Table F3. Frequency of patients with psychiatric adverse events in adult and pediatric ADHD safety and efficacy trials (Lilly response to September 14, 2005 letter)

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	1443	350.73	0	4	18
DB	Atomoxetine	2459	654.87	4	9	49
DB	Atomoxetine+Concerta	9	0.87	0	0	0
DB	Atomoxetine+Fluoxetine	114	11.92	0	2	0
DB	Fluoxetine	120	7.54	0	1	2
DB	Methylphenidate	515	69.21	0	1	7
Open	Atomoxetine*	5270	5095.27	12	44	198
Run-in	Atomoxetine	812	177.80	2	3	47

*This total is for atomoxetine without other drugs; there were no events among the small numbers of patients who received open label atomoxetine with another drug

Limiting the data to pediatric patients yields the following new totals for atomoxetine and placebo.

Table F4. Pediatric ADHD safety and efficacy trials: frequency of patients with adverse psychiatric events.

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	1056	256.02	0	3	15
DB	Atomoxetine	1939	524.64	4	8	45
DB	Atomoxetine+Concerta	9	0.87	0	0	0
DB	Atomoxetine+Fluoxetine	114	11.92	0	2	0
DB	Fluoxetine	120	7.54	0	1	2
DB	Methylphenidate	515	69.21	0	1	7
Open	Atomoxetine	4669	4546.74	12	44	191
Run-in	Atomoxetine	812	177.80	2	3	47

Note that there were proportionally more aggression events during run-in treatment than during double blind treatment with atomoxetine. It will be seen that there is an imbalance in the numbers of patients with events in all three categories for double blind atomoxetine versus placebo, even after accounting for the approximately 2:1 ratio of patient-years of exposure. However, the imbalance for suicidal events is not as great as it was in Lilly's previous analysis of suicidal adverse events. The present results include some additional clinical trial data that was not part of Lilly's previous analyses. Relapse prevention trials were not included in Lilly's analyses, and removing these two trials (HFBE and LYAF) from the pool of trials yields the following totals, which are more comparable to the previous analyses by Lilly. For simplicity, only the double blind data are shown, since the other data are not affected by removing the relapse prevention trial data.

Table F5. Pediatric ADHD safety and efficacy trials, omitting long term relapse prevention trials: frequency of patients with adverse psychiatric events.

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	839	144.54	0	1	12
DB	Atomoxetine	1616	296.50	4	4	38

This subgrouping yields an incidence rate ratio for the pooled data on suicidal events of 1.9, with wide confidence limits (0.19-96, Stata 7.0). The incidence rate ratio for aggression events is 1.5 (c.i. 0.8-3.2), and due to an absence of events on placebo the ratio is undefined for psychosis/mania events, with a p-value of 0.2 for the comparison between drug and placebo.

Differences in the search strategies employed seem to account for some of the differences in the numbers of cases. In their submission dated 12-8-05, Lilly was able to reconcile the counts of cases between their own analyses of aggression and suicidal events and their response to FDA's September 2005 request. Lilly found that certain cases from their previous analyses had not been returned in the FDA-requested search, because (1) in response to the FDA request (unlike their previous analyses) they had not searched comments fields from the case report forms, and (2) in their previous searches they had used more inclusive text strings resulting in greater sensitivity. Additionally, Lilly had potential cases adjudicated by experts prior to analyzing the data, and this was not part of the present analysis.

In addition to the pediatric ADHD trials, there was one pediatric study (LYBH) in patients with enuresis, and the data from this trial are displayed below.

Table F6. Frequency of patients with adverse events in enuresis trial LYBH

Study design	Treatment	N	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	43	0	0	2
DB	Atomoxetine	44	0	0	0
Open	Atomoxetime	64	0	1	1

The sponsor also provided the corresponding data for the adult depression trials, which is summarized below. Psychosis/mania events were more frequent among atomoxetine treated patients, while suicidal and aggressive events were less frequent, proportional to exposure time.

Table F7. Adult major depressive disorder safety and efficacy trials: frequency of patients with adverse psychiatric events.

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	653	156.99	1	5	3
DB	Atomoxetine	1178	333.31	6	5	3
Open	Atomoxetine	42	12.11	0	0	0

With respect to events occurring after treatment discontinuation, the sponsor provided listings of such events, but these proved difficult to analyze because the listings were not organized according to indication or category of event. The events occurring after treatment were not included in the data shown above.

G. Ritalin LA (NDA 21-284, Novartis)

Ritalin LA is an extended release formulation of methylphenidate. There were 5 controlled trials and one open label trial in the Ritalin LA development program, as summarized in Appendix table G. All trials involved only pediatric subjects.

The next table displays the summary data on the psychiatric events of interest.

Table G. Frequency of patients experiencing selected psychiatric events in Ritalin LA clinical safety and efficacy studies.

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	259	11.31	0	1*	0
DB	Ritalin LA	383**	25.66	2	0	2
Open	Ritalin LA OL	125	25.95	0	1	0
DB	Concerta	89	2.82	0	0	0

*One additional suicidal event occurred within 30 days of the end of treatment in a patient who had been randomized to placebo
**includes single blind Ritalin LA exposures in Protocol 07

Narratives for patients with serious adverse events and trial discontinuations for adverse events were reviewed, disclosing one event which could arguably have been included in the category of suicidal events but apparently was not: in Protocol 07, patient 503/6, an 8-year old male receiving double blind Ritalin LA, was hospitalized for suicidal ideation. The event was coded as depression and counted in the category "miscellaneous." Although the post-treatment suicidal event involving a placebo patient was designated serious, none of the events enumerated in the table above during study treatment were considered serious.

H. Focalin (NDA 21-278) and Focalin XR (NDA 21-802) (Novartis)

Focalin and Focalin XR are drug products with dextromethylphenidate (d-MPH) as the active ingredient. The XR product is an extended release formulation. In the following data presentations the two formulations will be combined and listed as d-methylphenidate (d-mph). The trials in the sponsor's development program for both formulations are summarized in Appendix table H. All trials involved pediatric patients except for one placebo-controlled trial in adults (E2302) which included open label follow-up treatment (designated E2302E).

The table below summarizes the numbers of events in trials with d-MPH. There were no events of interest with placebo treatment. Note that Novartis apparently included 3 events occurring after discontinuation of open-label d-MPH treatment in these counts, which was not the intention. However, because data on which category the event was classified in was not always provided in the listing of events, making it difficult to match the counts of events with particular cases in the patient listings, it was decided to leave the events in the counts displayed below rather than to try to correct the totals.

Table H1. Frequency of patients experiencing selected psychiatric events in Focalin and Focalin XR clinical safety and efficacy studies.

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	468	53.24	0	0	0
DB	d-MPH*	588	64.75	4	0	1
Open	d-MPH*	740	362.09	3	1	13
DB	Concerta	164	5.89	1	0	0
DB	dl-MPH	46	3.59	0	0	0

*Focalin and Focalin XR

Novartis' analysis of these data showed that aggressive events were more frequent among males than females (data not shown).

The sponsor reported that in the clinical pharmacology studies there were no relevant psychiatric adverse events. One pediatric patient (97 M 05/2708) had a psychosis/mania event three weeks after open label treatment was discontinued (psychotic depression with homicidal ideation, requiring hospitalization). Also, there was one miscellaneous event with a serious outcome, patient 22-03 in study 97 M 04, but this patient's event was also counted as psychosis/mania (see below).

The table below shows the data for the subgroup of trials involving only subjects of pediatric age.

Table H2. Summary data from pediatric trials in the d-MPH development program

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	415	48.47	0	0	0
DB	d-MPH*	420	49.73	1	0	0
Open	d-MPH*	570	302.87	2	1	11
DB	Concerta	164	5.89	1	0	0
DB	dl-MPH	46	3.59	0	0	0

*Focalin and Focalin XR

Review of the narratives for patients with serious adverse events and trial discontinuations disclosed two events which arguably could have been included in the category of suicidal events, but were not. Both patients were treated with open label d-MPH in study 97 M 04. Patient 22-03, a 7 year old boy, was hospitalized after placing a belt around his neck and showing aggressiveness, and hallucinating. This patient was counted in the psychosis/mania category. Patient 23-31, a 12 year old boy, was hospitalized with psychotic depression for violent behavior and suicidal and homicidal thoughts; this event was counted under psychosis/mania and aggression.

5. CONCLUSIONS

A. There are factors that limit the utility of these clinical trial data for determining whether any of these drugs are associated with the selected psychiatric events. Some of these limitations apply whenever clinical trial data are aggregated for analysis. For one, there is the issue of whether adverse events are ascertained with the same level of sensitivity by different investigators, and in different trials. This can present challenges when making comparisons between trials and between development programs. Secondly, there is the issue of whether cases could have been misclassified. The data presented herein were based upon each sponsor's adverse event classifications, but the methods employed to produce these classifications varied across sponsors. Third, the statistical power of such safety analyses are always limited by the sample sizes of the trials considered.

