Clinical Review for NDA 21-121 Supplement SE1-08

Approvable Action for Pediatric Supplement for Concerta in the Treatment of Adolescent Attention Deficit Hyperactive Disorder

Executive Summary

I. Recommendations on Approvability

I recommend that the Division take an approvable action on NDA 21-121 SE1-08. Based on the results of Study 01-146 I am convinced that Concerta is effective in the treatment of ADHD in adolescents. Though this was not a fixed dose study, there did not appear to be any correlation between dose and effectiveness from the data that was presented.

I also note that non-Caucasian patients exhibited a high placebo response and therefore a relatively low treatment effect from Concerta. Differences in the treatment versus pre-treatment structure of classroom behavioral intervention (e.g. teacher-to-student ratio, limit setting, availability of resources, etc) may be one hypothetical explanation of this differential placebo response in this study. In other words, if the classroom behavioral intervention in the pre-drug-treatment setting had not been optimized, then a large part of the response in the study may come from that classroom behavioral intervention. In clinical trial parlance this is called "placebo effect"; however, in this study (as in the case of clinical practice), this was truly an add-on design where either Concerta or placebo was "added-on" to a behavioral classroom setting.

Dr. Glass, the primary reviewer is reluctant to approve doses of Concerta greater than 54-mg/day because there is little experience with doses of 72-mg in adolescents. I note Dr. Glass's concern about the limited exposure of adolescents to the 72-mg dose; however, I believe that the 72-mg dose may safely be used if physicians do not exceed the usual limit of 2-mg/kg/day that is already in the labeling for immediate release methylphenidate products. I conclude that this is safe enough to do based on the following: 72-mg has been judged effective; the pharmacokinetics of 72-mg have been established as linear; and children have been exposed to levels as high as 2-mg/kg/day already in other marketed formulations. I therefore believe that the 72-mg/day dose is safe; however, physicians should not exceed the 2-mg/kg/day limit that is already the labeled limit with other methylphenidate formulations.

The sponsor needs to address the following outstanding review issues prior to final approval.

- Provide quantitative ECG data and its analysis from Study 01-146. This data should include baseline and on drug ECG data for patient with both "normal" and "abnormal" ECG. The analysis should include the standard quantitative ECG parameters as well as QTcF. The analysis should include a description of the mean values and incidence of outliers between patient taking placebo and Concerta.
- Explore the radio-opaque quality of the OROS delivery system since there has been a report Concerta tablets being confused with renal calculi on an abdominal radiograph.
- There were marked differences in the treatment effect of Concerta in the Caucasian versus non-Caucasian patients. Though both Caucasians and non-Caucasians in the Concerta treated group had relatively equal and positive overall changes from baseline to endpoint, the improvement seen in non-Caucasians could not be attributed to drug. Please explore why this might have been the case in this study.
- The sponsor must submit the raw data used in the analysis of growth effects. They should also submit the data for height weight and exposure from study 01-146. They should also re-analyze the growth data by dose and duration. Analysis by duration without respect to dose could only be found in the submission.
- Review and respond to the edited draft labeling.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

It should be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they are given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request of September 2, 2003.

Concerta is a controlled release form of methylphenidate that is approved for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in children ages 6-12 years. It is a psychostimulant that is a Category II controlled substance. Concerta was first marketed in August, 2000. Concerta is used extensively off-label for the treatment of adolescents with ADHD and the purpose of the written request was to gather efficacy and safety data for its use in this population.

This submission consisted of studies covering the areas of chemistry, pre-clinical pharmacology toxicology, biopharmaceutics, a controlled clinical trial, and open-label clinical safety exposure data. These included but were not limited to two new studies in dogs, a dose range-finding study (McNeil 02-155, (b)(4)----6731-110) and a four-week toxicity study (McNeil 02-157, (b)(4)----6731-111), a

multiple dose pharmacokinetic study (Study 12-001), and study (Study 01-146) in support of efficacy of Concerta in the treatment of adolescent ADHD.

B. Efficacy

Conclusions Regarding Efficacy Data

I believe that the sponsor has presented convincing evidence that Concerta is effective in the treatment of adolescent ADHD. Based on the results of Study 01-146, the sponsor claims that doses up to 72-mg are effective. Only about a third of patients that were randomized to drug treatment reached this dose level before randomization even though all patients had the opportunity to take it in the titration phase. Despite the lower statistical power at this dose than might have been expected by the sponsor, the patients who took 72-mg showed a significant improvement in ADHD-RS symptoms compared to placebo.

Change of ADHD Total Score at the end of Double blind Phase by dose group (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Dose Group	Treatment Group	Placebo Group	Treatment effect	p-Value
18 mg/day (SD)	-17.5 (8.81) n=4	-9.58 (9.73) n=89	-7.92 (9.70)	0.11
36 mg/day (SD)	-12.32 (9.93) n=25	-9.58 (9.73) n=89	-2.74 (9.77)	0.22
54 mg/day (SD)	-16.63 (10.12) n=24	-9.58 (9.73) n=89	-7.04 (9.81)	0.002
72 mg/day (SD)	-15.36 (11.91) n=33	-9.58 (9.73) n=89	-5.78 (10.36)	0.007

Even though patients were titrated to the highest tolerated dose, it appears that there is no dose relationship to treatment response.

