CLINICAL REVIEW

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Priority or Standard	S
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Division / Office	Division of Psychiatry Products/Office of Drug Evaluation 1
Reviewer Name(s)	Mark Ritter, MD RPh
Review Completion Date	September 8, 2009
Established Name	Dexmethylphenidate Hcl
(Proposed) Trade Name	Focalin XR
Therapeutic Class	Stimulant
Applicant	(b) (4)
Formulation(s)	Capsule
Dosing Regimen	Daily
Indication(s)	Attention Deficit/Hyperactivity Disorder
Intended Population(s)	Ages 6 and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that an approval action be taken for this efficacy supplement. Despite a lack of statistically significant incremental dose-dependant efficacy noted from both adult and pediatric fixed dose trials, numerical improvement in attention deficit/hyperactivity disorder symptoms were seen with doses above 20mg/day in the fixed dose trials.

In addition, drug utilization data analyses conducted by the Office of Surveillance and Epidemiology and the sponsor's analysis further demonstrates routine prescribing of Focalin XR in doses above 20mg/day in both the pediatric and adult populations.

1.2 Risk Benefit Assessment

There dose appear to be certain dose-related adverse events noted with use of higher doses of stimulants. However these adverse events as well-known and appropriately labeled and can be managed with reduction of dosing or other alternative treatment strategies.

The maximum recommended dose for methylphenidate, the 1:1 mix of the pharmacologically active d-threo enantiomer (dexmethylphenidate) and the much less active l-enantiomer, is currently 60mg/day. As dexmethylphenidate has:

- Already been administered in doses above 20mg in previous clinical trials and has labeled adverse events up to 40mg/day from the fixed dose adult study.
- Is *in vitro* twice as potent as methylphenidate, which has a maximum dose of 60mg/day and
- Doses above 20mg are clinically being used in 9-25% of different patient populations based on age and
- Dose-related adverse events are known, currently labeled and can be safely managed

This reviewer is of the opinion that the potential benefits of a higher dose of dexmethylphenidate outweigh the risk of adverse events for those patients who may require higher doses to achieve symptomatic control. In addition, it appears that patients who require higher doses are those patients who are older and have higher weights.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended at this time

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable to this submission.

2 Introduction and Regulatory Background

2.1 Product Information

Dexmethylphenidate hydrochloride, marketed in the United States under the brand name Focalin, is pharmacologically classified as a stimulant. Although the *in vivo* mechanism is not fully elucidated, *in vitro* studies demonstrate that dexmethylphenidate (the pharmacologically most active enantiomer of the methylphenidate, the d-threo enantiomer) increases synaptic concentrations of sympathomimetic via mediated pre-synaptic release of norepinephrine from central noradrenergic neurons. The mechanism by which increased synaptic norepinephrine levels reduces symptoms of attention deficit/hyperactivity disorder (ADHD) is not clearly understood, increase levels of noradrenergic compounds enhances alertness and focused attention in flight or fight responses. Thus a similar mechanism is hypothesized to be responsible for the clinical effect seen with administration of dexmethylphenidate in patients with ADHD.

2.2 Tables of Currently Available Treatments for Proposed Indications

Focalin (immediate release) and Focalin XR (Extended release) are indicated for the treatment of attention deficit/hyperactivity disorder in patients aged 6 years and older.

2.3 Availability of Proposed Active Ingredient in the United States

Dexmethylamphetamine HCL is available as an immediate release tablet in 2.5, 5 and 10mg strengths and as an extended release capsule as 5, 10, 15 and 20mg strengths.

2.4 Important Safety Issues With Consideration to Related Drugs

The Agency has recently approved class labeling changes to all stimulant products and atomoxetine to include the recent advisory committee decision to prominently warn and

inform parents of the higher risk for sudden cardiac death or cardiovascular events and worsening psychiatric events in current labeling.

Additional epidemiological studies, conducted under contract through the Agency and The Agency for Healthcare Quality and Research (AHRQ) will be forthcoming in the near future that will provide a greater sense of risk of sudden cardiac death, myocardial infarction and strokes in both children and adults. Additional regulatory action for the stimulant class of medications may be indicated based on review of this data.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency and the sponsor held a teleconference on 27 June 2008 to discuss revisement of the maximum dose state that is in current labeling. The basis for the teleconference was based on data submitted in the original NDA that contained safety and efficacy data for studies in ADHD up to 40mg/day in adults and 30mg/day in children. At the time of approval for Focalin, the Agency concluded that as a lack of incremental efficacy was seen beyond 20mg/day, labeling would set a maximum of 20mg/day.

After the teleconference, the Agency responded in a 2 Oct 2008 letter that dosing above 20mg is not precluded but would require further review based on the preliminary safety data from the submitted materials included as part of the briefing documents for the teleconference. On 31 March 2009, the sponsor formally submitted this efficacy supplement for review and revisement of the current maximum dose limit.

2.6 Other Relevant Background Information

No other relevant background information is available for dexmethylphenidate at this time.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

With the exception of one new phase IV study that has been submitted, no new efficacy or safety data has been submitted. As the new data contained in this NDA is not being used to support initial approval, clinical site investigations have not been conducted for this submission.

3.2 Compliance with Good Clinical Practices

All studies were conducted in compliance with the ethical standards according to the Declaration of Helsinki and the International Conference on Harmonization guidelines of Good Clinical Practice. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997.

3.3 Financial Disclosures

Financial disclosers were collected for 144 out of 145 clinical investigators for study 2305. Otherwise 100% disclosure was made. No significant financial interest was disclosed by any investigator during the clinical trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of this supplement submission, there did not appear to be any major CMC issues pending. However on June 25, 2009, the sponsor submitted a chemistry supplement for a new 30mg capsule strength for Focalin XR. Currently this supplement is under review.

Please see the formal CMC review for further details and analysis on issues related to this efficacy supplement.