In addition to these general limitations which apply to all such safety analyses, there are additional limitation specific to these data. First, as can be seen from the tables in the appendix, a large number of the controlled trials required subjects who were known to respond to stimulants, or who had no history of intolerance to stimulants. This tends to limit the external generalizability of safety data collected from samples of such subjects, especially when the data obtained from the subjects show relatively infrequent adverse events. Secondly, it will be seen that the duration of exposure in many of these trials was likely to have been insufficient for determination of infrequent adverse events; e.g., although over a thousand pediatric subjects received double-blind treatment in one set of clinical trials, the average duration of exposure to double-blind treatment was only 23 days. To a certain degree this can be (and was) mitigated by greater exposure time in open label trials, but open label data is of less inferential value than controlled data. The

exception to this was the development program for atomoxetine, which included over 500 person-years of double blind atomoxetine pediatric exposure.

B. Undertaking a more formal meta-analysis of the clinical trial data for these events would have presented challenges because of the sparse nature of the data; many trials had no events at all.

C. With respect to specific findings, suicidal events were more frequent with atomoxetine and modafinil treatment than with placebo. It should be noted that there were no completed suicides in ADHD trials with these drugs (one completed suicide was reported in a placebo patient in an atomoxetine trial for another indication). Aggressive events were more frequent with the methylphenidate transdermal patch, and to a lesser degree with atomoxetine, than with placebo. None of these imbalances in rates reached customary levels of statistical significance in this analysis, although Lilly's previous analysis of suicidal events with atomoxetine did show a statistically significant association, as was summarized above. For aggression events, there was little evidence in these trials that drug treatment reduced their frequency relative to placebo; only for modafinil was the event rate numerically lower than for placebo and this was not statistically significant.

D. With respect to psychosis and mania events, although the numbers of such events with drug treatment were small, the complete absence of such events with placebo treatment was notable. For 4028 pediatric ADHD patients in these trials, there were no such events in 425 person-years of aggregated placebo treatment. Statistically, observing no events in 425 person-years yields an upper one-sided 97.5% confidence limit to the "true" event rate of 0.9 per 100 person-years. (Similarly, there were no psychosis or mania events in these trials among 578 adult ADHD patients receiving placebo for a total exposure time of 111.5 person-years in the adult age group.) Psychosis/mania events occurred during double-blind treatment with every compound except Adderall XR (although there were psychosis/mania events with open label Adderall XR treatment). Furthermore, as noted above, some subjects in Phase I studies of these drugs experienced this type of event.

E. Patients and physicians should be aware of the possibility that these events, when they arise in the course of drug treatment of ADHD, may represent adverse reactions to drugs.

F. In terms of future clinical trial designs, it should be borne in mind that short-duration trials and trials which exclude subjects who are naïve to this class of drug, while they may be efficient for determining efficacy, have limitations for defining the safety profile of the drug.

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Appendix Table A. ADHD safety and efficacy studies with Concerta included in analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
C 97 025	1	6-12	6 3 way Xover	18-54	68	69	69 MPH	MPH users	Included laboratory school	1998
C 98 003	1	6-12	7 3 way Xover	18-54	62	61	63 MPH	MPH users	Included laboratory school	1999
C 98 005	14	6-12	28	18-54	104	98	104 MPH	MPH users or previous study subjects	Open label run-in phase was designated Study C 98 007	1998
C 98 007	14	6-12	21	18-54	110	-	-	Naïve or using drugs other than MPH	Open label run in for Study C 98 005	1998
C 98 012	14	6-13	> 1 yr	18-54	436	-	-	Subjects in previous trials	Long term open label	2000
C 99 018	118	> 6 incl. adults	9 mos.	18-54	1088	-	-	Naïve or previously drug treated	Long term open label	2001
01 146	15	13-18	14	18-72	87	90	-	ADHD	Randomized withdrawal design following open label run-in. Also included open label extension after DB phase	2002
12 101	323	6-12	21	18-72	~890	-	~445 atomox etine	Drug naïve patients allowed	Randomized, open label design	2003
C2000 045	11 in Europe	6-16	Up to 12 mos	18-54	105	-	-	MPH users	Long term open label	2003
CONCAN1	?	6-12	8 wks	18-54	~75	-	~75 MPH	ADHD	Randomized, open label	2005?
CONCAN2	?	6-13	6 mos.	18-54	109	-	-	CONCAN1 subjects	Open label extension	2004

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table B. ADHD safety and efficacy trials with Metadate CD included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
CD 00600	10	6-12	7 (3-way Xover)	20-60	173	181	180 Concerta	Mph users	Laboratory classroom study	2002
MAI 100102	1	7-12	7 (2 period Xover)	20 or 40	25	25	25 Mph	Mph users	Laboratory classroom study	1998
MAI 100104	32	School age, >6	21	20-60	158	163	-	Mph users	Single blind placebo run-in and double blind placebo exposure was combined in sponsor's analysis	1999
MAI 100302	44 (AUS CAN, & US)	6-12	21	20-60	139	46	133 Mph	Mph users		2003
CD00500	51	6-17	-	20-60	308	-	-	Mph users (59% of sample) or previously untreated ADHD	Open label	2001
MAI 100103	1	6-11	49	10-30	8	-	-	Previously untreated ADHD	Open label	1999

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table C. ADHD safety and efficacy trials with methylphenidate transdermal system (MTS) included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
N17-002	1	6-9	7 (3-way Xover)	10 cm^2	10	10	10 Mph	ADHD	Laboratory classroom	1999
N17-003	1	6-10	2 Xover	2.5-20 cm^2	13	13	-	ADHD	Laboratory classroom	1999
N17-009	3	6-12	1	6.25-25 cm^2	36	36	-	ADHD	Summer camp	2000
N17-015	1	6-12	1 (multiple Xover)	6.25-25 cm^2	27	27	-	No history of adverse responses to mph	Summer camp	2001
SPD485201	6	6-12	35d Open label, then 7d 2-way Xover	12.5-37.5 cm^2	80	79	-	ADHD and no comorbid disorders except ODD	Laboratory classroom	2005
N17-010	20	6-12	21	6.25-25 cm^2	101	109	-	ADHD		2001
N17-018	21	6-12	28	6.25-50 cm^2	106	105	-	ADHD with or without current drug treatment		2002
SPD485302	38	6-12	49	12.5-37.5 cm^2	98	85	91 Concerta	Stimulant nonresponders excluded		2005
N17-011	Multi	6-12	90	6.25-25 cm^2	118	-	-	ADHD	Open label only	2000
N17-013	Multi	6-12	Until NDA approved	6.25-37.5 cm^2	20 ongoing	-	-	Responders to mph patch in previous protocols	Continued open label treatment for patients who had positive response	Ongoing, interim data June 2005

N17-021	Multi	6-12	32 mos.	6.25-50 cm^2	191	-	-	Subjects from N17-018	Continued open label treatment	2004
SPD485-303	Multi	6-12	1 yr	12.5-37.5 cm^2	288 (ongoing)	-	-	Subjects from SPD485-102 and SPD485-302	Ongoing open label study	2006 projected. Interim data from June 2005

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table D. ADHD safety and efficacy studies with modafinil included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration	Dose (mg/day)	N		Population	Comments	Study completion date
					Drug	Placebo			
205	6 (phase A) 7 (phase B)	Adults 18-57	6 wks	100, 200, 400 (fixed)	109 (74 phase A, 35 phase B)	75 (38 Phase A, 37 Phase B)	ADHD without psychiatric comorbidity	Included 8 week open label extension	2001
207	3	6-13	1 wk 4 way Xover	0, 100, 200, 300/400	46	44	ADHD	Included 8 wk open label extension	2000
213	28	6-13	4 wks	300 or 400	197	51	ADHD, either stimulant -naïve or -tolerant	Included 8 wk open label extension	2002
309	18	6-17	9 wk	170-425	131	67	ADHD without psychiatric comorbidity	Parallel group, 2:1 randomization	2004
310	17	6-17	9 wk	340 or 425 according to wt	125	64	ADHD without psychiatric comorbidity	At week 7 modafinil patients were randomized to either modafinil or pbo for final 2 wks	2004
311	24	6-17	9 wk	170-425	164	84	ADHD without psychiatric comorbidity		2004
113	1	6-13	2 wks + 2 single doses	340,425	24	-	ADHD not responding well to medication	Bioavailability assessment was main objective	2003
206	3	6-12	4 wks	100-400	20	-	ADHD without	Included optional 8 wk	2000

							psychiatric comorbidity	extension	
312	56	6-17	1 yr	170-425	536	-	Tolerated modafinil in a previous ADHD trial		ongoing

