMH statistic showed a statistically significant correlation (Pc.OOl) between dose and the percentage of subjects considered improved by investigators (includes ratings of "very much improved" or "much improved" on the CGI-I scale) (Table 3).The post-hoc analysis of CGI-I indicated that, at week 2, when subjects assigned to the 40- and 60-mg groups received 40 mg/day, the linear relationship between dose and proportion of subjects considered improved was statistically significant (P=.O3). At weeks 3 and 4, when subjects were receiving assigned doses (20, 40, or 60 mg/day) according to the forced-dose-escalation design, the association between MAS XR dose and the proportion of subjects who were improved was statistically significant (P=.01 and P=.04, weeks 3 and 4, respectively [Figure 4]).These findings demonstrate a clear dose-response for efficacy as measured by the CGI-I.

FIGURE 4.

Linear dose-response relationship for the proportion of subjects rated by investigators as improved (includes "very much improved" and "much improved") on the CGI-I scale at week 4 (actual MAS XR dose). The linear dose-response trend is statistically significant (P=.O4 by the Mantel-Haenszel x^2 test)



CGI-I=Clinical Global Impressions-Improvement scale; MAS XR=mixed amphethamine salts extended-release.

Weisler RH, Biederman J, Spencer TJ, Wilens TE, Faraone SV, Chrisman AK, Read SC, Tulloch SJ. CNS Specie. Vol 11, No 8. 2006.

Substantially more subjects receiving MAS XR 20 mg/day (56%), 40 mg/day (59%), or 60 mg/day (60%) reported either "marked—vast improvement" or "moderate—decided improvement" on the CGI-E Therapeutic Effects scale than did subjects receiving placebo (25%). There was a suggestion of a dose-response effect as the proportion of subjects with "marked—vast improvement" increased with dose. Most subjects reported "none" or "do not significantly interfere with functioning" on the CGI-E Side Effects scale (placebo group: 97%; 20-mg group: 84%; 40-mg group: 84%; 60-mg group: 85%). Few subjects in any treatment group reported that side effects "outweighed therapeutic benefit" (placebo group: 3%; 20-mg group: 6%; 40-mg group: 6%; and 60-mg group: 5%).The post-hoc dose-response analysis of the CGI-E data suggested that there were significantly fewer side effects relative to therapeutic improvement in the higher-dose groups ($x^2(6)=21.1$; P=.002).This effect was stronger for subjects with high ADHD symptom severity at baseline.

Safety

All 259 subjects enrolled were included in the AE evaluation.The ITT sample (n=255) was evaluated for all other safety measures.

Adverse Events

No serious adverse events (AEs) were reported. The incidences of treatment-related AEs are summarized inTable 4.The most commonly reported AEs were dry mouth (27.4% of all subjects enrolled), anorexia/decreased appetite (25.5%), insomnia (23.9%), and headache (23.6%). Most AEs were mild or moderate in intensity. Insomnia was the only severe AE reported in two or more MAS XR-treated subjects (20-mg group: n=2; 40-mg group: n=3; 60-mg group: n=4). Most AEs occurred during the first treatment week.

Twenty-four subjects withdrew from the study due to AEs: one (1.6%) placebo-treated subject, nine (13.6%) MAS XR 20-mg subjects, 6 (9.4%) 40-mg subjects, and eight (13.1%) 60-mg subjects (Figure 2). The most common AEs leading to discontinuation were insomnia (10 [3.9%] subjects), agitation (four [1.6%] subjects), anxiety (four 1.6%), and nervousness (four 1.6%).

Three subjects were withdrawn from the study due to cardiovascular AEs (two tachycardia; one hypertension), one participant had increased liver enzymes, and one experienced chest pain of unclear etiology. None of the subjects required treatment for an AE.