4.2 Clinical Microbiology

Not Applicable

4.3 Preclinical Pharmacology/Toxicology

Although a formal pharmacology/toxicology review is not required with this submission, no issues have been raised to this reviewer with regards to the this application from a pharmacology/toxicology perspective. The reader is referred to review the pharmacology/toxicology review on file for Focalin under the original NDA application for full analysis and details of any pharmacology/toxicology issues.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The presumed *in vivo* mechanism of action is based on *in vitro* testing of methylphenidate. Stimulants, such as methylphenidate and the more potent enantiomer dexmethylphenidate, enhance norepinephrine release pre-snypactically thus leading to increased concentrations of norepinephrine in the synaptic cleft. For a more comprehensive review, the reader is referred to the original NDA submission for details

4.4.2 Pharmacodynamics

The pharmacodynamics of dexmethylphenidate has been previously reviewed. Please refer to the original NDA submission for details.

4.4.3 Pharmacokinetics

The pharmacokinetics of dexmethylphenidate has been previously reviewed. Please refer to the original NDA submission for details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Focalin XR® Table of Studies

Pediatric Studies	
CRIT124E2301 Flexible Dose	A seven-week (five week titration, two week maintenance), outpatient, multicentered, double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), flexible dose study of 103 pediatric patients (ages 6-17 years of age) with a current clinical diagnosis of attention deficit/hyperactivity disorder treated with doses of 5-30mg/day of Focalin XR.
CRIT124E2305 Fixed dose	A five week (three week titration, two week maintenance), outpatient, multicentered, double-blind, parallel group,

	placebo controlled, randomized, fixed dose study of Focalin XR 10, 20 and 30mg/day in 253 children aged 6-12 years old with a diagnosis of Attention deficit hyperactivity disorder
CRIT124EUS12	A 12-hour fixed dose laboratory classroom, double-blind, placebo controlled, active control (Concerta), five-period crossover study of Focalin XR 20mg and 30mg, Concerta 36mg and 54mg and placebo in 84 patients aged 6-12 years old with a diagnosis of ADHD
CRIT124EUS13	A 12-hour fixed dose laboratory classroom, double-blind, placebo controlled, active control (Concerta), five-period crossover study of Focalin XR 20mg and 30mg, Concerta 36mg and 54mg and placebo in 82 patients aged 6-12 years old with a diagnosis of ADHD
ADULT STUDY	
CRIT124E2302 Fixed Dose	A five week (three week titration, two week maintenance), outpatient, multicentered, double-blind, parallel group, placebo controlled, randomized, fixed dose study of Focalin XR 20, 30 and 40mg/day in 221 adults aged 18-62 years old with a diagnosis of Attention deficit hyperactivity disorder

5.2 Review Strategy

Table 2 below provides a listing of documents that were reviewed during the NDA review process.

Table 2: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
March 31, 2009	• Study reports: 2301,2302,2305, US12 and US13 • Clinical Safety Summary • Review of pertinent SAEs and safety data from previously un-reviewed study 2305 • Proposed labeling • Financial Disclosure Certification • Application Summary • Case Report Tabulations (.xpt files) • Case Report Forms
July 10, 2009	• Drug Utilization Review from the Office of Surveillance and Epidemiology

August 21, 2009	• Drug Utilization Review from the Sponsor

5.3 Discussion of Individual Studies/Clinical Trials

With the exception of study 2305, all of the studies submitted have been previously reviewed and thus will be discussed as pertinent to the review of this supplement. In particular, results from the fixed dose studies that have been submitted will be noted.

6 Review of Efficacy

Note: The original marketing application for Focalin XR contained the data for flexible dose (up to 30mg/day) pediatric study 2301 and the fixed dose (up to 40mg/day) adult study 2302. A recent efficacy supplement reviewed data submitted from studies US12 and US13. Therefore the efficacy review of this NDA will primarily focus on data obtained from the pediatric fixed dose study 2305.

Efficacy Summary

The sponsor has submitted a post marketing fixed dose study in children and has reanalyzed data from studies in children and adolescents focusing on dose response for efficacy with doses of 30mg/day in children and a fixed dose study dose in adults who were administered Focalin XR up to 40mg/day. A post-hoc analyses of these data does not demonstrate a statistically significant dose response for efficacy for the 30mg dose in children or the 40mg dose in adults, however a numerical dose-response was seen. Of note the studies were not powered to detect incremental dose-response.

A review of drug utilization data from both the Office of Surveillance and Epidemiology (OSE) and the sponsor both indicate that Focalin XR is being prescribed in daily doses above 20mg/day, with approximately 18% of all patients prescribed daily doses greater than 20mg/day from June 2008 to May 2009. Approximately 25% of adults, 24% of patients aged 13-17 years of age and 12% of patients aged 12 years of age or younger were dispensed prescriptions for daily doses >20mg/day as exhibited from the data presented by the sponsor.

6.1 Indication

With this submission, the sponsor is not seeking a new indication but proposes to eliminate from current labeling the maximum recommended daily dose language of 20mg/day.

6.1.1 Methods

Study 2305 was a U.S. multicenter (34 sites), five week, randomized, double-blind, placebo controlled 4 arm fixed dose (10, 20, 30mg and placebo) parallel group post-marketing commitment study of dexmethylamphetamine vs. placebo in children (exposed and de novo patients) aged 6-12 years of age with a DSM-IV diagnosis of ADHD. The study was conducted from 01 February 2006 to 13 December 2006.

Primary Objective
The primary objective of study 2305 was to evaluate the efficacy (defined as the change from baseline on the DSM-IV total subscale score of the Conners ADHD/DSM-IV Scales for teachers (CADS-T scale) of the three dosing arms compared to placebo in children aged 6-12 years old with ADHD.

The CADS-T has reported validity and reliability and has been previously accepted by the Agency as a standard measure for measuring ADHD symptom response in clinical trials, most notably for the clinical trials submitted with the initial NDA submission for Focalin. This measure also has wide acceptance and use within the pediatric population.

Secondary Objectives
Protocol 2305 did not pre-specify an *a priori* key secondary objective. However two secondary objectives were identified by the sponsor:

- "To evaluate the efficacy as change from the baseline of the CADS-P [parent version of the CADS-T] and ratings on the CGI-S and CGI-I at study end
- To evaluate the tolerability and safety of 10, 20 and 30mg Focalin XR administered once daily relative to placebo in pediatric patients 6-12 years of age who meet DSM-IV criteria for ADHD."