FDA subgroup analysis yielded statistical significance for males and females alike with a greater treatment effect in females. I believe that the lack of robustness in the p-value of the FDA analysis seems to be explained by the smaller number of females in the study.

Treatment effect on Change of ADHD Total Score according to Gender at the end of placebo controlled phase of Study 01-146 (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Sex	Therapy	Patient	Change	Treatment effect	p-Value
Male	**Any Concerta**	64	-15.70	-5.34	0.002
	Placebo	77	-10.36		
Female	**Any Concerta**	22	-12.68	-8.1	0.04
	Placebo	12	-4.58		

Analyses performed by both the sponsor and the FDA agree that non-Caucasian adolescents did not seem to significantly benefit from Concerta treatment in this study. Though there were fewer non-Caucasian patients, the treatment effect was very small and the placebo effect was fairly large. This leads me to hypothesize that the greatest benefit to the non-Caucasian patients in this study was the classroom structure and not the drug treatment.

Treatment effect on the change of ADHD Total Score according to Race Group at the end of the placebo controlled phase of Study 01-146 (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Race	Therapy	Patient	Change	Treatment effect	t-Value
Caucasian	**Any Concerta**	64	-15.05	-6.44	0.0005
	Placebo	67	-8.61		
Noncaucasian	**Any Concerta**	22	-14.59	-2.05	0.5
	Placebo	22	-12.55		

C. Safety

There were no deaths or drug related serious adverse events associated with study 01-146. Generally speaking, adverse events associated with treating adolescents were similar to those already associated with treating children with Concerta. There was a dose dependent increase in mean systolic and diastolic blood pressure. .

The ECG analysis of study 01-146 was only of a qualitative nature (e.g. normal or abnormal). The sponsor must present data and analysis on the standard ECG parameters and QTcF.

Dr. Glass, the primary reviewer is reluctant to approve doses of Concerta greater than 54-mg/day because there is little experience with doses of 72-mg in adolescents I share her concern if physicians only choose to dose based on fixed dose tolerability. Selection of a dose based on tolerability of a fixed dose and not mg/kg was the approach that was taken in study 01-146.

It appears that only about a third of adolescents could tolerate doses as high as 72-mg. I conclude this based on the following reasoning:
1) Clinicians only had the opportunity to titrate to the highest tolerated dose without time to factor in any dose adjustment based on optimal efficacy.
2) There were minimum required response criteria but no stopping criteria based on response.
3) Lack of efficacy was the most common cause of dropout in the double blind phase with roughly the same percentage of patients dropping out in the placebo group (26%) as in the 72-mg group (24%).

In summary, it seems that tolerability without much consideration of efficacy was the most important factor in dose selection in this study because of the 177 patients that entered the double blind phase, 171 returned for open-label extension treatment even though 24% of those patients treated with Concerta 72-mg dropped out during the double blind phase due to lack of efficacy. Again, I make these points not to criticize the choice of dose by the clinical investigators, but to support my conclusion that 72-mg may only be well tolerated by as few as a third of adolescents.

When lower weight adolescents are given 72-mg they may well be at dose levels that will simultaneously not be of any greater benefit and present greater known and unknown risks. By the same token, I do think that a 72-mg dose is safe provided that adolescents are not prescribed more than 2-mg/kg/day (the currently labeled limit for dosing of methylphenidate in children with a maximum dose of 60-mg/day). Based on Dr Tandon's OCPB review, children and some adolescents taking 54-mg are already exposed to more methylphenidate than heavier adolescents taking 72-mg. I do feel, however, that we have no data to support approving doses greater than 2-mg/kg/day in any case.

In summary, I note Dr. Glass's concern about the limited exposure of adolescents to the 72-mg dose; however, I believe that the 72-mg dose may safely be used if physicians do not exceed the usual limit of 2-mg/kg/day that is already in the labeling for immediate release methylphenidate products. I conclude that this is safe enough to do based on the following: 72-mg has been judged effective; the pharmacokinetics of 72-mg was established as linear; and children have been exposed to levels as high as 2-mg/kg/day already in other marketed formulations. I therefore see no need to restrict the use of the 72-mg dose; however, physicians should not exceed the 2-mg/kg/day limit that is already the labeled limit with other methylphenidate formulations.

I note Dr Mossholder's mention of the report of abdominal radiographic findings that were later attributed to Concerta capsules being mistakenly identified as renal calculi. I agree that the sponsor should test to see if Concerta Oros capsules are radio-opaque and place such a statement in labeling if they are found to be so.

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

/s/

Paul Andreason

3/4/04 03:09:09 PM