CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-121/S-004

ALZA Corporation
Attention: Tracy Lin
Associate Director, Regulatory Affairs
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Lin:

Please refer to your supplemental new drug application dated November 30, 2001, received December 3, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CONCERTA™ (methylphenidate hydrochloride) Extended-release Tablets.

We acknowledge receipt of your submissions dated February 14, March 1 and 4, 2002

This supplemental new drug application provides for an additional 27 mg dosage strength to be manufactured at the Vacaville manufacturing site and the requisite changes in the labeling for this new strength. In addition, the phrase, 'esophageal motility disorders' has been added to 'Potential for Gastrointestinal Obstruction' in the WARNINGS section of the labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling text dated November 30, 2001. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 30, 2001).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-121/S-004". Approval of this submission by FDA is not required before the labeling is used.

BIOPHARMACEUTICS

The previously approved *in vitro* specifications are also recommended for the 27 mg methylphenidate HCl OROS® formulation. The recommended *in vitro* specifications are as follows:

Time Point	Specification of label claim(%range) Specification
at 1 h	(b)(4)----------
at 4 h	----------

The *in vitro* testing is performed with USP Type VII dissolution apparatus with oral extended release tablet holder (spring holder) in pH 3 water with a fixed agitation rate of 30 cycles per minute, maintained at a temperature of 37±0.5° C.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you should have any questions, please call, Ms. Anna Marie Homonnay, Regulatory Project Manager, at (301) 594-5535.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
4/1/02 08:29:50 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

TEAR HERE

SEE INSIDE FOR PATIENT INFORMATION

00122481

CONCERTA®

CONCERTA®

00122481

SEE INSIDE FOR PATIENT INFORMATION

INFORMATION FOR PATIENTS TAKING CONCERTA® OR THEIR PARENTS OR CAREGIVERS

CONCERTA®
(methylphenidate HCl)
Extended-release Tablets ℂ

This information is for patients taking CONCERTA® Extended-release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking CONCERTA®. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA®, talk to your doctor or pharmacist.

What is CONCERTA®?

CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA® work?

Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA®?

You should NOT take CONCERTA® if:

- You have significant anxiety, tension, or agitation since CONCERTA® may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA®?

Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.

You may take CONCERTA® before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?

In the clinical studies with patients using CONCERTA®, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in CONCERTA®, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?

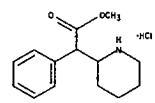
Talk to your doctor ***before*** taking CONCERTA® if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.

CONCERTA®
(methylphenidate HCl)
Extended-release Tablets ℂ

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36 or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is dl (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl methylcellulose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA® to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. CONCERTA® qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid (see Figure 1). The relative bioavailability of CONCERTA® qd and methylphenidate tid in adults is comparable.

FIGURE 1

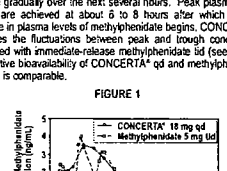


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA® 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.

TABLE 1
Mean ± SD Pharmacokinetic Parameters

Parameters	CONCERTA® (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{0-t} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{1/2}$ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated qd dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated qd dosing are similar to those following the first dose of CONCERTA® 18 mg.

Dose Proportionality

Following administration of CONCERTA® in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC_{0-inf} of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and AUC_{0-inf} increased disproportionately with respect to dose. Following administration of CONCERTA®, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of CONCERTA® was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to α-phenyl-piperidine acetic acid (PPA) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated qd doses of CONCERTA® is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC_{0-inf} values for CONCERTA® were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA®, dose-adjusted AUC_{0-inf} was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of CONCERTA® has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of CONCERTA® in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA®.

Hepatic Insufficiency

There is no experience with the use of CONCERTA® in patients with hepatic insufficiency.

Clinical Studies

CONCERTA® was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in three double-blind, active- and placebo-controlled studies in 416 children 6 to 12 years old. The controlled studies compared CONCERTA® given qd (18, 36, or 54 mg), methylphenidate given tid over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

The Diagnostic and Statistical Manual, 4th edition, of the American Psychiatric Association (DSM-IV) provides criteria for three subtypes of ADHD (Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type). These criteria were used for diagnosis in all three studies.

Symptoms of ADHD were evaluated by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA® qd . The scores for CONCERTA® and placebo for the three studies are presented in Figure 2.

FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners Inattention/Overactivity Scores

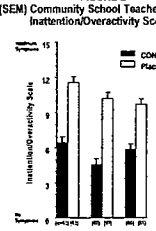
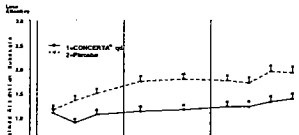


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® qd (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In two controlled studies (Studies 1 and 2), symptoms of ADHD were evaluated by laboratory school teachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory school teacher SKAMP ratings for CONCERTA® and placebo.

*Swanson, Kotkin, Agler, M-Fynn and Pelham

FIGURE 3
Laboratory School Teacher SKAMP Ratings
Mean (SEM) of Combined Attention (Studies 1 and 2)



INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of CONCERTA® in the treatment of ADHD was established in three controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

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

Special Diagnostic Considerations

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

Need for Comprehensive Treatment Program

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

Long-Term Use

The effectiveness of CONCERTA® for long-term use, ie, for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use CONCERTA® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Depression

CONCERTA® should not be used to treat severe depression.