Of note, comparative efficacy between the dosing arms was not pre-specified as an objective for this particular study, nor was the study powered to detect an efficacy dose response. The sponsor had analyzed comparative efficacy as a post-hoc comparison.

Study Design
The study design as seen below includes a two week screening phase preceding the baseline visit whereby baseline measurements are collected and patients are randomized (1:1:1:1) to Focalin XR 10,20,30mg or placebo respectively. Those patients who were randomized to receive Focalin XR received 5mg/day for the first week. At the second visit, patients receiving active drug would be increased to 10mg/day. For those patients in the 20mg and 30mg dosing arms, subsequent increases of 10mg/day were given weekly thereafter until final dose was achieved. Thus those patients in the 30mg/day dosing arm would have received 30mg/day for only 7 days.

Phase	Pre-randomization		Double-blind Treatment				
Treatment & Period			Focalin™ XR 10, 20 or 30 mg or matching placebo				
Week[a]	up to –2		1	2	3	4	5
Visit	1 **Screening**	2 **Baseline**	3	4	5	6	7
Day	up to –14	-1	7	14	21	28	35

[a]One week is 7±3 days.
↑
Randomization

Protocol Amendments

There were two protocol amendments to the study. The first protocol amendment dated 21 December 2005 was instituted after a teleconference between Novartis and the Institutional Review board. The amendment further restricted study entry to only those patients who were not currently receiving methylphenidate-related medication (defined as not taken any MPH-related medications within 4 weeks prior to screening) or who were inadequately treated with amphetamines of atomoxetine. In addition, patients with a history of cardiac problems or unstable medical conditions were excluded from the trial.

Protocol Amendment 2 (dated 13 June 2006) revised the protocol again to change: 1.) the assent age from 9yo to 7yo; 2.) the documentation of study drug administration; 3.) adding GGT to blood chemistry and 4.) adding clinically notable values for ECG findings.

Patient Inclusion/Exclusion
Important inclusion criteria were that children of both sexes were to be 6-12 years of age with a diagnosis of ADHD of any type via DSM-IV diagnostic criteria based upon both a psychiatric examination and employment of the kiddie schedule for affective disorders and schizophrenia, present and lifetime version (K-SADS;PL)semi-structured interview.

Patients who were homeschooled, history of seizures, psychotic disorders, severe OCD, autism, tic disorders, mood disorders or use of benzodiazepines, sedatives or MAO-I within two weeks of screening or use of atomoxetine or fluoxetine four weeks prior to screening were excluded from participating. In addition, patients who started psychotherapy within three months of screening, history of non-compliance or history of poor response or intolerance to pervious stimulant use were also excluded from the trial.

6.1.2 Demographics

Overall 332 patients were screened for entry into the study, with 253 being randomized to one of the four treatment groups as follows: 10mg-66, 20mg-62, 30mg-60 and placebo-65.

Baseline Demographics
As seen in the table below, the majority of patients in this study were white, pre-adolescent males aged 8.7-8.9 years old.

Table 3: Demographic Characteristics of Study (b) (4)

DEMOGRAPHIC VARIABLE	FOCALIN XR 10MG N=66	FOCALIN XR 20MG N=62	FOCALIN XR 30MG N=60	FOLCAIN XR TOTAL N=188	PLACEBO N=65
Male (%)	64%	61%	67%	64%	66%
White (%)	62%	58%	57%	59%	58%
Black (%)	29%	27%	25%	27%	34%
Mean Age (years)	8.3 ± 1.72	8.7 ± 1.88	9.0 ±1.92	8.7 ±1.85	8.9 ± 1.81

Baseline Psychiatric History

The duration of time with ADHD symptoms was similar between the placebo and Focalin XR treated patients. The majority of patients in this study were of the combined type ADHD diagnosis.

Table 4: Characteristics of the Presenting DSM-IV ADHD Diagnosis and co-morbidities

DSM-IV ADHD DIAGNOSIS	FOCALIN XR 10MG N=66	FOCALIN XR 20MG N=62	FOCALIN XR 30MG N=60	FOCALIN XR TOTAL N=188	PLACEBO N=65
Inattentive (%)	23%	18%	20%	20%	27%
Hyperactive (%)	0	0	7%	2%	5%
Combined	76%	81%	70%	76%	69%
Duration of ADHD Symptoms-yr (± SD)	3.5 (1.71)	4.0 (1.84)	4.1 (1.87)	3.9 (1.81)	3.9 (1.98)

Past ADHD medication use

The majority of patients in this study had not used any medications for ADHD prior to study enrollment. Only 25% of the Focalin XR-treated patients vs. 36% of placebo patients took any previous treatments for ADHD, with stimulant medication use being the most previously taken.

TABLE 5: Past ADHD Medication use In Study 2305

MEDICATION	FOCALIN XR 10MG	FOCALIN XR 20MG	FOCALIN XR 30MG	FOCALIN XR TOTAL	PLACEBO N=63

	N=64	N=60	N=58	N=182	
Any Medication	18 (28%)	16 (27%)	17 (29%)	51 (28%)	23 (36%)
Methylphenidate or Focalin	9 (14%)	3 (5%)	4 (7%)	16 (9%)	9 (14%)
Obeterol (Amphetamine)	8 (13%)	13 (22%)	11 (19%)	32 (18%)	14 (22%)
Atomoxetine	0	0	3 (5%)	3 (3%)	0
Clonidine	1 (2%)	0	0	1 (<1%)	0
Hyroxyzine HCL	1 (2%)	0	0	1 (<1%)	1 (2%)
Guanfacine	0	0	0	0	1 (2%)

Concomitant Medication Use

Although 39% of Focalin patients and 44% of placebo patients took a concomitant medication during the trial, the vast majority of the medication concomitantly used was over the counter pain relievers, antihistamines or oral asthma medications. It is unlikely that use of the concomitant medications would have significantly biased the efficacy results based on the review of the pharmacology of these medications and the roughly equal distributions between treated and placebo subjects.