Appendix Table E. ADHD Safety and Efficacy Studies with Adderall XR included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Pbo.	Active control			
201	4	6-12	1 wk X over (5 way)	Adderall 10, Adderall XR 10,20,30	50	49	-	Current users of Adderall or MPH	Laboratory school setting	1999
301	47	6-12	3 wks	10, 20, 30 (fixed)	10 mg 129; 20 mg 121; 30 mg 124	210	-	ADHD, known to be tolerant of stimulants		2000
302	49	6-12	24 mos.	10-30	568	-	-	Participants in previous trials	Open label, long term safety	2002
303	18	≥18	4 wks	20, 40, 60 (fixed)	191	64	-	Adults with ADHD and no history of intolerance to stimulants		2002
304	18	≥18	24 mos.	20, 40, or 60	223	-	-	Adults who participated in study 303	Open label, long term safety	2005
305	365	6-12	15 wks	10-40	2968	-	-	Responders to prior stimulant treatment	Open label safety and efficacy	2002
311	27	6-17	4 wks	10, 20, 30, 40 fixed dose	237	60	-	Oppositional defiant disorder (not ADHD)		2003
312	81 (U.S., Canada)	≥18	40 wks	10-60	725	-	-	Previously treated or naive		2005
314a	50	13-17	4 wks	10, 20, 30, 40 (fixed)	258	69	-	ADHD, no special requirements		2003
314b	32	13-17	6 mos.	10-60	138	-	-	Subjects in study 314a	Long term extension of 314a	2004

315	~50	13-17	24 mos.	10-60	255 planned	-	-	Subjects in study 314a	Long term extension of 314a, 314b	ongoing
316	1	19-25	3 wk Xover	20-50	19	15	8* Atomox etine	ADHD, not naïve to medication	Driving simulator study. Data from atomoxetine phase of study not provided.	2004
404	10	6-12	18 dys	10-30	107	211	108 atomox etine	ADHD, no history of failure on medication, no psychiatric comorbidity	Laboratory school setting; randomized, double blind, no placebo	2004

*data not provided

Appendix Table F. ADHD safety and efficacy studies with atomoxetine included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose *(mg/day)*	N			Population	Comments	Study completion date
					Drug	Place bo	Active control			
HFBD	9	7-12	9	2 mg/kg/d	65	62	20 Mph	ADHD, with or without prior stimulant tx		2000
HFBK	10	7-12	9	2 mg/kg/d	64	62	18 Mph	ADHD, with or without prior stimulant tx		1999
LYAA	17	≥18	10	60,90,120	141	139	-	Adult ADHD		2001
LYAC	13	8-17	8	1.2 or 1.8 mg/kg/d	213	84	-	ADHD		2000
LYAO	14	≥18	10	60,90,120	129	127	-	Adult ADHD		2001
LYAS	15	7-17.5	18	0.5,1,1.5 mg/kg/d	76	72	-	ADHD plus tic disorder		2003
LYAT	9	6-16	6	0.75-1.5 mg/kg/d	85	86	-	ADHD		2001

LYAW	11	8-12	7	0.8-1.8 mg/kg/d	101	52	-	ADHD		2002
LYAX	16	12-17	9	0.8-1.8 mg/kg/d	72	70	-	ADHD plus major depression	Included open label extension	2004
LYBG	12	6-12	8	0.8-1.8 mg/kg/d	133	64	-	ADHD		2002
LYBI	21	6-16	6	0.8-1.8 mg/kg/d	222	74	220 Concerta	ADHD	Included double blind continuation phase	2003
LYBP	14	8-17	12	0.8-1.8 mg/kg/d	87	89	-	ADHD plus anxiety disorder	Atomoxetine dosed either am or pm	2004
LYCC	14	6-12	6	0.8-1.4 mg/kg/d	195	93	-	ADHD per DSM-IV-TR		
HFBC	1	7-13	100 dys	10-90	29	-	-	ADHD	Open label	1998
HFBE	23	7-16	48 wks	5-90	184 OL 42 DB	23	44 Mph OL	ADHD	Relapse prevention design with open label tx followed by randomized withdrawal of active drug	2000
HFBF	24	≥6	96 wks	5-90	325	-	-	ADHD subjects from a previous atomoxetine trial	Open label	2001
LYAB	53	6-18	2 yrs	≤1.8 mg/kg/d	914	-	-	ADHD	Long term open label	2001
LYAF	33 International	6-15	78 wks	≤1.8 mg/kg/d	292	124	-	ADHD	Relapse prevention study. A total of 604 patients received open label atomoxetine during run-in	ongoing
LYAI	31	6-17	-	-	296	-	-	Subjects in previous atomoxetine trials	Long term open label	ongoing
LYAQ	21	6-17	6 wks	≤1.8 mg/kg/d	44 atomoxetine 120 Fluoxetine 44 placebo 114 atomoxetine+fluoxetine			ADHD plus anxiety or depressive disorder	Trial of combination therapy with fluoxetine, included open label and double blind	2001
LYAR	30	≥18	Open ended	Up to 120	383	-	-	Adult ADHD	Long term open label	ongoing
LYAU	1	6-13	6 wks, 2 way Xover	0.5 – 1.8 mg/kg/d	8	-	8 Mph	ADHD, right handed	Functional MRI study	2003

LYAV	2	6-14	6 wks, 2 wasy Xover	1.6 mg/kg/d	80	-	81 Mph	ADHD	Sleep study comparing effects of atomoxetine and methylphenidate	2002
LYBB	40	6-18	10 wks	1.8 mg/kg/d	357	-	-	ADHD	Open label	2001
LYBD	19 (Japan)	6-18	8 wks	1.8 mg/kg/d	37	-	-	ADHD		2003
LYBM	14	18-50	6 wks	80	218	-	-	Adult ADHD	Acute phase compared 40 mg BID to 80 mg QD. Included continuation phase with 160 mg/d dosing.	2003
LYBR	13 International	6-16	8 wks	0.8-1.8 mg/kg/d	164	-	166 Mph	ADHD	Randomized, double blind, without placebo	2004
LYBU	5	6-12	4 wks + 6 wks	1.4 mg/kg/d	Atomoxetine alone 12 Atomoxetine + Concerta 9			ADHD, with poor response to stimulants	Randomized, double blind comparison of atomoxetine plus placebo to atomoxetine plus Concerta. Included 6 wk extension phase	2005
LYBV	23	18-50	6 mos.	40-100	271	139	-	Adult ADHD with stable employment	Assessment of work productivity was primary endpoint. Included 4 mo. Extension	2005
LYCI	6	6-17	8 wk	1.2 mg/kg/d	62	-	-	ADHD with poor response to stimulant	Open label	2005

Appendix Table G. ADHD safety and efficacy trials with Ritalin LA included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
02*	2	6-12	1 day (5-way Xover)	17.5-25	34	34	-	Mph users	Laboratory classroom	1999
07	15 (U.S. and Canada)	6-12	14-28 single blind run-in, 14 DB	10-40	161 single blind, 66 double blind	71	-	Mph users or naïve		2000

US02		12-17	**	**	99	102	-	**	All females	**
US05	1	6-12	Single dose, 4-way Xover	20	36	36	36 Concerta	Mph users	Laboratory classroom	2002
US07	3	6-12	Single dose, 5-way Xover	20 and 40	53	53	53 Concerta (two doses0	Mph users	Laboratory classroom	2003
07 E1	**	<17	**	**	125	-	-	**	Open label	**

*There were no events in Protocol 02. Data were not available by specific treatment, and so were not included in the pooled analysis.
**information not available

Appendix Tables H. ADHD safety and efficacy trials with d-methylphenidate included in the analysis

Focalin XR

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
2301	12	6-17	49	5-30	53	47	-	Mph users or naïve		2004
2302	18	18-60	35	20,30,40 (fixed dose)	165	53	-	Adults with ADHD		2003
US08	3	6-12	6 (2-way Xover)	20	54	54	-	Mph users	Laboratory classroom setting	2004
2302E1	18	18-60	6 mos.	10-40	170	-	-	Adults with ADHD	Open label follow-up to study 2302	2004
US09	4	6-12	7 (2 way Xover)	20	68	68	-	Stable users of Mph	Laboratory classroom setting	2004
US12	*	6-12	*	20,30	84	83	83 Concerta	*		*
US13	*	6-12	*	20,30	82	81	81 Concerta	*	5-way Xover	*

*information not available

Focalin

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
97-M-02	12	6-17	28	5-20 d-mph; 10-40 mph	44	42	46 (mph)	ADHD		1999
97-M-03	7	6-17	42d open label; 14d DB; 44 wk open label	5-20	35	40	-	ADHD	Three phases: (1) 6-wk open label dose optimization; (2) 2-wk randomized withdrawal; (3) open label treatment	2000
97-M-04	8	6-17	1 yr	5-20	187	-	-	ADHD	Long term open label	2000
97-M-05	27 (U.S. and Canada)	6-17	6 mo	5-20	361	-	-	ADHD	Long term open label	2000
00-M-06	2	6-18	8 wk	2.5-30	22	-	-	ADHD	Open label pilot	2002
00-M-07	*?*	*Adult*	*12 wk*	*5-50*	*15*	-	-	*Adults with ADHD*	*Open label pilot, data not provided*	*?*

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/s/

Andy Mosholder
3/3/2006 02:11:38 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/3/2006 04:37:11 PM
DRUG SAFETY OFFICE REVIEWER

From: Player, Susan
Sent: Tuesday, February 14, 2006 12:56 PM
To: 'Rotman, Harris'
Subject: **URGENT** safety data request

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Good afternoon, Harris. The Drug Safety reviewers have the following request for information:

Thank you for your submission emailed Feb. 8. However, this new submission still does not resolve the issue of how many unique patients were exposed to MTS or placebo in each trial. For example, Study N17-009 was a crossover study with 36 patients, yet Table 7 in the amended report dated 2-7-06 shows 72 placebo exposed patients and 108 MTS exposed patients. Similarly, Study N17-010 in Table 7 shows 265 MTS patients rather than the expected 101, and study N17-015 shows 101 instead of the expected 27 MTS patients. Could you please assist us by clarifying the numbers of patients exposed to MTS or placebo in each trial? Thank you.