Other Safety Assessments

There was a slight decrease from baseline to endpoint in mean cholesterol (-2.4 mg/dL) for placebo, compared with larger, statistically significant (Pc.05), decreases for MAS XR 20 mg/day (-15.5 mg/dL), 40 mg/day (-16.0 mg/dL), and 60 mg/day (-18.6 mg/dL).There was also a slight decrease in triglycerides for placebo (-1.8 mg/dL) compared with larger, statistically significant (Pc.05), decreases for MAS XR 20 mg/day (-31.0 mg/dL), 40 mg/day (-20.0 mg/dL) and 60 mg/day (-42.4 mg/dL). Changes in mean laboratory values from baseline to endpoint were otherwise small in magnitude and showed no apparent trend. Changes in individual laboratory values observed during this study seemed to be spontaneous events and, with one exception (increased liver enzymes), were not considered clinically significant. Changes in physical examinations were similar across placebo and MAS XR groups. A statistically significant treatment effect of MAS XR on weight was observed (2-way ANCOVA, Pc.001): the mean weight loss between baseline and endpoint was 1.1 ±1.8 kg for the 20-mg group (P=.O1), 2.5±2.3 kg for the 40-mg group (Pc.001), and 2.5±2.5 kg for the 60-mg group (Pc.001) compared with a mean weight gain of 0.1±2.7 kg for subjects receiving placebo. However, weight loss was not considered clinically significant in any individual subject.

Vital Signs

Mean changes in vital signs were moderate and not considered clinically meaningful. A 2-way ANCOVA indicated a statistically significant treatment effect of MAS XR on pulse (P=.025) and systolic BP (P=.O15) but not on diastolic BP (P=. 135). Dunnett's test for multiple comparisons was used to further analyze mean changes in pulse and systolic BP for each MAS XR group compared with placebo. Between baseline and endpoint, mean±SD changes in pulse (beats per minute) were 4.2±9.7 (P=.582), 5.3±11.3 (P=.O53), 6.2±10.9 (P=.O16) in the 20-, 40-, and 60-mg groups, respectively, compared with 1.9±10.4 beats per minute for the placebo group. For systolic BP (mmHg), mean±SD changes were 0.3±11.2 (P=.191), 4.3±12.3 (P=.004), and 0.9±10.2 (P=.219) in the 20, 40-, and 60-mg groups, respectively, compared with -1.9±10.1 mmHg in the placebo group.

A post-hoc outlier analysis of vital signs did not reveal a dose-response relationship for MAS XR 20 mg/day to MAS XR 60 mg/day for pulse, systolic BP, or diastolic BP. Only one subject in each treatment group had a pulse ≥110 beats per minute at any point, and changes ≥25 beats per minute were transitory and not dose dependent. Although MAS XR appears to have a slight effect on systolic BP, the outlier analysis did not indicate a dose-response relationship. A small number of subjects receiving placebo or MAS XR had generally transient systolic BP increases of ≥20 mmHg and few subjects had two consecutive measurements ≥140 mmHg (one, four, one, and three subjects in the placebo, 20-, 40-, and 60-mg MAS XR groups, respectively). Similarly, few subjects had diastolic BP increases of ≥10 mmHg from baseline and few had measurements ≥90 mmHg at two consecutive visits (four, three, one, and three subjects in the placebo, 20-, 40-, and 60-mg MAS XR groups, respectively). No apparent trends were identified for any of the cardiovascular measurements with respect to absolute increases from baseline or increases above the threshold values on consecutive visits.

Electrocardiograms

The ECG data did not suggest any clinically significant cardiovascular treatment effects associated with MAS XR in adults. The incidence of qualitative ECG abnormalities was similar for subjects receiving placebo and for subjects receiving MAS XR, and the abnormalities were either normal variants or they were of limited clinical relevance.

Analyses of ECG interval measurements by 2-way ANCOVA revealed no clinically meaningful differences in PR (P=.354) or QRS (P=.204) intervals from baseline to endpoint between MAS XR (all doses) and placebo. Statistically significant treatment effects (ANCOVA) were noted for heart rate (Pc.001) and for QT (P=.OO2) and QTcB (P=.OO3) intervals.The mean changes for each treatment group were not considered clinically significant and were not statistically significant in many cases when further analyzed by dose (Dunnett's test was used for the construction of treatment group P-values).The mean changes from baseline to endpoint for heart rate (beats per minute) were -2.0±9 for the placebo group; 2.6±9 for the 20-mg group (P=.O35); 7.3±12 for the 40-mg group (Pc.001), and 4.8±11 for the 60-mg group (P<.001).The mean changes from baseline to endpoint for the QT interval (milliseconds) were 2.9±22 for the placebo group; -6.0±21 for the 20-mg group

(Ft.211); -11.7±25 for the 40-mg group (P=.OO1), and -7.1±21 for the 60-mg group (P=.O47). For the QTcB interval (milliseconds), mean changes from baseline to endpoint were -2.8±19 for the placebo group; 1.0±21 for the 20-mg group (Ft.101); 6.9±21 for the 40-mg group (P=.OO7), and 5.6±22 for the 60-mg group (P=.OO2). There were no apparent dose-response relationships.