TABLE 6: Concomitant Medication use during Study 2305

MEDICATION	FOCALIN XR 10MG N=64	FOCALIN XR 20MG N=60	FOCALIN XR 30MG N=58	FOCALIN XR TOTAL N=182	PLACEBO N=63
Any Medication	38%	43%	36%	39%	44%
Ibuprofen	6%	12%	10%	9%	8%
Acetaminophen	13%	7%	5%	8%	10%
Loratadine	0	12%	3%	5%	2%
Montelukast	3%	7%	5%	5%	0

6.1.3 Subject Disposition

Out of a total of 332 subjects screened, 253 were randomized to treatment, with 237 taking at least one dose of study medication (modified ITT population).

As seen below, the completion rates were 86% for Focalin XR vs. 88% for placebo. On visual inspection of the data, there appears to be a dose-related increase in the number of early dropouts related to adverse events.

TABLE 7: Study 2305 Completion rates

	FOCALIN XR10MG	FOCALIN XR 20MG	FOCALIN XR 30MG	PLACEBO
No. randomized	66	62	60	65
Total No. of early discontinuations	10 (15%)	8 (13%)	9(15%)	8 (12%)
Completed	56 (85%)	54 (87%)	51 (85%)	57 (88%)
Reason For Discontinuation				
Adverse event	1 (1%)	0	4 (7%)	0
Withdrew Consent	5 (8%)	1 (2%)	4 (7%)	1 (2%)
Lost to Follow up	2 (3%)	5 (8%)	0	3 (5%)
Protocol Violation	2 (3%)	1 (2%)	1 (2%)	2 (3%)
Unsat Therapeutic event	0	0	0	2 (3%)
Administrative Problems	0	1 (2%)	0	0
Total	**10**	**8**	**9**	**8**

Of the five patients that were discontinued for adverse events, 80% of the dropouts were from the 30mg/day dosing group. The most commonly reported adverse events were decreased appetite and insomnia. One patient who was taking 30mg/day and discontinued treatment also experienced tactical hallucinations and was also recorded as a serious adverse event (SAE). This case will be reviewed in detail in section 7.3.2 below.

TABLE 8: Adverse events leading to dropout

ADVERSE EVENT BY PREFERRED TERM	FOCALIN XR10MG N=64	FOCALIN XR 20MG N=60	FOCALIN XR 30MG N=58	PLACEBO N=63
Decreased appetite	0	0	2	0
Insomnia	0	0	2	0
Anger	1	0	0	0
Anxiety	1	0	0	0
Depression	0	0	1	0
Hallucination, tactile	0	0	1	0

Protocol Deviations

There were six (6) patients that were discontinued for protocol violations. However review of the data indicates that a significant number of patients had at least one protocol violation that was indicated, but not severe enough to warrant discontinuation from the trial (35% Focalin XR Vs. 28% placebo). The vast majority of the violations were due to dosing changes or interruptions during maintenance treatment.

TABLE 9: Study 2305 Protocol violations (at least one)
By treatment

	FOCALIN XR10MG	FOCALIN XR 20MG	FOCALIN XR 30MG	PLACEBO
At least one protocol violation	26 (40%)	15 (24%)	24 (40%)	18 (28%)
Dose Chg. Or interrupt during maintenance.	11 (17%)	7 (11%)	10 (17%)	8 (12%)

Statistical Plans
The population used for hypothesis testing was the Intent to treat population, defined as those randomized patients that received at least one dose of study drug and at least one post-baseline assessment of the CADS-T. Missing values were imputed using the LOCF approach.

ANCOVA was used for hypothesis testing, employing the Hochberg procedure for multiplicity and controlling for treatment center. Pooling of centers that had less than 12 patients was employed in order to obtain a sufficient center size. Should any of the three dosing arms tests have a p-value greater than 0.05 or if the smallest p-value was equal to or greater than 0.05/3, then efficacy could not be established.

6.1.4 Analysis of Primary Endpoint(s)

The results from the primary analysis clearly demonstrate that patients treated with Focalin XR demonstrate improvement of ADHD symptomatology when compared to placebo treatment at all doses administered. There is a numerical dose response for efficacy seen between 10mg and 30mg and 20mg and 30mg. However there is a lack of a dose response in efficacy seen between 10mg and 20mg doses when looking at the data visually. A similar pattern of efficacy and numerical dose response in efficacy was observed from data analyzed from the observed cases subpopulation.

As part of this submission, the sponsor has reanalyzed the data post hoc to examine the efficacy of the 30mg dose compared to the 10mg and 20mg doses. The results indicated that although a numerical dose effect was seen, a statistically significant dose response in efficacy was not established for the 30mg/dose in children aged 6-12 years old. The results of the post hoc analysis are highlighted below.

Table 10: Mean change from baseline Visit 2 at Visit 7 (LOCF) in the total subscale score of the CADS-T in the ITT population

STATISTIC	FOCALIN XR 10MG N=61	FOCALIN XR 20MG N=59	FOCALIN XR 30MG N=57	PLACEBO N=63
Visit 2 Baseline Mean (SD)	36.7 (9.88)	35.0 (9.42)	37.7 (9.78)	34.9 (8.80)
Visit 7/Final visit Mean (SD)	18.3 (12.12)	18.1 (13.31)	16.4 (13.44)	30.0 (13.01)
Adjusted Mean Change from baseline*	18.0	16.9	20.7	5.7
P-value	<0.001	<0.001	<0.001	
P-value[#]	0.204	0.081		

*Adjusted mean changes from the analysis of covariance model
[#]based on the difference between the 30mg and lower doses from the ANCOVA model.

6.1.5 Analysis of Secondary Endpoints(s)

Data obtained from the parent report of the CADS instrument indicate that parents generally rated patients ADHD symptoms worse when compared to teachers. The results of the analysis indicate that patients treated with all doses of Focalin XR had improved symptomatology when compared to placebo patients. In addition, a clear numerical dose-response for efficacy was seen for all doses of Focalin XR tested when parents were reporting the symptoms as compared to the teacher reports.