If you have any questions, please let me know. We need the data for the Pediatric Advisory Committee meeting in March.

Susan Player

Susan E. Player, MS, APRN, BC
Regulatory Project Manager

CDER/ODEI/DPP
White Oak Building 22
Room 4392, HFD-130
Phone 301-796-107

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/s/

Susan Player
2/15/2006 10:29:21 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-514

Noven Pharmaceuticals, Inc.
Attention: Jeff Dow, Esq.
Director, Regulatory Affairs
11960 SW 144th St.
Miami, Fl 33186

Dear Mr. Dow:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for methylphenidate transdermal system.

For the period January 1, 2000 through June 30, 2005, please provide an estimate of worldwide utilization of methylphenidate transdermal system with a breakdown by year and by country. Some of this information may be referenced at the upcoming Advisory Committee meeting on drug treatment of ADHD.

This request is being sent to all products approved for the treatment of ADHD and for products with pending NDA applications under review for the treatment of ADHD.

We ask that you respond to this request by March 1, 2006.

If you have any questions, call Richardae Araojo, Pharm.D., Regulatory Health Project Manager, at (301) 796-1152.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
12/23/2005 02:05:02 PM

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: December 23, 2005

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Approvable Action for Methlyphenidate Transdermal System (MTS) for ADHD

TO: File NDA 21-514
[Note: This overview should be filed with the 6-28-05 re-submission of this NDA.]

1.0 BACKGROUND

MTS is a patch formulation of methylphenidate, a stimulant that is available in a variety of immediate and controlled release forms for the treatment of ADHD. This NDA provides data in support of a claim for MTS in the short-term treatment of ADHD in children aged 6 to 12. The recommended doses are 10, —, 20, and — mg/day (this corresponds to patch sizes of 12.5, 18.75, 25, and 37.5 cm2). The patch is administered in the morning and is to be left on for 9 hours. The intended advantage of the patch is in patients who have difficulty with pill-taking. The patch would also have the advantage of not interacting with food consumption and of flexibility in early removal if desired.

This NDA was first submitted to the FDA on 6-27-02. FDA issued a non-approvable letter on 4-25-03. This letter acknowledged positive efficacy findings, but noted concerns about unacceptable levels of certain adverse events, including insomnia, anorexia, and weight loss. The letter also raised concerns about the potential for diversion and abuse, and of skin sensitization. FDA suggested shorter wear times and additional studies to demonstrate efficacy and acceptable safety at the shorter wear times, including a skin sensitization study. FDA also requested that the sponsor propose a comprehensive risk management plan. The sponsor conducted the additional studies requested and resubmitted the NDA on 6-28-05. The resubmission included responses to CMC issues raised in the 4-25-03 letter, additional pharmacokinetic information, and revised product labeling.

The review of the additional efficacy and safety data was done by Robert Levin, M.D., from the clinical group. Fanhui Kong, Ph.D., from the biometrics group, also reviewed the efficacy data. A review of new CMC information was done by Sherita McLamore, Ph.D. from chemistry. A

review of new pk information was done by Ron Kavanagh, Ph.D. from OCPB. Linda Fossom, Ph.D. from the pharmacology group reviewed data provided on residual monomers. Geoffrey Zeldes, M.D., from CSS, reviewed the abuse liability aspects of the resubmission.

This application was discussed at a 12-2-05 meeting of the PDAC.

2.0 CHEMISTRY

CMC staff determined that the response is acceptable and this product can be approved from a CMC standpoint. The proposed name Daytrana was deemed to be acceptable by DMETS.

3.0 PHARMACOLOGY

Pharmacology staff reviewed the revised package insert and made recommendations for changes that have been included in FDA's draft labeling. As part of the review of the sponsor's response to the nonapproval letter, the CMC group asked the sponsor to provide information about the controls for residual monomers from the acrylic adhesive in the patch. There were 2 monomers of interest, and Dr. Fossom from the pharmacology staff has concluded that the levels of these monomers are low enough so as not to be a source of concern.

4.0 BIOPHARMACEUTICS

OCPB staff also reviewed the revised package insert and made recommendations for changes that have been included in FDA's draft labeling. One noteworthy pk finding observed by both the sponsor and the OCPB reviewer is that, with repeat dosing, the 9-hour plasma d-methylphenidate concentrations seen with flexible dosing with MTS in children aged 6 to 12 are almost double those seen with Concerta when flexibly dosed. This relatively greater exposure for MTS was not seen in single-dose studies, and is not explained by increased accumulation. The clinical significance is unknown, as the safety profile for the 2 products was roughly comparable (see 5.2, safety data).

5.0 CLINICAL DATA

5.1 Efficacy Data

The original NDA for MTS included several efficacy trials, and one in particular (i.e., study 18) was the basis for the view expressed in the division's NA letter that the sponsor had demonstrated efficacy of MTS in ADHD. This was a 6-week, parallel group, flexible-dose trial involving patches ranging in size from 12.5 cm2 to 50 cm2, and the wear time was 12 hours. Although this study was positive, as noted, there was concern that the level of adverse events

was unacceptable. Thus, the sponsor was asked to conduct additional studies utilizing a shorter wear time. In response, the sponsor conducted studies SPD485-201 and SPD485-302.

Study 201 was a laboratory classroom study in children aged 6-12 with ADHD. The primary goal was to assess the behavioral efficacy of MTS on the SKAMP deportment scale at multiple timepoints throughout the day. This was a double-blind crossover trial involving n=79 randomized ITT patients. There was a 5-week dose optimization phase before randomization to find the optimal patch strength for each patient (one of the 4 available strengths—wear time was 9 hours) and that strength was used for that patient in the randomized phase. The randomized phase consisted of 1 week of treatment on each of MTS and placebo, with laboratory classroom testing on the last day of each week. On that test day, assessments were done at 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours. The results significantly favored MTS over placebo, beginning at 2 hours, and continuing at each assessment through the 12 hour timepoint.

Study 302 was a 7-week, double-blind, parallel group outpatient study of children aged 6-12 with ADHD. It was flexible dose, comparing MTS (12.5 to 37.5 cm2—wear time was 9 hours), Concerta (18 to 54 mg), and placebo. The total ITT sample was n=270 (roughly 90 per group). MTS was statistically significantly favored over placebo on mean change from baseline in the ADHD-RS-IV. Although this study was not designed specifically to evaluate dose response, in general there did not appear to be any additional effectiveness accomplished by increasing the patch size to 37.5 cm^2 from 25 cm^2 (see slide 41 of sponsor's presentation for PDAC meeting).

Both Drs. Levin and Kong considered these trials positive support for the sponsor's claim of efficacy, and I agree.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

This NDA resubmission included safety data from a total of n=765 unique subjects exposed to 1 or more doses of MTS utilizing wear times of 9 hours across a total of 8 trials involving MTS (this total does not include subjects from the original NDA utilizing the 12 hour wear times). Among these 765 subjects were 571 pediatric patients with ADHD.

5.2.2 Adverse Event Profile for MTS in ADHD

There were no deaths or SAEs among the MTS-exposed patients in these trials. The most common drug-related AEs, and also those leading to discontinuation, were the familiar AEs for methylphenidate products, in particular, anorexia and insomnia. There were, of course, application site reactions that were limited to the MTS formulation. There were also the expected weight changes.

5.2.3 Safety issues that clinical reviewer was particularly concerned about for MTS in ADHD

Dr. Levin, in his original review, recommended against the approval of MTS based on his concern that the safety profile is unacceptable. He stated the following:

> "Specifically, treatment with MTS was associated with a high incidence of insomnia, anorexia or decreased appetite, headache, and gastrointestinal symptoms including vomiting, nausea, and upper abdominal pain. These adverse events were significantly more common in the MTS group than in the active comparator group (Concerta) and the placebo group. MTS treatment was also associated with decreased weight in these short-term studies.
>
> In addition, treatment with MTS was associated with a relatively high risk of developing tic disorder, compared to the active comparator group (Concerta) and the placebo group. Also, treatment with MTS was associated with a significant degree of dermal reactions and symptoms at the patch application site."