Fatigue

CONCERTA® should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (ie, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

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

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Hypertension and other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension. In the laboratory classroom clinical trials (Studies 1 and 2), both CONCERTA® and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age

CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients
Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patient information is printed at the end of this insert. To assure safe and effective use of CONCERTA®, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions
Because of possible effects on blood pressure, CONCERTA® should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, pemidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively.

Pregnancy: Teratogenic Effects
Pregnancy Category C: Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

Pediatric Use
The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS
The premarketing development program for CONCERTA® included exposures in a total of 755 participants in clinical trials (469 patients, 286 healthy adult subjects). These participants received CONCERTA® 18, 36, and/or 54 mg/day. The 469 patients (ages 6 to 13) were evaluated in three controlled clinical studies (Studies 1, 2, and 3), two uncontrolled clinical studies (including a long-term safety study), and one clinical pharmacology study in children with ADHD. Of the 469 patients in this program, 68 CONCERTA®-treated patients in one uncontrolled dose-initiation study were naive to any pharmacologic therapy for their ADHD. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA®
Adverse Events Associated with Discontinuation of Treatment
In the 4-week placebo-controlled, parallel-group trial one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In uncontrolled studies up to 12 months with CONCERTA®, 6.6% (29/441) patients discontinued for adverse events. Those events associated with discontinuation of CONCERTA® in more than one patient included the following: twitching (tics, 1.8%); anorexia (loss of appetite, 0.9%); aggravation reaction (0.7%); hostility (0.7%); insomnia (0.7%); and somnolence (0.5%).

Adverse Events Occurring at an Incidence of 1% or more Among CONCERTA®-Treated Patients
Table 2 enumerates, for a 4-week placebo-controlled, parallel-group trial in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which 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 non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2

Incidence of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA®

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract infection	8 %	5 %
	Cough increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

[1]: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

Tics
In a long-term uncontrolled study (n=407 children), the cumulative incidence of new onset of tics was 8% after 10 months of treatment with CONCERTA®.

Adverse Events with Other Methylphenidate HCl Products
Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance
See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE
Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment
Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdosage has not been established.

The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

Poison Control Center
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

DOSAGE AND ADMINISTRATION
CONCERTA® is administered orally once daily in the morning.

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS: Information for Patients).

CONCERTA® may be administered with or without food and should be administered once daily in the morning.

Dosage should be individualized according to the needs and responses of the patient.

Patients New to Methylphenidate
The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Dosage may be adjusted to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Patients Currently Using Methylphenidate
The recommended dose of CONCERTA® for patients who are currently taking methylphenidate bid, tid, or sustained-release (SR) at doses of 10 to 60 mg/day is provided in Table 3. Dosing recommendations are based on current dose regimen and clinical judgement.

Dosage may be adjusted to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

TABLE 3

Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Dose
5 mg Methylphenidate bid or 5 mg Methylphenidate tid or 20 mg Methylphenidate-SR	18 mg q am
10 mg Methylphenidate bid or 10 mg Methylphenidate tid or 40 mg Methylphenidate-SR	36 mg q am
15 mg Methylphenidate bid or 15 mg Methylphenidate tid or 60 mg Methylphenidate-SR	54 mg q am

Other methylphenidate regimens: Clinical judgement should be used when selecting the starting dose.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages. Daily dosage above 54 mg is not recommended.

Maintenance/Extended Treatment
There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation
If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED
CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg	100 count bottle	NDC 17314-5850-2
27 mg	100 count bottle	NDC 17314-5853-2
36 mg	100 count bottle	NDC 17314-5851-2
54 mg	100 count bottle	NDC 17314-5852-2

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

REFERENCE
American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

Distributed and marketed by
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- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking CONCERTA®.

Can I take CONCERTA® with other medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take CONCERTA® with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take CONCERTA® with monoamine oxidase (MAO) inhibitors.

While on CONCERTA®, do not start taking a new medicine or herbal remedy before checking with your doctor.

CONCERTA® may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA®.

Other Important Safety Information

Abuse of methylphenidate can lead to dependence.

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

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Before taking CONCERTA®, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking CONCERTA®.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your CONCERTA® treatment.

Call your doctor ***immediately*** if you take more than the amount of CONCERTA® prescribed by your doctor.

What else should I know about CONCERTA®?

CONCERTA® has not been studied in children under 6 years of age.

The CONCERTA® tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

CONCERTA® may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA® with anyone else and take only the number of CONCERTA® tablets prescribed by your doctor.

CONCERTA® should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

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INFORMATION FOR PATIENTS TAKING CONCERTA® OR THEIR PARENTS OR CAREGIVERS

CONCERTA®

(methylphenidate HCl) Extended-release Tablets Ⓒ

This information is for patients taking CONCERTA® Extended-release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking CONCERTA®. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA®, talk to your doctor or pharmacist.

What is CONCERTA®?

CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA® work?

Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA®?

You should NOT take CONCERTA® if:

- You have significant anxiety, tension, or agitation since CONCERTA® may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA®?

Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.

You may take CONCERTA® before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?

In the clinical studies with patients using CONCERTA®, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in CONCERTA®, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?

Talk to your doctor ***before*** taking CONCERTA® if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.

- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking CONCERTA®.

Can I take CONCERTA® with other medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take CONCERTA® with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take CONCERTA® with monoamine oxidase (MAO) inhibitors.

While on CONCERTA®, do not start taking a new medicine or herbal remedy before checking with your doctor.

CONCERTA® may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA®.

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Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking CONCERTA®, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking CONCERTA®.

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CONCERTA® may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA® with anyone else and take only the number of CONCERTA® tablets prescribed by your doctor.

CONCERTA® should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

For more information call 1-888-440-7903 or visit www.concerta.net

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0011157-2 PPI Edition March/2002

00111572

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-121
SPONSOR: ALZA
DRUG: CONCERTA (METHYLPHENIDATE)
MATERIAL SUBMITTED: SCM-004 (SUPPLEMENT FOR NEW 27 MG STRENGTH)
DATE SUBMITTED: 11-30-01
DATE RECEIVED: 12-3-01
USER FEE DUE DATE: 4-3-02

This supplement provides for a new 27 mg strength. The sponsor has proposed some corresponding changes to the Dosage and Administration section, and an entirely unrelated change to the Warnings section that I will comment upon here. Originally Alza planned to make the change in the Warnings section under a separate "changes being effected" supplement, but for the sake of expediency has included it in this submission.

Labeling changes

Related to new dosage strength

Under Dosage and Administration, for the sections on patients new to methylphenidate and patients currently using methylphenidate, the following sentence has been edited as shown:

> Dosage may be adjusted [redacted] to a maximum of 54 mg/day taken once daily in the morning.

Also, under Table 3 ("Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA"), the following statement has been added:

> A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

Additionally, the How Supplied and Description sections have been revised to reflect the availability of the new dosage strength.

Reviewer Comment: In my opinion these labeling changes are appropriate and may be approved.

Additional labeling change

In the Warnings section, under the heading, "Potential for gastrointestinal obstruction," there is a list of conditions causing gastrointestinal narrowing, and the labeling states that Concerta should not ordinarily be administered to patients with such conditions. Alza has added the term "esophageal motility disorders" to the list of such conditions. This change is based upon a MedWatch report of a 16 year old boy who had a Concerta 36 mg tablet "wedged in the spasm of the cricopharyngeus muscle." The tablet had to be removed by direct laryngoscopy/esophagoscopy. The patient apparently had a long history of trouble swallowing.

Reviewer Comment: It is not entirely clear to me that this subject had an esophageal motility disorder; nonetheless, I see no harm in adding this term as proposed by the sponsor.

Andrew D. Mosholder, M.D., M.P.H.
Medical Officer, HFD-120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Mosholder
3/7/02 01:31:12 PM
MEDICAL OFFICER

Thomas Laughren
3/10/02 08:44:05 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

CHEMISTRY REVIEW

NDA 21-121, SCM-004

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-121 **DATE REVIEWED: 3/21/02**

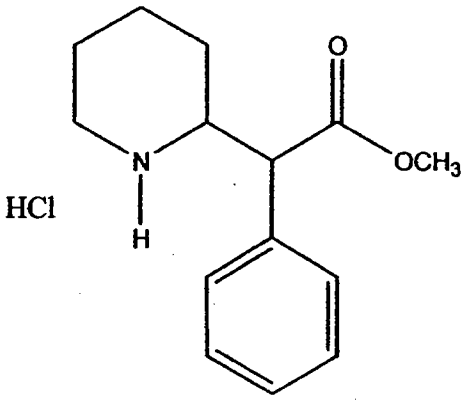
REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Prior-Approval	11/30/01	12/3/01	12/13/01
(BC) Amendment	2/14/02	2/15/02	2/22/02
(BC) Amendment	3/1/02	3/4/02	3/6/02

NAME & ADDRESS OF APPLICANT:
ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

DRUG PRODUCT NAME:
Proprietary: CONCERTA®
Established(USAN): methylphenidate hydrochloride, USP

PHARMACOL. CATEGORY/INDICATION: Attention Deficit Hyperactivity Disorder (ADHD)
DOSAGE FORM: Osmotic Tablet
STRENGTHS: 27mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: *Rx*
SPECIAL PRODUCTS: __Yes xx No
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: 2-piperidineacetic acid, α-phenyl-, methylester, hydrochloride, (R*,R*)-(±)-
Molecular formula: $C_{14}H_{19}NO_2$. HCl
MW: 269.77
CAS Registry Number: CAS-298-59-9



RELATED APPLICATIONS: N21-121, approved 8/1/00 for the 18mg and 36mg tablets; N21-121, SCM-001, approved on 12/8/00 for the 54mg tablet; N21-121, SCM-003, approved on 3/4/02 for alternate drug substance source; [redacted]

CONSULT: BioPharmaceutics submitted on 12/17/01; completed 3/8/02.

SUPPLEMENT PROVIDES FOR: 27mg dosage strength.

CONCLUSIONS: Recommend Approval of the CMC section of N21-121, SCM-004.