The post-hoc analysis using the Fridericia method of correction indicated no statistically significant change from baseline in the QTcF intervals for MAS XR (all doses) versus placebo (ANCOVA, P=.132).The mean QTcF interval changes (milliseconds) from baseline to endpoint were —1.5±16 for the 20-mg group (P=. 149); —1.1 ±21 for the 40-mg group (P=.465); and —1.1 ±19 for the 60-mg group (P=.O75). Dunnett's test was used for the construction of treatment group P-values. At endpoint, mean QT intervals did not exceed 436 milliseconds for the MAS XR groups or 433 milliseconds for the placebo group. A few 30-59 milliseconds increases were recorded, but these changes were evenly distributed across the placebo and MAS XR groups. None of the subjects in any treatment group experienced a ≥60 milliseconds increase in QT or QTcF intervals.

DISCUSSION

In this largest adult ADHD stimulant study to date, results indicate that once-daily MAS XR 20 mg/day, 40 mg/day, and 60 mg/day doses were safe and effective in the treatment of adult ADHD, combined type. Subjects treated with MAS XR had significantly improved symptoms compared with placebo, as determined by the ADHD Rating Scale. Improved symptoms were detected within the first treatment week and maintained throughout the study. Although the lowest dose used in this study (20 mg/day) led to some improvement, the 40 mg/day and 60 mg/day doses led to increasing levels of efficacy.The dose-response of efficacy seemed to be related to symptom severity: adults with mild symptoms had significantly greater improvements with the lowest MAS XR dose (20 mg/day), whereas those with severe symptoms had significantly greater improvements with the highest dose (60 mg/day). The mean effect size for MAS XR 20, 40, and 60 mg/day was 0.8 based on ADHD Rating Scale total scores at endpoint.

Treatment efficacy is arguably most difficult to demonstrate in combined-type adult ADHD, because hyperactive/impulsive symptoms become less problematic in adulthood.[12] Significant improvements in ADHD Rating Scale inattentive and hyperactivity/impulsivity subscale scores were demonstrated in all MAS XR groups compared with placebo, but a dose-response effect was not observed for either subscale.

As expected, daily symptom relief continued for up to 12 hours for all MAS XR doses as demonstrated by CAARS-S-S ADHD index scores. This is an important benefit for individuals with ADHD, given the potential for missed doses with multiple daily dose regimens. Additionally, compliance with XR stimulant medications is improved,[31] and the XR platform of these formulations may result in a lower abuse liability relative to IR stimulant formulations.[31]

Subjects receiving MAS XR had greater improvements on all CGI measures compared with those receiving placebo. Nearly 30% of MAS XR-treated subjects achieved remission, as defined by CGI-S scores of 1 or 2 at endpoint.The CGI-I indicated statistically significant global improvements, with a clear dose response for efficacy for all MAS XR groups when analyzed by final dose. Analysis of the CGI-ETherapeutic Effects and Side Effects scales suggests that the therapeutic benefit of treatment outweighs the impact of side effects in the higher-dose groups, particularly for subjects with higher symptom severity at baseline.

ADHD medications modulate the cognitive processes of attention and impulse control through effects on both dopaminergic and noradrenergic neurotransmitter systems.[32] Stimulants are indirect agonists of catecholaminergic transmission in the central nervous system and increase the amount of dopamine and norepinephrine available presynaptically.[32] The differences in synaptic mechanisms of action of amphetamine and methylphenidate (MPH) may explain the differential response to these medications in some patients.[33] Both medications block the reuptake of catecholamines by binding to catecholamine reuptake transporter proteins, but amphetamine can also be transported into the nerve terminal via the transporter proteins and enhance the release of neurotransmitters stored in cytoplasmic vesicles.[34] Bupropion, atomoxetine, and tricyclic antidepressants also affect catecholaminergic transmission, although the clinical effect of

these medications appears to be somewhat less robust than that of stimulant medications.