[Note: Between the time of entering his review into DFS on 11-7-05 and the 12-2-05 PDAC meeting, Dr. Levin reconsidered his position and recommended that the application could be considered approvable (he notified me of his change in view in a 11-19-05 e-mail). After reconsidering the safety data, he concluded, in his statements at the PDAC meeting (see slides and meeting transcripts), that the overall risk profile for MTS, when used with a 9-hour wear time, was not substantially different than that for other modified release methylphenidate formulations.]

Comment: I think probably the best source of comparative spontaneously reported adverse event information is Study 302, and what follows is the risk data (% of patients experiencing the event in question) for the events of concern to Dr. Levin:

Adverse Event	MTS (%)	Concerta (%)	Placebo (%)
Insomnia	13%	8%	5%
Anorexia	5%	3%	1%
Decreased appetite	26%	19%	5%
Headache	15%	20%	12%
Vomiting	10%	10%	5%
Nausea	12%	8%	2%
Upper abdominal pain	7%	10%	6%
Weight decreased	9%	8%	0%
Tics	7%	1%	0%

-For insomnia, anorexia, decreased appetite, nausea, and weight decreased, the risk for MTS is higher than for Concerta, however, the differences are quite modest, in my view.

-For headache and upper abdominal pain, the risk is actually higher for Concerta and not much different than placebo.
-For vomiting, the risks are the same for MTS and Concerta.
-Thus, it is really only for tics where there appeared to be a meaningful difference: 7% for MTS vs 1% for Concerta. However, it is noteworthy that there was not a difference between Concerta and MTS for tics in earlier studies utilizing the longer wear times and higher doses, suggesting the differences seen in this single study may not be representative.

Since weight was also measured, there was objective data for comparison. At approximately 5 weeks, the mean decreases in weight for MTS and Concerta were -2.2 and -2.1 lbs, compared to a mean increase of 2.1 lbs for placebo.

Note: As part of its presentation for the PDAC meeting, the sponsor provided Forest plots for safety data from published studies of methylphenidate, focusing on the common adverse events of interest for this drug, i.e., tics, anorexia, decreased appetite, and insomnia, and were able to effectively make the case that the findings for the 2 MTS studies utilizing 9-hour wear times fell well-within the range of outcomes for these safety events across the published data for different formulations of methylphenidate.

Dermatological Findings

Erythema at the site of MTS application was observed in about 25-30% of patients, but in almost all cases was only mildly irritating. The greater concern is the potential for sensitization to methylphenidate.

A provocative skin sensitization study revealed a signal for MTS to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, MTS was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to MTS based on the results of the challenge and/or re-challenge phases of the study. Sensitization could not be excluded for an additional 11 subjects, and if these subjects are considered to have been sensitized, the rate of sensitization becomes 21.8% (29/133 subjects).

Using MTS as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. [Note: At the 12-2-05 PDAC meeting, the sponsor reported that there had been a single case of sensitization observed, i.e., patient 31-002 in Study SPD485-303. However, after further review of that case, they subsequently have concluded that was not a documented case of sensititization, and our dermatology consultants have agreed with that assessment. The problem is that, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when MTS is used as directed.

Our dermatology consultants have advised that patients sensitized to methylphenidate from use of MTS, as evidenced by development of an allergic contact dermatitis, may experience systemic contact dermatitis (systemic eczematous reaction) or other systemic reactions if methylphenidate or related drugs are taken via other routes, e.g. orally. Thus, they have advised that individuals who develop contact sensitization to MTS should avoid exposure to methylphenidate and related drugs in other dosage forms. As noted, erythema is commonly seen with use of MTS, and is not by itself an indication of sensitization. However, sensitization should be suspected if erythema is accompanied by edema, papules, vesicles, or other evidence of a more serious local reaction. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing (e.g., injection of methylphenidate into the skin or application of methylphenidate to the skin).

It will be important to try to better estimate what the true incidence of sensitization will be under the usual conditions of use, and we will request the sponsor to conduct a study post–approval to assess this risk. We have suggested to the sponsor a large cohort of patients who would be followed carefully to identify patients who might have developed sensitization (e.g.,erythema plus some other indication of a more serious skin reaction, such as edema, papules, or vesicles. These patients would need additional testing. In the meantime, it will also be important to further discuss how best to educate prescribers in identification of patients who might need more specific skin testing to assess for sensitization.

5.2.4 Potential for Diversion and Abuse

CSS concluded that this formulation poses no greater risk of diversion and abuse than is inherent in other methylphenidate formulations. They did have advice for the package insert and patient labeling, and for the risk management program, and these comments will be conveyed to the sponsor. ODS also has some advice regarding the risk management program that will be conveyed to the sponsor.

5.2.5 Conclusions Regarding Safety of MTS in the Treatment of ADHD

In my view, all of the safety issues for this drug can be adequately addressed in labeling. As noted, however, additional information is needed from the sponsor, as well as a commitment to conduct a postmarketing study to better understand the risk of sensitization.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling. In particular, we have added a Warning statement noting the risk of sensitization and the need to avoid further methylphenidate in any form if sensitization is documented to occur.

6.0 WORLD LITERATURE

There was no literature for MTS to review.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, MTS is not approved anywhere at this time for the treatment of ADHD.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was discussed at a 12-2-05 meeting of the PDAC. The committee was asked the usual 2 questions about efficacy and safety. The vote was unanimous (12-0) on both general questions. However, the issue the committee was most focused on and concerned about was the possibility of developing sensitization to methylphenidate as a result of exposure to MTS. Given the importance of methylphenidate products in the treatment of ADHD, they expressed great concern that a substantial (but at this time, unknown) fraction of patients with ADHD who are exposed to MTS might develop sensitization to methylphenidate and never again be able to take methylphenidate in any form. Thus, there was unanimous agreement that this concern should be prominently placed in MTS labeling (i.e., Warnings). There was considerable discussion about the type of advice to be given to clinicians. In the end, a single committee member voted in favor of strong language advising clinicians to use MTS only in patients who were not able to take oral formulations (11-1 against on this vote). On the other hand, the vote was unanimous (12-0) that language advising clinicians to generally consider restricting the use of MTS to this population would be appropriate. The population in question would be those, among others, who cannot swallow tablets, who have significant compliance problems with oral formulations, or who have a medical condition that limits the administration of oral formulations. We have included a Warning and other language in Indications and elsewhere in labeling to convey this recommendation.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 sites (2 from study 302 and 1 from study 201). These sites were Drs. Burnside, Turnbow, and Americo. Drs. Burnside and Turnbow were classified NAI and Dr. Americo was classified VAI. Overall, the data from all sites were deemed to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included a modified version of labeling with the approvable letter.

10.2 Foreign Labeling

MTS is not approved anywhere at this time for the treatment of ADHD.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for additional information and for a commitment to conduct a phase 4 study to further evaluate the potential for sensitization.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Noven has submitted sufficient data to support the conclusion that MTS is effective and acceptably safe in the treatment of ADHD. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 21-514 (MTS/ADHD)
HFD-130
HFD-130/TLaughren/PAndreason/RLevin/RTaylor

DOC: Methylphenidate TS Laughren AE Memo.doc

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/s/

Thomas Laughren
12/23/2005 08:51:06 AM
MEDICAL OFFICER

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: December 19, 2005

FROM: Paul J. Andreason, M.D.
Acting Deputy Director,
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Approvable Action for Methylphenidate Transdermal System for the Treatment of Attention Deficit Hyperactivity Disorder in Children Aged 6-12 Years.

TO: File NDA 21-514
[Note: This memo should be filed with the original June 28, 2005 submission of this NDA.]

1.0 BACKGROUND

This submission represents a complete response to the Division's Not Approved Action (NA) letter dated April 25, 2003. The Division convened a meeting of the Psychiatric Drug Advisory Committee on December 2, 2005 to present data from the submission and discuss the safety and efficacy of the Methylphenidate Transdermal System (MTS) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children ages 6-12 years.

Robert Levin, MD was the primary Medical Officer who reviewed the submission and also presented his findings at the PDAC meeting. Notably, Dr. Levin's original review that was provided as part of the background package recommended a Not Approved Action; however, the PDAC was convened as the Division as a whole had not reached a final conclusion on the most appropriate action to take. During the time that past between Dr. Levin filing his original review and the time of the PDAC he reconsidered his recommendation and suggested that MTS could be approvable. He felt that after having more time to consider the adverse event (AE) profile and the relative rates of AE incidence, that MTS was not unduly clinically different from the other available oral long-acting stimulant formulations already available for ADHD.

2.0 CHEMISTRY

The primary Chemistry Team (CMC) reviewer was Sherita McLamore, Ph.D. CMC found the sponsor's reply to the comments in the Divisions April 25, 2003 action letter adequate and recommended approval from a CMC point of view with the total expiry granted of 26 months. CMC went on to say that a 24 month expiry is granted for drug product stored in the enclosed tray. Once the tray has been opened, the drug product has a 2 month expiry.