Table 11: Mean change from baseline Visit 2 at Visit 7 (LOCF) in the total subscale score of the CADS-P in the ITT population

STATISTIC	FOCALIN XR 10MG N=60	FOCALIN XR 20MG N=58	FOCALIN XR 30MG N=57	PLACEBO N=63
Visit 2 Baseline Mean (SD)	41.1 (10.35)	39.8 (9.74)	40.4 (10.28)	40.7 (10.24)
Visit 7/Final visit Mean (SD)	24.9 (14.18)	21.4 (13.97)	19.6 (12.75)	35.9 (13.03)
Adjusted Mean Change from baseline*	15.8	17.8	20.5	4.6
P-value	<0.001	<0.001	<0.001	

For the CGI-I Scale, improvement was pre-specified as having a final visit score of 1 (very much improved) or 2 (much improved) on the CGI-I scale. Results from the study

also support the efficacy results seen with the primary efficacy variable and demonstrate that a clinical improvement in symptoms is seen with Focalin XR use as compared to placebo patients. Similar results were obtained on the CGI-S scale where the majority of the patients at final visit were mildly to moderately ill.

Table 12: Proportion of patients with improvement (LOCF) on the CGI-I scale by treatment at final visit

STATISTIC	FOCALIN XR 10MG N=61	FOCALIN XR 20MG N=59	FOCALIN XR 30MG N=57	PLACEBO N=63
Improvement	74%	71%	77%	22%
No Improvement	26%	27%	23%	78%
P-value	<0.001	<0.001	<0.001	

6.1.6 Other Endpoints

No other efficacy endpoints were analyzed

6.1.7 Subpopulations

Not evaluated

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This reviewer requested an internal review from the Office Of Surveillance and Epidemiology (OSE) of Focalin XR drug usage data with specific focus on Focalin XR usage <20mg/day and >20mg/day by age groups and practitioner specialty. In addition a review of drug utilization data from the sponsor was also requested. The OSE review of the data was performed by Grace Chai, PharmD on July 10, 2009 and the sponsor review of drug utilization data was received by the Agency on 21 August, 2009.

In general, the OSE review of the data focused on data from SDI, Vector One: National (VONA) and Total Patient Tracker (TPT) databases from the years 2005-2008. Prescriber specialties were obtained from SDI, Physician's Drug and Diagnosis Audit (PDDA). Results demonstrated that 91% of prescriptions were distributed in an outpatient setting, primarily retail pharmacies. A total o (b) (4) patients are projected to have been exposed to Focalin XR since marketing in 2005. In 2008, patients aged 6-9 years were dispensed the greatest market share of Focalin XR prescriptions (33%), followed by 10-12 (29%), 13-17 (24%) and patients aged 18 or older (12%). Approximately 2% of patients aged 0-5 were prescribed Focalin XR in 2008. With regards to daily doses prescribed in 2008, daily doses greater than 20mg/day occurred less than 10% of the time, with a daily dose of 30mg/day reported 3%, 40mg/day at 4% and 60mg and above at 1%. It was noted that since the

occurrences of daily doses above 20mg/day in this database were infrequent, the results are not reliable from a statistical standpoint. Nonetheless, the results indicate that Focalin XR is being prescribed in doses above the maximum labeled dose of 20mg/day. For an in-depth review of the OSE data, the reader is referred to the OSE consult of July 10, 2009 OSE RCM # 2009-929.

The sponsor's analysis of drug utilization data were obtained from SDI and based on drug usage from the time period of June 2008-May 2009. Based on the sponsor's review of this data, 18% of all patients were taking Focalin XR in doses above 20mg/day. Data based on the number of prescriptions dispensed by age group demonstrated that 12% of prescriptions in patients 12 years of age or younger were for daily doses greater than 20mg/day. For the 13-17 year old age group, approximately 24% of the prescriptions dispensed were for daily doses >20mg/day and for adult patients age 18 or old, 25% of all prescriptions in the SDI database were dispensed for doses greater than 20mg/day. In the sponsor's review of the data, psychiatrists were somewhat more likely (23%) to prescribe Focalin XR at doses above 20mg/day as compared to primary care practitioners or pediatricians (14% each) or neurologists (15%).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable for this submission

6.1.10 Additional Efficacy Issues/Analyses

As part of this submission, the sponsor has reanalyzed the efficacy data for the primary efficacy endpoint for four of the five submitted studies, with the purpose to examine an efficacy dose response by comparing the efficacy results from the largest dosing arm compared to the lower doses for the fixed dose studies. The results are seen below.

Study 2301
This study employed a flexible dose study design. Thus a dose-response for efficacy cannot be determined from this study.

Study 2302 (Adult Study)
The re-analysis of the adult data from the initial NDA application demonstrates that a dose response for efficacy was not seen with the 40mg/day dose when compared to the 30mg or 20mg doses despite a numerical improvement in the symptomatology. As with the pediatric study 2305, a lack of numerical dose responsiveness was seen with the 30mg dose as compared to the 20mg dose.

Table 13: Study 2302 Mean change from baseline in the DSM-IV RS score (LOCF) in the ITT population by treatment

STATISTIC	FOCALIN XR 20MG N=57	FOCALIN XR 30MG N=54	FOCALIN XR 40MG N=54	PLACEBO N=53
Visit 2 Baseline Mean (SD)	36.8 (7.20)	36.9 (8.07)	36.9 (8.25)	37.5 (7.82)
Visit 7/Final visit Mean (SD)	23.1 (11.65)	23.5 (11.80)	20.0 (11.50)	29.6 (13.58)
Adjusted Mean Change from baseline*	13.3	12.9	16.5	7.6
P-value	0.006	0.012	<0.001	
P-value[#]	0.115	0.081		

*Adjusted mean changes from the analysis of covariance model
[#]based on the difference between the 40mg and lower doses from the ANCOVA model.

US 12
For this double-blind, five period cross over study (Focalin 20, 30mg, Concerta 36, 54mg, placebo) in children, the reanalysis of efficacy again shows a lack of dose responsiveness of the 30mg when compared to the 20mg dose at the two hr time point (the defined primary efficacy variable for this study). A small numerical improvement was noted.