The average effect size of MAS XR (calculated without regard to severity of illness at baseline) was 0.8 in this study, which is similar to effect sizes reported for other studies of stimulant medications in adults with ADHD. Faraone and colleagues[36] completed a meta-analysis of six placebo-controlled studies of MPH in adults with ADHD and reported a mean effect size of 0.9. The treatment effect sizes for stimulant medications are higher than those for nonstimulant medications in adults with ADHD. An effect size of 0.6 based on ADHD Rating Scale total scores was reported for a short-term, placebo-controlled, flexible-dose study by Wilens and colleagues[36] of an extended-release bupropion formulation (bupropion XL). Effect sizes of 0.35 and 0.40 based on the investigator-rated CAARS-S-S were reported for two short-term, placebo-controlled, flexible-dose atomoxetine studies.[33] Demographic characteristics and baseline symptom severity were similar for both the MAS XR and atomoxetine adult study samples,[37] whereas subjects in the bupropion XL study had more severe symptoms at baseline (mean baseline ADHD Rating Scale score of 36) and 37% of the subjects had ADHD, inattentive subtype.[36]

Response rates for MAS XR (defined as ≥30% improvement on the ADHD Rating Scale total score at endpoint) are similar to those reported for other large, well-controlled studies in adults with ADHD. In a forced-dose-escalation study of dexmethylphenidate extended-release (D-MPH XR) in 221 adults,[38] response rates were 34% for placebo; 58% for D-MPH XR 20 mg/day; 54% for D-MPH XR 30 mg/day, and 61% for D-MPH XR 40 mg/day. In the Wilens and colleagues[36] study of bupropion XL in 162 adults with ADHD, ~50% of subjects achieved at least a 30% reduction in ADHD Rating Scale total scores compared with 30% of placebo subjects.The magnitude of difference in response rates for the placebo versus active groups in all these large, well-controlled, multicenter studies appears to be =20 percentage points. Higher response rates may be achieved with higher doses. In smaller (N≤40), single-site studies of adults with ADHD,[18,19,38] response rates of 70%, 78%, and 76% have been reported for MAS IR 54 mg/day, MPH IR 0.9 mg/kg/day, and bupropion 362 mg/day, respectively.

An MAS XR dose relationship was not established for any safety assessment. Overall, treatment-related AEs (eg, dry mouth, anorexia, insomnia, and headache) were similar in type to those reported in children. Most adults in this study were stimulant naive, which may account for the higher incidence of AEs compared with studies of children with ADHD, who typically have a history of stimulant treatment. Of note, side effects diminished rapidly over time; >40% of the treatment-emergent AEs were reported during the first week of treatment and <10% were reported during the fourth week.

MAS XR appears to have an acceptable cardiovascular safety profile in adults with ADHD. Group mean changes in vital signs were not clinically significant. Individual changes in BP and pulse were sporadic and resolved spontaneously. The ECG data indicated no clinically relevant effects on ECG measurements, and no clear dose-response relationships were evident for any cardiovascular safety measures. No treatment-emergent abnormalities in cardiac conduction were found.

Based on an August 2004 MAS XR product label revision[40] cautioning against the use of MAS XR in patients with structural cardiac abnormalities, Health Canada suspended the sale of MAS XR throughout Canada in February 2005. Despite the action of this regulatory agency, the Food and Drug Administration took no additional action, having concluded that the sudden death rate associated with MAS XR was no greater than that expected in patients not exposed to MAS XR. In August 2005, Health Canada reinstated the marketing authorization of MAS XR. Nevertheless, like other stimulants, the FDA labeling for MAS XR carries a warning against the misuse of amphetamine because of the risk for sudden death and serious cardiovascular adverse events. Hence, clinicians are urged to follow the recommendations of the American Heart Association[41] suggesting a careful patient history, evaluation of symptoms, and evaluation of medication use, including over-the-counter medications, with the detection of symptoms or risk factors prompting a cardiovascular examination, prior to being prescribed MAS XR or any other stimulant medication, in light of the potential for significant increases in heart rate and BP associated with amphetamines in a small percentage of patients.[41]

Limitations of this 4-week study relate primarily to the diagnostic criteria for adult ADHD, combined type. Because many adults with ADHD are below the diagnostic threshold for hyperactivity/impulsivity, the study sample (ADHD, combined type) may not be representative of the general adult ADHD sample. In addition, the forced-dose-escalation study design may have underestimated efficacy because subjects assigned to higher doses did not achieve their final assigned dose until midway through the study, or overestimated side effects because AE reports were cumulative for all doses.