3.0 PHARMACOLOGY

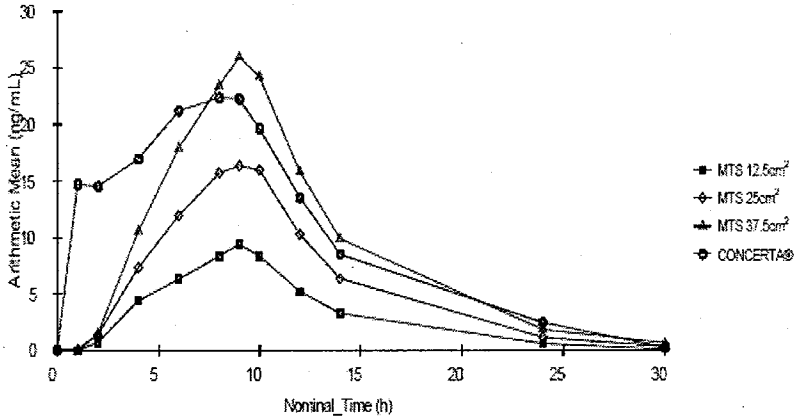
The Pharmacology Toxicology Team comments are pending at the writing of this memo.

4.0 BIOPHARMACEUTICS

Ron Kavanagh, PhD was the primary OCPB reviewer for this submission. OCPB found this application acceptable. However, Dr. Kavanagh stated that the biopharmaceutics and clinical pharmacology of methylphenidate transdermal system raised concern whether this formulation should be reserved for patients for whom therapy with oral methylphenidate is not an appropriate option regardless of whether it induces contact sensitization or not. OCPB in the end felt that this was a clinical decision.

The following is a summary of my own conclusions on human pharmacokinetic issues.

Generally speaking, single dose PK studies of MTS shows that the 37.5- cm^2 has a similar Cmax and AUC as the Concerta 54-mg capsule. The 25- cm^2 has a similar Cmax and AUC as the 36-mg capsule. Therefore, single dose exposures of Concerta and MTS are generally comparable with respect to plasma concentrations and AUC.



Treatment	C_{max} (ng/mL)	T_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2,Kel}$ (h)
MTS 12.5cm²	9.78	8.99	1.94	86.3	90.0	3.80
	(49.8)	(5.95-10.2)	(0-4.0)	(54.3)	(52.3)	(19.0)
MTS 25cm²	17.8	9.93	1.98	164	170	3.81
	(50.2)	(7.97-12.0)	(0-4.0)	(55.5)	(53.6)	(15.4)
MTS 37.5cm²	27.2	9.00	1.00	251	255	3.87
	(44.7)	(5.95-12.0)	(0-2.03)	(44.8)	(44.5)	(12.2)
54mg CONCERTA®	24.2	7.99	0.00	281	282	3.22
	(43.4)	(2.12-10.0)	(0-0.00)	(60.7)	(44.3)	(18.6)

In study 302 the sponsor performed sparse sampling at 9-hours after the patch was applied. It was noted that the mean plasma concentrations for patients on the MTS was roughly twice that of patients taking the oral Concerta form. There are several factors that could explain the difference.

Study 302 was a flexible dose clinical trial that was designed to study efficacy under what approximated a realistic clinical setting. Doses were not matched in study 302 as they were in the PK study. Patients were titrated individually to tolerance and clinical effect. The timing of sampling was tailored to detect an estimated peak plasma concentration for MTS

not Concerta; however, this PK sampling bias does not seem to explain the entirety of a two-fold difference.

The sampling was done blindly which meant that Concerta patients had their sample drawn 7-hours after dosing. At this point the sponsor noted at the PDAC that the peak plasma concentration for Concerta did not match the estimated peak time for Concerta; however if one examines the above time-concentration curves for Concerta and MTS, one can see that though peak times do not completely coincide, this does not explain a two-fold difference under conditions that approximate a setting of usual use.

It seems that under conditions of usual use patients in Study 302 were exposed to roughly two-fold higher *d*-methylphenidate levels in the MTS group. One could hypothesize that patients in this setting are titrated to tolerance as opposed to response and might be able to tolerate higher plasma concentrations of methylphenidate when using the MTS over Concerta. One might also hypothesize that if using the MTS patients must be exposed to higher plasma concentrations of *d*-methylphenidate to get a comparable effect due to the presence of higher concentrations of circulating *l*-methylphenidate with the patch. Both or neither of these hypotheses might contribute to the finding. Sampling timing though contributory does not appear to be a complete explanation for the Concerta and MTS group mean concentration differences in *d*-methylphenidate. A fixed-dose comparison trial of MTS and Concerta could help answer these questions; however, I do not believe that this kind of study is necessary prior to approval of MTS.

5.0 CLINICAL DATA

In the April 25, 2003 letter, the Division noted four clinical points as deficiencies that lead to the NA. They are enumerated below with summary of the sponsor's response.

1. *Though you have produced one positive study to support the efficacy of [redacted], this efficacy was achieved at the expense of excess drug exposure and an unacceptable incidence of significant adverse events, specifically insomnia, anorexia, and significant weight loss in the short-term. These adverse events would be expected to result in possible growth retardation or other serious adverse consequences with more chronic treatment. Importantly, other products approved for once a day dosing in this population are not associated with these risks.*
2. *The data suggest that patients who suffered from insomnia might benefit from decreasing the wear-time of the patch. Given that large numbers of both stimulant naïve and stimulant experienced patients suffered insomnia, anorexia, and weight loss, it would seem possible that generally decreasing the wear-time might decrease the incidence of these adverse events to acceptable levels. However, this would need to be demonstrated prospectively in another trial that documented that decreased wear-time was both safe and effective.*

The sponsor submitted data from two new clinical studies of MTS in children (ages 6 to 12) with ADHD. Study 201 was a phase 2, multi-center, randomized, double-blind, placebo-controlled dose optimization and analog classroom, crossover study. The main objectives were to assess the time course of treatment effect, and the safety and tolerability of MTS treatment. The study began with a 5-week open-label dose optimization phase in which all subjects were treated with MTS. Individual subjects' doses were titrated weekly, depending on the subject's clinical response and tolerability. Patch sizes used included 12.5-cm^2, 18.75-cm^2, 25-cm^2, and 37.5-cm^2. At the end of 5 weeks, there was a 2-week

double-blind, placebo-controlled crossover phase. In the controlled crossover phase, each subject had one week of MTS treatment and one week of placebo treatment, in one of two randomized sequences.

The primary efficacy endpoint was the change from baseline in the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) deportment scale. The SKAMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS. MTS was statistically superior to placebo at all time points.

Analysis of Mean SKAMP Deportment Score during Patch Application (Hours 2.0 – 9.0): ITT Population			
	MTS (N=79)	Placebo (N=79)	p-value
Mean (SD)	3.2 (3.64)	8.0 (6.33)	
LS Mean (SE)	3.2 (0.58)	8.0 (0.58)	<0.0001a
Difference and 95% CI of LS Means (MTS-Placebo)	-4.8 (-5.89, -3.63)	NA	

a: The p-value is obtained using the mixed effects model.

Study 302 was a phase 3, multi-center, outpatient, randomized, double-blind, placebo and active-controlled, parallel group dose optimization study, designed to evaluate the safety and efficacy of MTS compared to matching placebo transdermal system as well as Concerta and matching oral placebo in children (ages 6-12 years) with ADHD. The duration of the dose optimization phase was 5 weeks, and the duration of the maintenance phase was 2 weeks. MTS patch sizes used included 12.5-cm^2, 18.75-cm^2, 25-cm^2, and 37.5-cm^2. Concerta doses used were 54, 36, and 18-mg. There was a matching placebo Transdermal System patch and oral capsule.

The primary efficacy endpoint was the change from baseline in mean clinician-rated ADHD-Rating Scale-IV (ADHD-RS-IV) among treatment groups (MTS, placebo TS, Concerta, and matching placebo). MTS was superior to placebo and statistically indistinguishable from Concerta (MTS being slightly numerically better).

Analysis of the Change from Baseline of ADHD-RS-IV Total Score (ITT Population)			
	MTS (N=96)	Concerta (N=89)	Placebo (N=85)
LOCF analysis			
N	96	89	85
Mean (SD)	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
LS Mean (SE)	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
Difference and 95% CI of LS Means (Active-Placebo)	-13.89 (-18.06, -9.72)	-11.32 (-15.58, -7.06)	
p-value	<0.0001	<0.0001	

Study 302 was designed to compare relative safety of Concerta and MTS when prescribed in a clinical setting where flexible dosing occurs. The Adverse event profile of MTS with the decreased wear-time and patch size was comparable to the adverse event profile of Concerta except with respect to tics.