Table 14: Study US12 Mean change from pre-dose to 2 hour post dose in the SKAMP-combined score by treatment

STATISTIC	FOCALIN XR 20MG N=83	FOCALIN XR 30MG N=82	PLACEBO N=81
Pre-dose (Hour 0) Mean (SD)	20.3 (11.95)	21.5 (11.27)	17.2 (10384)
Hour 2 Mean (SD)	10.1 (7.96)	10.0 (8.20)	24.0 (12.80)
Adjusted Mean Change from baseline*	-10.6	-11.2	4.0
P-value	<0.001	<0.001	
P-value[#]	0.613		

*Adjusted mean changes from the analysis of covariance model
[#]based on the difference between the 30mg and lower doses from the ANCOVA model.

US 13
Similar to all the previous dose-response reanalysis, dose response was not established for the 30mg dose when compared to the 20mg dose at 2 hours post dose in this double-blind three-period crossover study in children.

Table 15: Study US13 Mean change from pre-dose to 2 hour post dose in the SKAMP-combined score by treatment

STATISTIC	FOCALIN XR 20MG N=81	FOCALIN XR 30MG N=81	PLACEBO N=79
Pre-dose (Hour 0) Mean (SD)	23.2 (13.88)	25.6 (13.74)	17.7 (11.77)
Hour 2 Mean (SD)	8.3 (6.98)	8.6 (7.08)	21.7 (11.96)
Adjusted Mean Change from baseline*	-13.5	-13.9	1.3
P-value	<0.001	<0.001	
P-value#	0.701		

*Adjusted mean changes from the analysis of covariance model
#based on the difference between the 30mg and lower doses from the ANCOVA model.

7 Review of Safety

Safety Summary

Overall the adverse event profile for the 30mg dose was comparable to the adverse events seen in adults at the 30mg and 40mg dose level. Dropouts due to adverse events was higher (7%) at the 30mg dose in children for the fixed dose 2305 study compared to lower doses. However these adverse events are known effects of stimulant medications and are appropriately labeled in the current approved labeling.

Generally gastrointestinal disorders, metabolic and nutritional disorders, psychiatric adverse events were reported in a dose-dependant fashion in study 2305. Specifically vomiting, anorexia, insomnia, depression, mood swings, irritability, nasal congestion and pruritis were noted to be dose-dependently-reported in study 2305. This reviewer recommends additional inclusion of these dose-dependant adverse events in the proposed labeling to better inform clinicians and caregivers the incidence rates of these dose-dependant adverse events in children with Focalin XR administration.

There were no clinically significant laboratory or vital sign abnormalities noted. With regards to clinically notable weight loss, defined as >7% of body weight loss from baseline in study 2305, patients taking the 30mg/day dose had the highest incidence of weight loss compared to 10 and 20mg doses. However the incidence rate was not dose-dependant due to a decreasing incidence of weight loss for the 20mg dosing cohort (>7% weight loss incidence: 10mg-6%, 20mg-4%, 30mg-8%, placebo-0%).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

With the exception of study 2305, all the studies submitted with this supplement have been previously reviewed for safety. The focus of the safety review for this submission will focus on safety findings from study 2305 and a summary of safety from the submitted studies, with particular attention paid to dose dependant adverse events occurring in the fixed dose adult and pediatric trials.

7.1.2 Categorization of Adverse Events

Standard adverse event dictionaries were used to categorize both documented and verbatim reports of all adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The investigators' terminology (i.e. the 'verbatim' report) was preserved and made available.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For this submission, the sponsor did provide a separate report of pooled safety data across the different studies for purposes of exposure and analysis of adverse events. However as the focus of the safety review for this application was to elucidate dose-dependant adverse events, the pooled data was reviewed with only pertinent safety signals reported for purposes of this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure Data

The mean duration of exposure for study 2305 in the Focalin XR group was 33.3 days vs.34.3 days in the placebo controlled group.

TABLE 16: Duration of Exposure
By treatment

	FOCALIN XR10MG N=64	FOCALIN XR 20MG N=60	FOCALIN XR 30MG N=58	FOCALIN XR TOTAL N=182	PLACEBO N=63
Duration-Days (+SD)	32.5 (9.58)	33.7 (6.95)	33.8 (6.13)	33.3 (7.74)	34.0 (6.55)

7.2.2 Explorations for Dose Response

The sponsor has submitted a summary of safety that includes safety data from all five submitted studies, both flexible and fixed dose. The focus of the explorations for dose-responsiveness for adverse events will focus on results from the fixed dose studies 2305, 2302 and US12 and US13.

7.2.3 Special Animal and/or *In vitro* Testing

Not applicable for this submission.

7.2.4 Routine Clinical Testing

Routine clinical testing for adverse events was adequate for all the submitted studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported from both the fixed dose pediatric study 2305 and the previously submitted studies are generally similar and are consistant with the adverse events seen from studies performed with other stimulant products.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in any of the submitted clinical trials.

7.3.2 Nonfatal Serious Adverse Events

For study 2305, one patient (0510/00006) experienced a non-fatal, serious adverse event during the trial. This patient, a 6 year old African American male with a history of lymphadenopathy and ADHD previously treated with herbal medications, experienced tactile hallucinations and musculoskeletal stiffness 19 days after treatment with Focalin XR. Additionally three days prior to this event, he was found crying and socially isolative for one day which was described as depression He was treated in the emergency room, discontinued the study medication and had completely recovered from the event with no sequelae noted one day after discontinuation.

These adverse events are known side effects of stimulant medications and have been well characterized in both literature and in current labeling for the stimulant class of medications. Therefore this reviewer recommends that no additional labeling changes are indicated for these adverse events in question.

7.3.3 Dropouts and/or Discontinuations

As seen in the table below, five patients or 3% of the total patient population dropped out or was discontinued for an adverse event. The vast majority of the dropouts occurred in the 30mg dosing arm. The adverse events associated with the dropouts are all commonly associated with stimulant-class medication use thus no additional language is recommended at this time.

Table 17 Study 2305-patients who discontinued treatment due to adverse events-by preferred term and treatment arm.

	FOCALIN XR 10MG N=64	**20MG XR N=60**	**30MG XR N=58**	**PLACEBO N=63**
Total No of patients DCed for Adverse events	1 (2%)	0	4 (7%)	0
Adverse Events Reports by Preferred Term				
Decreased Appetite	0	0	2 (3%)	0
Insomnia	0	0	2 (3%)	0
Anger	1 (2%)	0	0	0
Anxiety	1 (2%)	0	0	0
Depression	0	0	1 (2%)	0
Hallucinations, tactile	0	0	1 (2%)	0

7.3.4 Significant Adverse Events

There were no significant adverse events noted for study 2305. The adverse events reviewed are consistent with what has been described previously in labeling.