CONCLUSION

This short-term, placebo-controlled, forced-dose-escalation study found that once-daily doses of MAS XR 20 mg, 40 mg, and 60 mg were safe and effective in adults with ADHD. Treatment response based on post-hoc analysis was related to ADHD symptom severity: MAS XR 20 mg/day was effective for subjects with low symptom severity at baseline, and a trend toward dose response for efficacy was observed for adults with higher baseline symptom severity. All doses of MAS XR adequately controlled ADHD symptoms for up to 12 hours and were well tolerated, with no evidence of a dose-response relationship for safety assessments. Because treatment response appears to depend on baseline symptom severity, MAS XR should be dosed to optimal efficacy based on an objective symptom rating scale. Additional research is needed to document whether these short-term benefits are sustained during long-term treatment. **CNS**

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SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy with lithium or divalproex, and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL.

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Precautions include the risk of seizures, orthostatic hypotension, and cataract development.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

'All atypical prescriptions: Total prescriptions. Jan. 05-Feb. 06. New prescriptions. Sept. 04-Feb. 06. IMS Health. National Prescription Audit.

* Significant improvement in all 11 YMRS items was measured at Day 21 and continued through Day 84 in monotherapy mania trials.

Please see Brief Summary of Prescribing Information on adjacent page.

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BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing information.