Most Commonly Reported Treatment-Emergent Adverse Events in Study 302 (≥5%; all Causalities in any Treatment Group) – Safety population						
System Organ Class* Adverse Event (Preferred Term)	Number (%) of subjects reporting AE					
	MTS (N=98)		CONCERTA□ (N=91)		Placebo (N=85)	
No. subjects with ≥1 AE	74	(75.5)	63	(69.2)	49	(57.6)
Gastrointestinal Disorders						
Abdominal pain upper	7	(7.1)	9	(9.9)	5	(5.9)
Nausea	12	(12.2)	7	(7.7)	2	(2.4)
Vomiting	10	(10.2)	9	(9.9)	4	(4.7)
General Disorders and Administrative Site Conditions						
Pyrexia	2	(2.0)	4	(4.4)	8	(9.4)
Infections and Infestations						
Nasopharyngitis	5	(5.1)	4	(4.4)	2	(2.4)
Investigations						
Weight decreased	9	(9.2)	7	(7.7)	0	
Metabolism and Nutrition Disorders						
Anorexia	5	(5.1)	3	(3.3)	1	(1.2)
Decreased appetite	25	(25.5)	17	(18.7)	4	(4.7)
Nervous System Disorders						
Headache	15	(15.3)	18	(19.8)	10	(11.8)
Psychiatric Disorders						
Affect lability	6	(6.1)	3	(3.3)	0	
Insomnia	13	(13.3)	7	(7.7)	4	(4.7)
Irritability	7	(7.1)	7	(7.7)	4	(4.7)
Tic	7	(7.1)	1	(1.1)	0	
Respiratory						
Cough	7	(7.1)	5	(5.5)	4	(4.7)
Nasal congestion	6	(6.1)	3	(3.3)	1	(1.2)
Pharyngolaryngeal pain	6	(6.1)	3	(3.3)	5	(5.9)

The effect of MTS on sleep was also measured systematically using the Children's Sleep Habits Questionnaire (CSHQ). Dr Levin stated that there appeared to be little difference in the effect of treatment on sleep between the three groups.

Weight-loss in the MTS treatment group was numerically greater than for Concerta or placebo; however, this is an adverse event that is easily monitored with treatment.

Therefore, the MTS system was proven effective at clinically appropriate time points and has a safety profile that is generally comparable to available long-acting oral stimulant formulations that are approved for the treatment of ADHD. The decreased wear-time as well as the decrease in patch-size was useful at reducing unacceptable adverse events associated with the MTS product. I believe that efficacy has now been proven with the MTS without an unreasonably increased risk of adverse events over oral formulations.

Generally speaking, a drawback to the MTS system over the available oral forms is that it requires more planning. It must be placed on the skin two hours prior to the start of the needed treatment-period and must be removed after nine hours of wear-time. If not removed, the child will receive inappropriately high doses of methylphenidate. These higher doses would likely produce unacceptable levels of insomnia and anorexia (as was demonstrated in the sponsor's previous development program with the 50-cm^2 patch with the 12-hour wear-time) but not commonly lead to serious adverse events. On the other hand, oral forms may be taken in closer temporal proximity to the needed treatment-period and forgotten.

I therefore believe that the sponsor has adequately addressed the deficiencies outlined in points 1 and 2 of the April 25, 2003 letter.

3. *We disagree with your assertion that ——— ® offers a decreased abuse liability. It appears that the methylphenidate in ——— ® may be extracted with common household solvents. This makes it available to be diverted and abused in a non-patch-bound form. Even if the methylphenidate contained in ——— ® could not be extracted, significant amounts of methylphenidate remain in the patch to be diverted and abused. Additional amounts of methylphenidate would be available for diversion if wear-time were decreased.*

The primary reviewing Medical Officer from the Controlled Substance Staff (CSS) was Geoffrey Zeldes, MD, PharmD. CSS did not feel that MTS presented an undue abuse potential after review of this submission. The sponsor showed that the matrix of the patch made extraction of methylphenidate quite difficult with household solvents. CSS concurred. They stated:

The abuse potential of the methylphenidate patch should be similar to other MPH formulations. The abuse potential of an individual patch, due to the relatively small of amount of drug in each patch, compared to reported amounts utilized by abusers, and the difficulty of extracting that drug into an abusable form, is not a large cause for concern. Diversion of the intact product would have a higher risk of abuse potential. While easy to share a patch, the long delay in reaching peak drug effect, would make this type of abuse less likely.

CSS made recommendations on the Risk Management Program as well as labeling that may be conveyed in an action letter. After reaching acceptable labeling and clarifying the remaining ambiguities in the Risk Management Program the sponsor will have adequately addressed this deficiency. This task is eminently possible for the sponsor to do and should not stand long in the way of eventual approval.

4. *Our Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6-week duration would be helpful in investigating this potential signal.*

The sponsor performed a skin exposure study as suggested. Brenda Carr, MD was the Division of Dermatology and Dental Products (DDDP) Consultant who reviewed this submission. It was ultimately found that there was a statistically significantly increased risk for skin sensitivity to MTS exists over placebo. This difference was great enough that the study, being under-powered, nonetheless demonstrated a signal. 194 subjects were enrolled in the study producing 145 evaluable subjects, though at least 200 evaluable subjects was considered the needed amount to rule out sensitization.

According to Dr Carr, MTS was more irritating than the placebo TS and the negative control (saline). The irritation analysis reflected scoring of dermal responses such as erythema, edema, papules, and vesicles. She stated:

A total of 36 of 133 subjects participated in the re-challenge phase, and 18 of these subjects (13.5%) were considered to have manifested sensitization (based on the challenge and/or re-challenge periods). For 3 additional subjects, irritation was the assessment following re-challenge; however, sensitization could not be excluded, and the applicant considered that a second re-challenge might have been helpful in elucidating the nature of the reaction. Eight subjects had readings at challenge that could have indicated sensitization but were not re-challenged. Thus, there were 11 subjects for whom re-challenge (8 subjects) or a second re-challenge (3 subjects) might have proven helpful. If it is considered that these 11 subjects were indeed sensitized, the rate of sensitization increases to 21.8%. Thus, under the conditions of study, the rate of sensitization ranged from 13.5% to 21.8%.

Thus, the MTS can lead to skin sensitization. The question remains of what the rate of sensitization might be in usual clinical use. In the clinical trials database, there was one reported case of skin sensitization that produced repeated skin sensitivity when given the oral formulation (i.e. a skin reaction in response to the taking the drug orally). Though one might be able to generate a point-prevalence for this type of reaction based on one case using the number of patients exposed for some period of time, this is probably not wise since this was a spontaneously reported adverse event and not a systematically collected piece of data.

I concur with the PDAC's recommendation that labeling reflect that prescribers should generally choose oral formulations of methylphenidate over the dermal application due to this risk of sensitization. I also believe that prescribers should be able to differentiate the appearance of contact dermatitis versus "mild skin irritation". I, however, feel strongly that labeling is not an appropriate place to educate prescribers on how to make that differentiation. In my opinion, if instruction is necessary, then this is the purview of post-graduate medical education and not federal drug regulation. Such instruction would conceivably take one hour or less and would be reasonable CME activity.

I believe that the sponsor should perform a study to more accurately estimate the risk of skin sensitivity to MTS under conditions of usual use. This could possibly be an open-label study of 1000 patients who used the MTS for an appropriate period; however, the sponsor should make a proposal.

The DDDP recommended that patients, once sensitized to a dermal application, should not take methylphenidate by any route of administration. This has implications in which route of administration a clinician might make as a first choice for methylphenidate treatment. Allergic reaction to the oral

formulation is not particularly high based on the clinical experience of the PDAC. They felt that the loss of methylphenidate as a treatment option because of skin sensitization would be significant. They therefore reasoned that use of the patch in lieu of an oral formulation should not be taken lightly because of this perceived difference in the dermal vs. oral formulation's tendency to produce immunologic sensitivity.

6.0 FOREIGN REGULATORY ACTIONS

To my knowledge, MTS is not approved anywhere in the world as yet.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

The PDAC voted that MTS was both acceptably safe (12 for; 0 against) and effective (12 for; 0 against) and should be made available as there is a significant minority of children who can not or will not tolerate oral formulations. The PDAC felt a recommendation (as opposed to a restriction [11 for recommendation but against restriction and 1 for restriction as well as recommendation]) should be made in labeling that MTS be reserved for children who either can not or will not tolerate oral formulations of methylphenidate. They felt that the evidence suggesting an increased risk of immunologic sensitization (allergy) to methylphenidate while using the patch over the lesser perceived level risk while using the oral formulation justified this recommendation. They felt that if children were sensitized to methylphenidate through indiscriminate use of the patch over the oral forms then, after developing sensitivity, it would make methylphenidate treatment unavailable to sensitized patients in perpetuity.

This labeling recommendation by the PDAC for using MTS as essentially a second-line agent might take the following form, "Physicians should generally consider oral methylphenidate and use the MTS for patients who do not tolerate oral formulations, this is due to the risk of skin sensitization associated with MTS use."