File: C:\HFD120\21121\N21121SCM004rvw32102.doc

ATTACHMENT A

19 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donald Klein
3/21/02 01:59:19 PM
CHEMIST

revisions made as discussed this morning

Hasmukh Patel
3/21/02 03:29:22 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-121/SCM-004	Submission Dates:	Nov. 30, 2001, Feb. 12, Mar. 1, 2002
	OCPB Reviewer received:	Dec. 17, 2001
Brand Name	Concerta®	
Generic Name	*d,l-threo*-methylphenidate	
Reviewer	Maria Sunzel, Ph.D.	
Team Leader (acting)	Vanitha Sekar, Ph.D.	
OCPB Division	HFD-860	
ORM Division	HFD-120	
Sponsor	Alza Corporation, 1900 Charleston Rd, Mountain View, CA 94039-7210	
Relevant IND(s)	54,575	
Submission Type; Code	SCM-004 Supplement (new dosage strength)	
Formulation; Strength	Extended release tablet (OROS®); 27 mg	
Indication	Attention Deficit - Hyperactivity Disorder (ADHD)	

1 EXECUTIVE SUMMARY

This review evaluates the approved *in vitro-in vivo* correlation (Type A IVIVC) applied to *in vitro* dissolution data to support a biowaiver for a new tablet strength of 27 mg of Concerta extended release tablets (*d,l-threo*-methylphenidate), and finds the IVIVC prediction acceptable.

Therefore, the sponsor's bioavailability waiver request for the 27-mg Concerta tablet is granted, and the Office of Clinical Pharmacology and Biopharmaceutics recommends approval of the new Concerta tablet strength of 27 mg methylphenidate, manufactured at the site in Vacaville, CA.

The sponsor has withdrawn the second manufacturing sit[redacted] from the current supplement (submission dated March 1, 2002).

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the IVIVC predictions acceptable for the 27-mg Concerta tablet and recommends approval of the new tablet strength, manufactured at the site in Vacaville, CA.

The sponsor's proposed label changes regarding the label sections 'Description', 'Dosage and Administration' and 'How Supplied' are acceptable. However, the acceptability of the proposed label change to the WARNINGS section is deferred to the Medical Division.

The currently approved *in vitro* dissolution specifications for all marketed Concerta tablets (18 mg, 36 mg, and 54 mg) are also applicable for the new Concerta tablet strength of 27 mg.

2 TABLE OF CONTENTS

3 SUMMARY OF CPB FINDINGS

3.1 Background

Racemic *d,l-threo*-methylphenidate hydrochloride (*d,l*-MPH), a mild CNS stimulant, has been marketed in the US since 1955 for various indications. It is currently marketed for treatment of attention deficit/ hyperactivity disorders (ADHD) and narcolepsy, in daily doses up to 60 mg as immediate and sustained release formulations.

The sponsor is currently marketing three different approved dose strengths of Concerta tablets (*d,l*-MPH HCl - 18 mg, 36 mg, and 54 mg), an OROS® (osmotic drug delivery system) extended release (ER) formulation. The OROS system delivers methylphenidate by a combined process of aqueous dissolution of the drug overcoat (immediate release) and osmotic delivery of the core drug (extended release).

The 18 mg and 36 mg Concerta tablets manufactured by ALZA were approved for the treatment of ADHD on Aug. 1, 2000. The full Clinical Pharmacology and Biopharmaceutics (CPB) reviews of the original NDA 21-121 are dated Feb. 10, and Apr. 17, 2000, where the latter is an addendum that contains the dissolution specifications based on the approved Type A *in vitro-in vivo* correlation. A higher strength, the 54 mg Concerta tablet, was approved in December 2000 (CPB review dated 11/27/00). These are extended release formulations intended for once daily oral dosing, with an approved maximal daily dose of 54 mg.

The earlier submissions have shown that methylphenidate has dose-proportional pharmacokinetics (18-54 mg Concerta tablets), and that the pharmacokinetics are not altered with concomitant food intake (36 mg and 54 mg tablets).

3.2 Current Submission

The sponsor has submitted this prior approval supplement (NDA 21-121/SCM-004) for a new, 27 mg, strength of the Concerta extended release (ER) tablet. Two earlier OCPB reviews regarding a biowaiver request (review dated Jun. 7, 2001), and a bioequivalence study protocol (review dated Aug. 31, 2001) have been completed with regard to the 27 mg Concerta tablet strength. The current submission contains information regarding CMC (both development and final processes and validation), as well as an application of the approved Type A *in vitro-in vivo* correlation based on the *in vitro* dissolution data from the 27 mg Concerta tablet. The IVIVC is the basis for a biowaiver request for the new 27 mg strength.