Increased Mortality In Elderly Patients wftfi Dementia-Related Psychosis
Elderty patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an Increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration ol 10 weeks) In these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen In placebo-treated patients. Over the course of a typical 10 week controlled trial, the rale ol death In dreg-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or Infectious (eg, pneumonia) In nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS AND USAGE: Bipolar Mania SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy Inals and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mama. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient Schizophrenia SEROQUEL is indicated for the treatmen! of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effect.veness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.
CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.
WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) Is not approved lor the treatment ol patients with dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS). A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g.,pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic tax city, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the undertying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved tor patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. Hyperglycemia and Diabetes Me 11 Itus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes meliitus in patients with schizophrenia and the increasing incidence of diabetes meliitus in the general population. Grven these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes meliitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes meliitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.
PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its a,-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension ana syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. Cataracts: The development of cataracts was observed in association with quetiapine tzaalmafrt In chronic in rtudiea (see Animal Toxicology), Lens changes have alio been observed In pallente during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as silt lamp exam or other appropriately sensitive methods, Is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment. Seizures: During clinical trials, seizures occurred In 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) or placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer s dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) ol SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mama adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH leveis Of me SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. Cholesterol and Triglyceride Elevations: In schizophrenia trials, SEROQUEL treated patients had increases from baseline in cholesterol and triglyceride of 11% and 1 /%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL treated patients. Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed In rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time Transaminase Elevations; Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits ol the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. Potential lor Cognitive and Motor Impairment Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dcse-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. Wnile a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Use In Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially (luring the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases m dose. Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. Pregnancy: Patients should be advised to notify their physician it they become pregnant or intend to become pregnant during therapy. Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL. Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. Alcohol: Patients should be advisedtoayoidwhsulnwalcoholicbeverag^wtilelal<IngSEROOUELH<atEiposinsndDfiM SIS regarding appropriate care in avoiding ove"J" ?nt, deh y«raMr Uboralory Tests: No steal- ... are recommended. Drug Interactions: The r... ated in systematic studies. 'SiSEPrKXSriSWn? <"fin*»ractloiisonthebasisolger<ler,aoe.andracedIdni>trevBalaayclliilcallymeanInofullIltfererces'niheadverae ... drugs. SEROQUEL potentiated the ... disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. The Effect ol Other Drags on Quetiapine: Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g„ valproate). Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance. Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment tor quetiapine is not required when it is given with cimetidine. P450 3A Inhibitors: Coadministration of ketoconazole 1200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g,. .itraconazole, fiuconuole. and erythromycin). Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics ... Effect of Quetiapine on Other Drugs: Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11 % in the presence of quetiapine (150 mg bid). The changes were not significant. Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a id schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significant^ induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. Carcinogenesis, Mutagarvesis. Impairment of Fertility: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20,75,250, and 750 mg/kg and to rats by gavage at doses of 25,75, and 250 mg/kg for two years. These drees are equivalent to 0.1,0.5,1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m² basis (mice) or 0.3,0.9, and 3.0 times the maximum human dose on a mg/m² basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m² basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all drees tested (25,75, and 250 mg/kg or 0.3,0.9, and 3.0 times the maximum recommended human dose on a mg/m² basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas tc human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurement in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in PRECAUTIONS, General). Mutagenreis: The mutagenic potential of quetiapine was tested in six in vitro bacterial gene mutation assays and in an in vitro mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one Salmonella tvplmiriumtester strain in the presence of metabolic activation. No evidence ot clastogenic potential was obtained in an mwfro chromosomal aberration assay in cultured human lymphocytes or in the in vivo micronucleus assay in rats. Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral drees of 50 and 150 mg/kg or 0.6and 1.8 times the maximum human dose on a mg/m² basis. Drug-related effects included increases in interval to matei and in the number ot matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week penod without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m² basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of ... mg/kg, or ... times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was obsarwd at dases di fo and 50 rngltg, or 0,1 and 0.0 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mgkg, or 0,01 lines the maximum human dose on a mg/m² oasis. Pregnancy: Pregnancy Category C: The teratogenic polental of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenes s No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 m^kg or 0.3 to 2.4 tirrtes the maximum human dree on a mg/m² basis or in rabbits at 25 to 100 mgkg or 0.6 to 2.4 times the maximum human dose on a mg/m² basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dree on a mg/m² basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose ona mg/m² basis). Fetol body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis for both species). There was an increased incidence of a minor soft tissue anomaly (carjortarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1,10, and 20 mg/kg or 0.01,0.12, and 0.24 times the maximum human dose on a mg/m² basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown. Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Geriatric' Use: Ot the approximate?3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence ot factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration ot a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderty patients when compared to younger patients.
ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patents exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed tc 1 or more doses of SEROQUEL for the treatment of schizophrenia Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who partic-ipated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. Refer to the full Prescribing information for details of adverse event data collection _Adverse Findings Observed In Short-Term, Controlled Trials: Adverse Events Associated with Dlscontinuafion of Treatment in Mort-Term, Placebo-Controlled Trials: Bipolar Mania: Overall, discontinuations due to adverse events were ... SEROQUEL vs. 5.1% tor placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see PRECAUTIONS): Somnolence 0.8% vs 0% for placebo and Hypotension 0.4% vs 0% for placebo. Adverse Events Occurring at an Incidence ol 1% or More Long SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations in the full Prescribing Information cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and rondrug factors to the side effect incidence in the population studied. Table 1, in the full Prescribing Information, enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Treatment-Emergent Adverse Experience Incidence In 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia end Bipolar Mania (monotherapy): Body as a Whole: Headache, Pain, Asthenia, Abdominal Pain, Back Pain, Fever; Cardiovascular.' Tachycardia, Postural Hypotension; Digestive: Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased; Metabolic and Nutritional: Weight Gain, SGPT Increased, SGOT Increased; Nervous: Agitation, Somnolence, Dizziness, ...; Respiratory: Pharyngitis, Rhinitis; Skin and Appendages: Rash; Specie I Senses: Amblyopia. 'Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, ... paresthesia, peripheral edema, sweating, tremor, and weight loss. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%), Table 2, from the full Prescribing Information, enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patents treated with SEROQUEL was greater than the incidence in placebo-treated patients. Tteatmeni-Emerjent Advene Experience Incidence in 3-Week Placebo-Controlled Clinical Triale' for the Treatment of Bipolar Mania (Adjunct Therapy): Body as a Whole: Headache, Asthenia, Abdominal Pain, Back Pain; Cardiovascular: Postural Hypotension; Digestive: Dry Mouth, Constipation; Metabolic and flutrlthiwl: Weight Gain; Nervous: Somnolence, Dizziness, ...; Respiratory: Pharyngitis. 'Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: akathisia, diarrhea, insomnia, and ... In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (Incidence of 5% or greater) and observed at a rate on SEROQUEL at least twee that ol ptaito win somnolence I34%|, dry mouth (19%). a ... hypotension (7%), ... and weight ... Explorations ... occurrence on te basis ol test dmopraptic factors. Don Dtptmbnq of Advin Ends In Stiort-Tenn Placebo-Controlled Trials: ... Stntiantously elicited adarsi awt daa tarn a sidy d schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo ... expected dose-related ... response ... following ... Twi 2 tedness of adverse events. Logistic regression analyses ... adverse e'/ents: dyspepsia, abdominal pain, and weight ga-i. E ... Increased noses of ^f^M^fa from one 6-week clinical tr^ of schizophrenia companng five fixed doses ... and 7® nwy) provided evidence for the lack of treatment-emergent extrapyramidal symptoms ... Caution elatedness for EPS associated with SEROQUEL treatment. Three ... Angus total score (mean change from baseline) which evaluates parkinsonism ... neous complaints of EPS (akathisia, akinesia, cogwheel rigidity ... neck rigidity, and tremor), and (3) use of anticholinergic medication ... Laboratory Studies: Vital Sign Changes: SEROQUEL is associated ... Weight Gain: In schizophrenia trials the proportions of patients meeting ... were compared in a pool of four 3- to 6-week placeborcontrolled ... greater incidence of weight gam for SEROQUEL (23%) compared to ... proportions of patients meeting the same weight gain criterion were ... adjunct therapy trials the proportion of patients meeting the same ... placebo. Laboratory Changes: An assessment of the premarketing experience ... associated with asymptomatic increases in SGPT and increases in ... CAUTIONS). An assessment of hematological parameters in short-term, placeborcontrolled trials ... ly if11portant dterees between SER0QUEL and placetl0 ECG Ch,nyBS: Betwesn oroup com)arisons ,or P«l&d placebo<ontrolled tnals revealed no statistically significant SEROQUE/placebo differences m the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the critena for tachycard ai were ... schizophrenia revealing a 1% (4/399) incidence ... (1/156) incidenceifor placebo. In acute (monotherapy) bipolar mama trials ... tachycardia was 0.5% (1/192) for SEROQUEL comjiared to 0% ... (adjunct) trials the proportions of patients meeting the same ... pared to 0% ((VI71) incidence for placebo. SEROQUEL use was associated ... assessed by ECG, of 7 beats per minute compared to a mean increase ... This slight tendency to tachycardia may be related to SEROQUEL's ... CAUTIONS). Other Adverse Events Observed During the Pra-Martteting Evaluation ... COSTART terms that reflect treatment-emergent adverse events as defined ... REACTIONS section reported by patients treated with SEROQUEL at multiple doses ... a trial within the premarketing database of approximately 2200 patients ... are included except those already listed in Table 1 or elsewhere in labeling ... remote, and those event terms which were sc general as to be uninformative ... although the events reported occurred during treatment wnh SEROQUEL ... Evenls ar9 fur1her cateoorized by body system and listed in order of decreasing frequency according ... least 1/100 patients (only three not already listed in the tabulated listing); infrequent adverse events are tnose occurnng in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Nervous System: Frequent: hypertonia, dysarthria; Infrequent: abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; Rare: aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased', neuralgia, stuttering, subdural hematoma. Body as a Whole: Frequent: flu syndrome; Infrequent: neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; flare: abdomen enlarged. Digestive System: Frequent: anorexia; Infrequent: increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; Rare: glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. Cardtovasctilar Systwi: Frequent palpitation; infrequent: vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; Re/s: angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. Respiratory System: Frequent pharyngitis, rhinitis, cough Increased, dyspnea; Infrequent: pneumonia, epistaxis, asthma; Rare: hiccup, hyperventilation. Metabolic and Nutritional System: Frequent: peripheral edema; Infrequent: weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; Rare: glycosuria, gout, hand edema, hypokalemia, water intoxication. Skin and Appendages System: Frequent: sweating; Infrequent: pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; Rare: exfoliative dermatitis, psoriasis, skin discoloration. Urogenital System: Infrequent: dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence, dysuria, vagina moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea, female lactation, leukorrhea, vaginal hemorrhage*, vulvovaginitis*, orchitis*; Rare: gynecomastia*, nocturia, polyuria, acute kidney failure. Special Senses: Infrequent: conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain, flan: abnormality of accommodation, deafness, glaucoma. Musculoskeletal System: infrequent pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. Hemic and Lymphatic System: Frequent: leukopenia; Infrequent: leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; tymphadenopathy, cyanosis; Rare: hemolysis, thrombocytopenia. Endocrine System: Infrequent hypothyroidism, diabetes meliitus; Rare: hyperthyroidism. *adjusted for gender. Post Marieting Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy indude: leukopenia'neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for isukopen'a/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylactic reaction, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens Johnson Syndrome (SJS)

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a oontroH substance. FHyskal and Psychologic dependence: SEROQUEL has not wan systwnatloal^ studied. In animals or humans, tor Its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.
OVERDOSAGE: Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical tnal database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e, drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mo, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. Management ot Overdosage: In case ol acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If anliarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard ot additive QT-prolonging effects vrtien administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to exoect that the aloha adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms^ anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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