7.3.5 Submission Specific Primary Safety Concerns

Since common adverse events have been adequately studied and labeled based on reviews of safety data from previous submissions, this review focused on adverse events that were dose related, serious and/or unusual adverse events. As a result, the focus on these adverse events, particularly those that occurred in the fixed dose trials, will be reviewed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Those events that were common (i.e. greater than 5% incidence) and drug related (i.e. twice the rate over placebo) for the entire Focalin XR population compared to the placebo group were decreased appetite (12% vs. 5%), insomnia (10% vs. 3%), and vomiting (6% vs. 0%). These events are consistent with common adverse events seen with current labeling.

Table 18: Study 2305 Common and Drug-related Adverse events by treatment group

ADVERSE EVENT PREFERRED TERM	FOCALIN XR N=182	PLACEBO N=63
Decreased Appetite	12%	5%
Insomnia	10%	3%
Vomiting	6%	0

Patients who received Focalin XR were on a whole more likely than placebo patients to experience a psychiatric adverse reaction or metabolic/appetite events or were likely to exhibit a dermatological reaction or an abnormality in a laboratory/vital sign parameter. For a more detailed review, please refer to section 7.5.1 for details.

Table 19: Study 2305 Common and Drug-related Adverse events by treatment group

ADVERSE EVENT SYSTEM ORGAN CLASS	FOCALIN XR N=182	PLACEBO N=63
Investigations*	5%	0
Metabolism and nutrition	18%	5%

disorders		
Psychiatric disorders	25%	8%
Skin and subcutaneous tissue disorders	6%	3%

*includes weight decreased (2%), blood glues increased, ECG QTc prolongation, ECG abnormal, heart rate increased or hepatic enzyme increased (1% each respectively)

7.4.2 Laboratory Findings

Elevated potassium levels that were at 'clinically notable' levels (defined as >5.00 mmol/L) from baseline were seen in 5% of all Focalin XR treated subjects compared with none in the placebo group. This mean change was not dose-dependant. This effect appears to be transient and with the absence of notable arrhythmias, the clinical significance of this finding is likely minimal.

Also the number of patients with newly occurring-clinically notable abnormalities in alkaline Phosphatase and total bilirubin levels was also increased in Focalin XR treated patients when compared to placebo (3% for each respectively vs. 0% respectively for placebo). Again these levels were not dose-dependant.

No patients were discontinued for abnormal laboratory values. A review of the laboratory values that were considered clinically notable did not reveal any clinically significant laboratory abnormalities, as compared with the reference parameters for the labs.

7.4.3 Vital Signs

In general, Focalin XR patients were not more likely than placebo patients to exhibit clinically notable changes in blood pressures and pulses as compared to placebo patients. However 3% of patients in the 30mg treatment arm compared to no patients in the other two arms or placebo experienced a clinically notable elevation in systolic blood pressure. Clinically notable elevations in systolic blood pressures was defined as >125 mmHg and an increase of 20mmHg in patients less than 12 or >180mmHm and an increase of 30mmHg in patients 12 yeas of age or older. Elevated systolic blood pressures are a well-described and currently labeled adverse effect of dexmethylphindate use. Therefore no additional labeling changes are indicated based on the review of this data at this time.

As weight loss is a known adverse event with stimulant use, clinically notable weight loss, defined as >7% of body weight, was consistently noted in the Focalin 10, 20 and 30mg XR treatments arms (6%, 4% and 8% respectively vs. none in the placebo group. Although the greatest percentage of weight loss occurred in the 30mg dosing cohort, the effect as not dose-dependant.

7.4.4 Electrocardiograms (ECGs)

Compared to placebo subjects, the incidence and types of ECG abnormalities was generally similar between all dosing arms in the Focalin XR treatment group compared with placebo. However the most frequently reported for the Focalin XR group (though not dose dependant) was an intraventricular conduction delay with 4% for the 10mg XR dosing arms and 2% each for the 20 and 30mg arms respectively compared to none in the placebo arm.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted or submitted with this efficacy supplement.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A review of the adverse events by treatment arm for the fixed dose study 2305 reveals that the incidence of gastrointestinal disorders, metabolism and nutritional disorders and psychiatric disorders appear to increase in a dose-dependant manner. This reviewer recommends that this table be incorporated into labeling for adverse events under the pediatric use section of the label that describes study 2305.

Table 20: Dose-related Adverse Events from Study 2305 By Organ-System and Preferred Term

ADVERSE EVENT	**XR 10 N=64**	**XR 20 N=60**	**XR 30 N=58**	**PLACEBO N=63**
Gastrointestinal disorders	22%	23%	29%	24%
-vomiting	2%	8%	9%	0
Metabolism and nutritional disorders	16%	17%	22%	5%
-anorexia	5%	5%	7%	0
Psychiatric Disorders	19%	20%	38%	8%
-insomnia	5%	8%	17%	3%

-Depression	0	0	3%	0
-mood swings	0	0	3%	0
Other Adverse events				
-Irritability	0	2%	5%	0
-Nasal Congestion	0	0	5%	0
-Pruritis	0	0	3%	0

7.5.2 Time Dependency for Adverse Events

Time dependent studies were not performed as part of this NDA efficacy supplement submission.

7.5.3 Drug-Demographic Interactions

Specific safety analyses regarding drug-demographic interactions were not conducted with this efficacy supplement.

7.5.4 Drug-Disease Interactions

Specific safety analyses regarding drug-disease interactions were not conducted with this efficacy supplement.

7.5.5 Drug-Drug Interactions

Specific safety analyses regarding drug-drug interactions were not conducted with this efficacy supplement.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Preclinical human carcinogenicity studies were not conducted with this efficacy supplement. Please review the currently approved labeling for Focalin XR and original pharmacology/toxicology reviews that are filed under the initial NDA submission for specific details.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy and human reproduction data was not submitted with this efficacy supplement. Please review the currently approved labeling for Focalin XR and original pharmacology/toxicology reviews that are filed under the initial NDA submission for specific details.