The submission contains information stating that the 27 mg tablet:

- has the same rate-controlling membrane as the other approved tablets
- is formulated to specifically achieve the required release profile for a 27 mg dose, which has been verified by release rate testing
- has the same release mechanism as the other approved strengths
- has a similar dissolution profile as the other approved strengths in the approved medium
- is manufactured by use of the same process, equipment and site as the other approved strengths

The sponsor proposed two manufacturing sites for the new 27 mg MPH HCl Concerta tablets, namely Vacaville, CA, and [redacted] The two sites have different batch quantities due to a difference in the [redacted] coating equipment used at the two sites. Both manufacturing sites are approved for manufacturing of the 18 mg, 36 mg, and 54 mg Concerta tablets. In the current application for the 27-mg tablet strength, the *in vitro* dissolution data and thereby the IVIVC is based on data from one lot produced at the Vacaville site. No 27-mg Concerta tablet batches

have been manufactured at the ——— to date. A teleconference was held between Alza and CDER representatives on March 1, 2002. The OCPB representatives (Drs Sekar and Sunzel) requested the sponsor to submit a full *in vitro* release profile in the compendial medium from one batch ——— manufactured at the ——— Following the teleconference, the sponsor chose to withdraw the manufacturing site (——— rom NDA 21-121/SCM-004 on March 1, 2002.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the IVIVC predictions acceptable for the 27-mg Concerta tablet and recommends approval of the new tablet strength, manufactured at the site in Vacaville, CA.

The sponsor's proposed label changes regarding the label sections 'Description', 'Dosage and Administration' and 'How Supplied' are acceptable. However, the acceptability of the proposed label change in the WARNINGS section is deferred to the Medical Division.

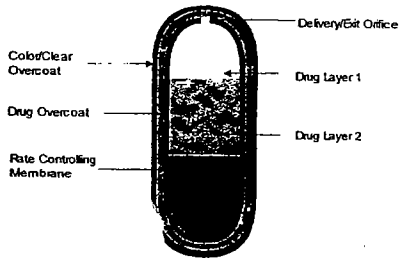
The currently approved *in vitro* dissolution specifications for all marketed Concerta tablets (18, 36, and 54 mg) are also applicable for the new Concerta tablet strength of 27 mg.

4 QUESTION BASED REVIEW

4.1 General Biopharmaceutics

4.1.1 Formulations

How is the Concerta extended release formulation constructed and how does it function?



	OROS (MPH HCl)			
	18 mg	**27 mg**	**36 mg**	**54 mg**
Weight	268 mg	**283 mg**	515 mg	526 mg
Diameter	5.3 mm	**5.3 mm**	6.8 mm	6.8 mm
Length	12 mm	**12.2 mm**	15 mm	15.4 mm

The OROS® systems deliver MPH HCl by a combined process of aqueous dissolution of the drug overcoat and osmotic delivery of the core drug. The system resembles a conventional tablet in appearance, is comprised by an osmotically active tri-layer core surrounded by a semi-permeable membrane with an immediate release drug overcoat (see figure and table above). The tri-layer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-drilled orifice on the drug-layer end of the tablet.

When the OROS system is ingested, the drug in the overcoat is quickly released and is available for absorption. After the dissolution of the drug overcoat, an osmotic gradient is established across the rate-controlling membrane, and water is imbibed into the system at a controlled rate, yielding controlled delivery of MPH for approximately ——— . The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as the tablet-shell along with insoluble core components.

Is the new 27 mg dose strength compositionally similar to the approved strengths and did the sponsor perform adequate comparative tests?

The composition of the 27 mg OROS formulation is within the limits of the approved strengths of 18 mg and 54 mg MPH HCl, with respect to components, membrane, drug overcoat and clear overcoat, as shown in Appendix, subsection 7.1. The 27 mg tablet is gray, and has 'ALZA 27' imprinted on the tablet. [redacted]

A series of experiments were conducted to establish the manufacturing processes that would yield comparable performance between all dose strengths of the OROS delivery system. The equivalency of the four different strengths was assessed (drug layer weights, push layer weights, drug particle size, orifice diameter, final compression force, receptor media and agitation rate) and were found functionally comparable, according to the sponsor.

What manufacturing sites are proposed for the production of the new 27 mg Concerta tablets?

The sponsor proposes two manufacturing sites for the new 27 mg OROS formulation, namely Vacaville, CA and [redacted] The two sites have different batch quantities due to a difference in the [redacted] coating equipment used at the two sites. Both manufacturing sites are approved for manufacturing of the 18 mg, 36 mg, and 54 mg Concerta tablets.

The sponsor has only produced one batch at the manufacturing site at Vacaville, CA. This batch was used for the in vitro drug release profiles and the IVIVC calculations. The sponsor has not manufactured the 27-mg Concerta tablets at the second site [redacted] and therefore no *in vitro* drug release data is available from that site. A teleconference was held between Alza and CDER representatives on March 1, 2002. The OCPB representatives (Drs Sekar and Sunzel) requested the sponsor to submit a full *in vitro* release profile in the compendial medium from one batch [redacted] for the 27-mg Concerta tablet manufactured at the [redacted] site. Following the teleconference, the sponsor chose to withdraw the second manufacturing site [redacted] from NDA 21-121/SCM-004 on March 1, 2002.

4.2 In vitro dissolution comparisons

Do all strengths of the Concerta tablets containing MPH HCl give similar in vitro dissolution profiles?

The cumulative *in vitro* dissolution/release profiles of all Concerta tablet strengths, including the new 27 mg strength, manufactured at the Vacaville site, were similar, as depicted in Figure 1 (by use of approved method). See Section 4.4, for details regarding the method. The tabulated values for the mean (n=24) cumulative *in vitro* drug release profile of the 27 mg MPH HCl tablet strength are shown in the Appendix, Subsection 7.2.

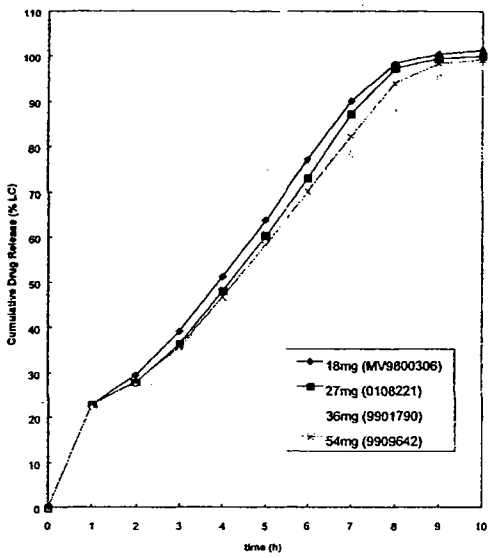


FIGURE 1. Comparative cumulative *in vitro* drug release curves (x-axis: 0-10 h; y-axis: mean % cumulative drug release) for all Concerta tablet strengths (27 mg denoted as large solid squares).

The sponsor also compared the 27 mg strength to the approved 18 mg, 36 mg, and 54 mg strengths by calculating the similarity factor (f_2 values; 27 mg *vs.* each approved strength) from the data depicted in Figure 1. The f_2 values were within acceptance criteria ($50 \leq f_2 \leq 100$), and the % drug released at 1, 4, and 10 h, were similar between all tablet strengths, as shown in Table 1.

TABLE 1. Comparisons of cumulative *in vitro* drug release of all Concerta tablet strengths at the time points in the approved dissolution method (1, 4, and 10 h), and the calculated f_2 values.

Dosage Strength (mg)	I.D. No.	Similarity Factor, f_2	Cumulative Drug Release (% LC) 1h	4h	10h
18	MV9800306	83	22.8	51.2	101.4
27	0108221	-	22.9	48.0	100.1
36	9901790	70	22.7	45.3	97.3
54	9909642	84	22.8	46.7	99.2

In conclusion, the *in vitro* dissolution data showed that the new Concerta 27 mg tablet strength of methylphenidate HCl, manufactured at the Vacaville site, has similar *in vitro* drug release properties to the approved Concerta tablets (18, 36, and 54 mg strengths).

4.3 In vitro – in vivo correlation

What method was used for the approved Type A in vitro – in vivo correlation (IVIVC)?

A Type A *in vitro–in vivo* correlation by the use of a convolution method was approved in the original NDA 21-121 in 2000. The convolution method is a robust method, since it does not rely

TABLE 2. The sponsor's summary of the prediction errors (%PE) of the 27-mg Concerta tablet for C_{max} and AUC predictions. The values depicted as actual are the C_{max} and AUC values predicted in the original IVIVC. (%PE calculated as [(actual-predicted)/ actual x 100] in each case).

	Strength	Study	Actual	Predicted[a]	%PE
Cmax	18 mg	C-98-024	3.65	3.91	-7.1
(ng/mL)	18 mg	C-99-001	3.76	3.91	-4.0
	18 mg	C-98-002	3.60	3.91	-8.6
	36 mg	C-99-005	7.27	7.82	-7.6
	36 mg	C-99-005	8.27	7.82	5.4
Mean					-4.4
AUCinf	18 mg	C-98-024	40.2	39.8	1.0
(ng.h/mL)	18 mg	C-99-001	40.8	39.8	2.5
	18 mg	C-98-002	40.1	39.8	0.7
	36 mg	C-99-005	79.1	79.6	-0.6
	36 mg	C-99-005	80.2	79.6	-0.7
Mean					0.6

[a] Data for 27 mg are scaled proportionally to appropriate dose (18 or 36 mg)

Although the mean prediction errors in Table 2 were not calculated as the mean of the absolute values, this does not change the conclusion that the PE% is less than 10% for both C_{max} and AUC (mean of absolute values for %PE of C_{max}: 6.6%; mean of absolute values for %PE of AUC: 1.1%).

In conclusion, the results of the application of the IVIVC were within the acceptance criteria, and indicate that a biowaiver can be granted for the 27-mg Concerta tablet strength.

4.4 In vitro dissolution method and specifications

Are the currently approved in vitro dissolution method and specifications also applicable to the new 27 mg dosage strength?

The previously approved *in vitro* dissolution specifications for the 18 mg, 36 mg, and 54 mg MPH HCl Concerta tablets are also recommended for the 27 mg dosage strength manufactured at the Vacaville site. The recommended *in vitro* dissolution specifications are as follows:

The *in vitro* dissolution testing is to be performed with USP Type VII dissolution apparatus with oral extended release tablet holder (spring holder) in pH 3 water with a fixed agitation rate of 30 cycles per minute, maintained at temperature of 37 ± 0.5°C.

4.5 Supportive in vivo data

Has the sponsor investigated the in vivo performance of the 27-mg Concerta tablet strength? What were the results of the in vivo study?