7.6.3 Pediatrics and Assessment of Effects on Growth

Methylphenidate use over time in children has been associated with suppression of growth rates when compared to placebo controlled patients. Both suppression in height and in weight have been documented.

The effects of longer term suppression of growth with methylphenidate use in currently labeled for the stimulant class medications, including Focalin XR.

Based on the data contained in this submission, this reviewer finds the adverse effects on growth acutely as consistent with current labeling. Therefore I recommend no changes to this section of labeling at this time.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Focalin XR is a schedule II controlled substance. As such, the current Focalin XR label contains a black boxed warning regarding the abuse and dependence that can occur with its use. No additional changed to labeling are indicated at this time based on the data contained within this submission.

Although no cases of overdose were noted in study 2305, cases of overdose have been reported in post-marketing reports. The current label adequately addresses the signs and symptoms of acute methylphenidate overdose and treatment options. As this submission contains no additional data regarding overdose cases, this reviewer recommends no changes to the label at this time.

7.7 Additional Submissions / Safety Issues

The sponsor has included with this submission a summary of clinical safety that summarizes the pertinent safety data from all of the previously submitted studies, both flexible and fixed dose. Although the focus of this review is primarily on dose-dependant adverse events seen in fixed dose trials, a brief review of safety findings from flexible dose studies are discussed below.

Study 2301

During this flexible dose pediatric study, the greatest incidences of adverse events in the 30mg treated group were decreased appetite (24%), headache (24%), nasopharyngitis (17%), nausea and insomnia (10% each). Of note, there was one reported case of rhabdomyolysis in the 30mg dosing group.

US12 and US13

The safety data from these two cross-over pediatric studies reveal that headache (15%); insomnia and nausea (6% each), decreased appetite and abdominal pain (3% each) were most commonly reported in patients when receiving 30mg of Focalin XR.

Adult Fixed dose study 2302

For the adult fixed dose study, headache, dry mouth, anxiety and dyspepsia appeared to be dose dependant adverse events. In addition, abdominal pain, chest discomfort, cold sweat and flatulence were only reported at the 40mg dose.

Table 21: Dose-Related Adverse Events from Adult Fixed Dose Study 2302

ADVERSE EVENT	**XR 20 N=57**	**XR 30 N=54**	**XR 40 N=54**	**PLACEBO N=53**
Headache	26%	30%	39%	19%
Dry Mouth	7%	20%	20%	4%
Anxiety	5%	11%	11%	2%
Dyspepsia	5%	9%	9%	2%

SAEs

There was only one SAE reported in the pediatric trial. This was the case previously described in this review who experienced tactile hallucinations.

Two SAEs were reported from the fixed dose study 2302 and both occurred in the 40mg Focalin XR group. One patient with a history of ulcerative colitis (UC) was hospitalized for UC and hypovolemic shock while a second patient was hospitalized for a high fever and loss of consciousness. For additional details on these SAEs, the reader is referred back to the original reviews for initial marketing application for Focalin XR on file within the Agency database.

Dropouts

In the pediatric studies, the only reported dropouts occurred in study 2305 which has been reviewed as part of this application.

For the adult application, 11% , 13%, 9% and 8% of patients dropped out due to adverse events from the 20, 30 , 40mg and placebo groups respectively.

8 Postmarket Experience

According to the sponsor, post-marketing safety data seen for the 20mg dose worldwide is consistent with the safety profile of the 30mg and 40mg doses reviewed with this application.

9 Appendices

Schedule of Assessments-Study 2305

Phase	**Pre-randomization**		**Double-blind Treatment**				
Treatment			**Focalin® XR or placebo**				
Week[a]	**up to -4**		**1**	**2**	**3**	**4**	**5**
Day	**up to -28**	**-1**	**7**	**14**	**21**	**28**	**35**
Visit	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7 PD**[d]
Assent/Informed consent[b]	X						
Inclusion/exclusion[b]	X	X					
Randomization		X					
Demography	X						
Medical & psychiatric history	X						
Diagnostic interviews (K-SADS-PL)[b]	X						
Urine drug screen[c]	X						
Serum pregnancy test, if applicable[c]	X						X
Urine pregnancy test, if applicable[b]		X					
Physical exam[b]	X						X
Routine laboratory tests (blood/urine)	X						X
ECG	X						X
Height		X					
Weight		X					X
Vital signs	X	X	X	X	X	X	X
CGI-S		X					X
CGI-I			X	X	X	X	X
CADS-T		X	X	X	X	X	X
CADS-P		X	X	X	X	X	X
Study drug onset & duration			X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X

Phase	Pre-randomization		Double-blind Treatment				
Treatment			Focalin® XR or placebo				
Week[a]	up to -4		1	2	3	4	5
Day	up to -28	-1	7	14	21	28	35
Visit	1 Screening	2 Baseline	3	4	5	6	7 PD[d]
Serious Adverse events	X	X	X	X	X	X	X
Study drug dispensing		X	X	X	X	X	
Dose Administration Record			X	X	X	X	X
Study completion							X

[a]One week is 7±3 days.

[b]Procedures or assessments recorded only in the source documentation (not in eCRFs or database).

[c]Assessments collected electronically (not in eCRFs) and transferred directly to the database.

[d]PD = Premature discontinuation

9.1 Literature Review/References

No reviews were performed at this time.

9.2 Labeling Recommendations

For the dosage and administration section of the label, this reviewer agrees with removal of the statement "…to a maximum of 20mg/day." This reviewer recommends that the proposed language not be adopted. However the following sentence is recommended to be added in the second bullet of the dosage and administration section of the highlights: "Doses above 30mg in children and 40mg in adults have not been clinically studied."

In section 2 of proposed labeling, this reviewer recommends removing (b) (4) from the proposed language.

In section 6.2, this reviewer recommends inclusion of dose-related adverse events data table from study 2305 (fixed dose pediatric study) as reviewed above into the current labeling.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21802	SUPPL-14	NOVARTIS PHARMACEUTICALS CORP	FOCALIN XR CAPS

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/s/

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