The sponsor has also performed an *in vivo* bioequivalence (BE) study, to fulfill regulatory requirements in countries outside the U.S. An *in vivo* BE study is not a regulatory requirement in the U.S., since a Type A IVIVC has been approved for the Concerta tablets. However, the sponsor submitted a study protocol for a bioequivalence study in 2001. Therefore, this reviewer contacted the sponsor and requested the summary findings from the study, if available. The sponsor submitted a study summary with the pharmacokinetic data (submission to IND 54,575 dated Feb. 12, 2002), which showed that the 27 mg MPH HCl Concerta tablet was bioequivalent to the approved Concerta tablets (2x27 mg test tablets *vs.* 3x18 mg reference tablets).

5 LABELING

What changes have been made to the approved label? Are these changes acceptable?

The Sponsor has proposed minor editorial revisions to the approved label. New information is included in the Sections 'Description', 'Dosage and Administration' and 'How Supplied'. In addition, Concerta is now a registered trademark, and that has been inserted throughout the label (i.e. ™ has been replaced by ®). In addition, the sponsor has made a change in the WARNINGS section of the label, the review of that change is deferred to the Medical Division. A summary of the proposed label revisions can be found in the Appendix (subsection 7.3).

The Office of Clinical Pharmacology and Biopharmaceutics finds the sponsor's proposed label changes regarding the label sections 'Description', 'Dosage and Administration' and 'How Supplied' acceptable.

6 SIGNATURES

Maria Sunzel, Ph.D. _____

RD/FT initialed by Vanitha Sekar, Ph.D. _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

c.c.: NDA 21-121/SCM-004, HFD-120 (Homonnay, Klein, Mosholder, Laughren), HFD-860 (Mehta, Marroum, Sekar, Uppoor, Sunzel)

ATTACHMENT C.

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

7.3 The sponsor's proposed labeling changes

Volume 38.1

LABELING

Changes have been made to the labeling for Concerta® to reflect the addition of the 27 mg dosage strength. Additionally, a change to the WARNINGS section (addition of "esophageal motility disorders" to the "Potential for Gastrointestinal Obstruction" section) is reflected and will be submitted to the NDA separately in a CBE labeling supplement. McNeil Consumer & Specialty Pharmaceuticals (formerly McNeil Consumer Healthcare) Distribution/Marketing information and logo have also been added to the physician insert and container labels. McNeil Consumer & Specialty Pharmaceuticals is a partner company to ALZA (Johnson & Johnson being the parent company for both). Finally, Concerta is now a registered trademark, so all ™ symbols have been replaced with ® symbols throughout. These changes are outlined below. The revised labeling components: bottle labels (text and layout), physician and patient insert (both a strikethrough version and a clean copy), are provided immediately following the description of changes. A diskette containing the electronic files for the physician insert is provided for the reviewers' convenience.

Container Labels

The dosage strength, NDC number, and color bar have been changed in the labels for the 27 mg bottles [redacted] 100 count). McNeil Consumer & Specialty Pharmaceuticals (formerly McNeil Consumer Healthcare) Distribution/Marketing information and logo have been also been update in the container labels. While approval is sought for both [redacted] and 100 count bottle configurations, initial marketing will only be in the 100 count bottles. This is reflected in the Physician Insert "HOW SUPPLIED" section. The Physician Insert will be updated to include the [redacted] bottles when they are introduced to the market.

Physician Insert

The additions/changes to the affected portions of the physician insert are shown below in **bold/double underline** for additions and strikethrough mode for deletions.

Section: Description

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in [redacted] **four** tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, **27**, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$.

Section: WARNINGS - Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: **esophageal motility disorders**, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in

patients with known strictures in association with the ingestion of ~~other~~ drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Section: Dosage and Administration (Patients New to Methylphenidate)
Dosage may be adjusted [redacted] to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Section: Dosage and Administration (Patients Currently Using Methylphenidate)
Dosage may be adjusted [redacted] to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Section: Dosage and Administration (Text below TABLE 3)
A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages. Daily dosage above 54 mg is not recommended.

Section: How Supplied
CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, **27 mg**, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". **The 27 mg tablets are gray and imprinted with "alza 27".** The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All **four** dosage strengths are supplied in bottles containing 100 tablets.

18 mg	100 count bottle	NDC 17314-5850-2
27 mg	**100 count bottle**	**NDC 17314-5853-2**
36 mg	100 count bottle	NDC 17314-5851-2
54 mg	100 count bottle	NDC 17314-5852-2

Manufactured [redacted] by
ALZA Corporation, Mountain View, CA 94043.
Distributed and marketed by
McNeil Consumer & Specialty Pharmaceuticals [redacted], Fort Washington, PA 19034.

[ALZA logo] **[McNeil Consumer & Specialty Pharmaceuticals logo]**

XXXXXXX-X PI

Edition: XX/2001

Patient Insert
The following changes have been made to the end of the Patient Insert :

Manufactured ———— by
ALZA Corporation, Mountain View, CA 94043.
Distributed and marketed by
McNeil Consumer & Specialty Pharmaceuticals ———— , Fort Washington, PA 19034.

[ALZA logo] **[McNeil Consumer & Specialty Pharmaceuticals logo]**

XXXXXXX-X PI

Edition: XX/2001

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/s/

Maria Sunzel
3/8/02 03:35:33 PM
BIOPHARMACEUTICS

Vanitha Sekar
3/8/02 03:39:37 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 29, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for new 27 mg strength tablet for Concerta extended release tablets (methylphenidate)

TO: File NDA 21-121/S-004
[Note: This memo should be filed with the 11-30-01 original submission.]

Concerta is an approved drug product, for the treatment of ADHD, currently available in 18, 36 and 54 mg OROS formulation tablet strengths. This supplement provides for a new 27 mg strength tablet for this formulation, that would permit more refined titration, i.e., between 18 and 36 mg and between 36 and 54 (you could give 27 + 18 = 45).

This supplement included CMC information, along with dissolution data, for the 27 mg tablet, and a request for a biowaiver for this strength, based on IVIVC for the dissolution data.

The biowaiver request was considered by Maria Sunzel, Ph.D. from OCPB. The sponsor had proposed two manufacturing sites for the 27 mg tablet, but provided dissolution data from only the Vacaville, CA site. Following a request for dissolution data from the other si ———— the sponsor chose to withdraw th ———— OCPB has found the IVIVC predictions acceptable for the 27 mg strength and recommends approval of this strength from the Vacaville site. They also found the labeling changes in the Description, D&A, and How Supplied sections acceptable, and recommended the same dissolution specifications for this strength as for the other three marketed strengths.

Dr. Klein from chemistry has reviewed the CMC information, to include the following: drug substance; drug product; manufacturing process; container closure system; stability; establishment inspection; labeling; and analytical methods. He recommended approval of this tablet, along with a 24 month expiry.

The only clinical issues for this application were labeling changes in the D&A section, and an unrelated change in Warnings. The Warning change involved the addition of "esophageal motility disorders" to the

list of comorbid conditions for which Concerta would ordinarily be avoided. Dr. Mosholder agreed with changes in both sections, and I do as well.

Recommendation

I agree with the recommendations of all reviewers that this supplement can be approved, with the agreed upon dissolution method and specifications and proposed labeling.

cc:
Orig NDA 21-121/S-004
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AHomonnay

DOC: NDA21121.03

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/s/

Thomas Laughren
3/29/02 11:00:42 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

NDA: 21-121

DRUG: Concerta

SPONSOR: Alza Corp

DATE: 3/13/02

TELEPHONE NUMBER: (650) 564-4135

CONVERSATION WITH: Tracy Lin

CONVERSATION:

I contacted Tracy Lin to convey some additional advice from OCPB concerning their planned supplement to add the [redacted] as a manufacturer of the 27 mg strength. I told her that their proposal as outlined in the March 6, 2002, fax to Dr. Klein, was acceptable. In addition, I reminded her that the pilot lot should be at least [redacted] the commercial batch size and that they should also include in the supplement predictions of AUC and Cmax utilizing the IVIVC and the in vitro dissolution data from the [redacted].

Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager

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/s/

Anna-Marie Homonnay
3/13/02 02:17:56 PM
CSO

April 15, 2002

NDA 21-121/S-004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
1451 Rockville Pike
Rockville, MD 20852-1420

Attention: Russell Katz, MD, Director
Division of Neuropharmacological Drug Products

Re: Final Printed Labeling for Approved Supplement NDA 21-121/S-004
Concerta® (methylphenidate HCl) Extended-release Tablets

Dear Dr. Katz:

In response to your approval letter dated April 1, 2002 and in accordance with 21 CFR 314.70 (b)(3), ALZA is submitting the Final Printed Labeling for the approved physician/patient combined insert and 27mg bottle label as well as labeling for the 18mg, 36mg and 54mg container (bottle) labels and patient insert for Concerta® (methylphenidate HCl) Extended-release Tablets.

This submission is submitted in electronic format. Both the cover letter and FDA form 356h are also accompanied by a paper copy, which includes the original signature.

The electronic submission consists of the approved physician/patient package insert and 27mg container (bottle) label; the patient insert; the 18, 36 and 54 container (bottle) labels. The submission is approximately 2.5 MB in size. One CDROM is provided as the archive copy.

The CDROM has been screened for viruses using McAfee VirusScan v 4.5.1 SP1, using virus definitions 4.0.4196 and scan engine 4.1.60.

If you have any questions concerning this matter, please call me at (650) 564-4282 or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Sue Rinne, Vice President of Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Steve Ketchum for

Janne Wissel
Sr. Vice President, Operations

Enclosures: (1) Archival Copy

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-121

PRIOR APPROVAL SUPPLEMENT

Alza Corporation
Attention: Tracey Lin, Associate Director, Regulatory Affairs
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Lin:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Concerta™ (methylphenidate HCl) Extended Release Tablets

NDA Number: 21-121

Supplement number: 004

Date of supplement: November 30, 2001

Date of receipt: December 3, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act February 2, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Anna Marie Homonnay, Regulatory Project Manager, at (301) 594-5535

Sincerely yours,

Robert H. Seevers, Ph.D.
Chemistry Team Leader
Psychiatric Drugs for the
Division of Neuropharmacological Drug Products
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Robert H. Seevers
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