8.0 DSI INSPECTIONS

Roy Blay PhD was the DSI reviewer. He stated that the inspections of Drs. Turnbow and Burnside did not identify any significant observations. The inspection of Dr. Padilla identified two subjects (34001 and 34006) who met exclusionary criteria but remained in the study. Overall, DSI felt that the data appeared acceptable to support of the respective indication. The effect of dropping these two subjects could not reasonably affect the overall outcome of the study. The significance of the treatment effect is high and the treatment effect is consistently positive across all measured time points. I do not believe a re-analysis of the data dropping these two patients is justified.

9.0 CONCLUSIONS AND RECOMMENDATIONS

Based on the data presented in the resubmission as well as the deliberations of the PDAC, I believe that the MTS is approvable.

The following issues remain to be resolved in order to complete labeling:

- Contact Sensitivity Questions for the Sponsor
    - What was the estimated incidence of contact sensitivity in the clinical trials database if one counts patients who showed confirmed sensitivity by re-challenged with MTS or oral forms?
    - There is a case of a patient who developed MTS contact sensitivity that showed a sensitivity reaction after re-challenge with oral methylphenidate. What is the risk of

showing a sensitivity reaction to oral formulations after skin sensitization with MTS based on the clinical trials database? Choosing an appropriate denominator is crucial. What is this clinical risk of this type of problem with other drugs (e.g. clonidine)?
    - What is an appropriate education program and labeling to help prescribers distinguish minor patch irritation versus contact sensitivity?
    - What would be a reasonable trial design to measure the risk of developing contact sensitivity under conditions of usual use?
- Controlled Substance Staff -The proposed risk management program is broad and general in scope, designed to address issues of abuse and diversion, but not of drug safety, specifically the risks of misuse and potential overdose. Further clarification is needed regarding how the various components of the program will actually impact the risk of this product. For example, the role of the risk management coordinator, a liaison position to interface with the various stakeholders, must be clearly defined, including method and frequency of reporting data to the FDA. Specific educational programs must be developed for both the physician and the patient (and families) to address the safety concerns of using a stimulant chronically.
- Completion of draft labeling based on the above reviews and consults
- I do not believe that any new studies need to be performed by the sponsor prior to approval
- I recommend that the Division include a phase 4 commitment that the sponsor performs:
    - A study to evaluate the risk of skin sensitization under conditions of usual use of MTS in children who do not tolerate oral formulations.
    - Though a fixed dose trial of MTS versus placebo and Concerta in children and adolescents with ADHD would usually be desirable, I believe that it should be deferred in light of the risk of skin sensitivity

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/s/

Paul Andreason
12/19/2005 01:36:03 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Padilla Americo, M.D.
7500 SW 87th Avenue, Suite 202
Miami, Florida 33173

Dear Dr. Americo

Between September 28 and October 5, 2005], Ms. Jennifer Menendez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol SPD485-302, entitled "A Phase III, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo-Controlled, Dose Optimization Study, Designed to Evaluate the Safety and Efficacy of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in Pediatric Patients aged 6-12 with Attention-Deficit/Hyperactivity Disorder") of the investigational drug methylphenidate transdermal system (MTS), performed for Noven Pharmaceuticals Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We are aware that at the conclusion of the inspection, Ms. Menendez presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

    a. The protocol required a washout period at screening of up to 28 days depending upon the nature of the subject's medication requiring washout. Subject 34006 had a positive drug screen for ritalinic acid at his screening visit on October 4, 2004. You did not review this laboratory report until October 14, 2004, three days after the Baseline visit on October 11, 2004. The subject did not undergo a washout period. We note your acknowledgement that you should have reviewed the laboratory results prior to the subject's Baseline visit.

Padilla Americo, M.D.

b. The protocol required that subjects who did not demonstrate an acceptable condition (i.e., a 25% reduction in ADHD symptoms with minimal side effects) by Visit 7 be withdrawn from the study. At Baseline on September 27, 2004, subject 34001 scored a "43" on the ADHD Rating Scale. By Visit 7 on November 1, 2004, the subject scored a "48". As a result of this increased score, the subject should have been withdrawn from the study.

2. You did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].

   The Baseline blood pressure on September 20, 2004, for subject 34001 was 121/73. This blood pressure reading was revised to 118/78 without explanation. The original reading of 121/73 would have excluded the subject from the study since the value is outside of the 95th percentile for this subject.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Menendez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Ni Aye Khin

12/14/2005 10:34:03 AM

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

DATE: November 30, 2005

TO: Thomas Laughren, M.D., Director
Division of Psychiatric Products, HFD-120

THROUGH: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety (ODS), HFD-400

FROM: Methylphenidate Patch Risk Management Program Review Team

DRUG: Daytrana® (methylphenidate transdermal system)

NDA: 21-514

APPLICANT: Shire Development Inc., Pennsylvania
Noven Pharmaceuticals, Inc., Florida

SUBJECT: Risk Management Program, submitted June 28, 2005

PID: D050537

1 EXECUTIVE SUMMARY

This consult is in response to a request from the Division of Psychiatric Products (DPP) to comment on risk management program for the methylphenidate transdermal system (MTS), as treatment for Attention Deficit Hyperactivity Disorder (ADHD), submitted on June 28, 2005. The originally submitted [redacted] tradename has been replaced by the proposed tradename Daytrana®. If approved, Daytrana® will be the first methylphenidate-containing transdermal product available in the U.S. Currently, methylphenidate is available orally in several immediate release and long-acting formulations.

The primary "risk" issue appears to be the potential for abuse and diversion in children that may occur to a greater extent with this novel delivery system as opposed to the once-a-day oral methylphenidate formulations. Additional concerns include anorexia, insomnia, and weight loss. The sponsor has proposed to address the issue of abuse and diversion with a risk management program that focuses on surveillance and on the education of health care providers and consumers regarding safe storage, use, collection and disposal of the MTS. This document

conveys comments from the divisions in the Office of Drug Safety on the surveillance and education plan currently proposed by the Sponsors as well as additional recommendations to address the abuse/diversion potential (see Section 6: Recommendations).

2 INTRODUCTION/BACKGROUND

Methylphenidate Transdermal System (MTS) is once-a-day transdermal system (patch) that delivers a continuous dose of methylphenidate. The four proposed dosage strengths (10, — 20, and — mg) would be delivered over a 9-hour period. The methylphenidate content per patch is approximately three times the amount that will be delivered during the dosing period, meaning that there is a considerable amount of methylphenidate remaining in the patch after the 9-hour wear time.

The original NDA (21-514) was submitted on June 27, 2002. It received a nonapprovable action from the Agency on April 25, 2003, in part, because of clinical deficiencies. Some of these deficiencies were unacceptable incidences of insomnia, anorexia and significant weight loss, which may lead to growth retardation.

Potential abuse and diversion were also of concern because methylphenidate in MTS can easily be extracted from the patch with common household solvents. This makes it available to be diverted and abused in a non-patch-bound form. Also, significant amounts of methylphenidate remain in the patch after the 9-hour dosing period to potentially be diverted and abused. If the patch's wear-time was decreased, additional amounts of methylphenidate would be available for diversion. (i.e., The patient removed the patch before the full day's dosage was released.)

For the above reasons, DPP felt the potential benefits of MTS relative to other once-a-day oral products available for this population did not outweigh the risks associated with MTS treatment. In the nonapprovable letter, the Sponsor was requested to address the issue of abuse and diversion with a risk management program that focuses on the education, safe storage, use, collection and disposal of the MTS.

3 SAFETY CONCERNS

3.1 SYNOPSIS OF DPP SAFETY CONCERNS

- Treatment with MTS was associated with a high incidence of insomnia, anorexia or decreased appetite, headache, and gastrointestinal symptoms including vomiting, nausea, and upper abdominal pain. These adverse events were significantly more common in the MTS group than in the active comparator group, an oral once-a-day formulation (Concerta), and the placebo group. MTS treatment was also associated with decreased weight in these short-term studies.

- Treatment with MTS was associated with a relatively high risk of developing a tic disorder, compared to the active comparator group (Concerta) and the placebo group.

- Treatment with MTS was associated with a significant degree of dermal signs and symptoms at the patch application site.

- Methylphenidate can easily be extracted from the patch with common household solvents. Because of this, DPP is concerned about abuse and diversion. In contrast, the Sponsor does not expect MTS to be "attractive to abusers or diverters because applying a system (new or used) will not produce the stimulant euphoria of pills (swallowed or "snorted"), and because extraction from a transdermal patch to obtain an abusable form of methylphenidate requires several chemical processes and relies upon a relatively expensive and limited supply as compared to presently available pills"[1].

3.2 SYNOPSIS OF ODS SAFETY CONCERNS

The ODS Divisions have expressed the following concerns regarding the safety of the MTS:

- **Concerns regarding abuse potential**
  While the sponsor states that the patch dosage form is not expected to be a desirable form for drug abusers who generally prefer rapid absorption, the patch may be attractive for its therapeutic effects of enhancing work or school performance in adolescents and adults. The residual drug in the patch after use by the patient would allow a second individual to obtain this benefit from a used patch. Younger children may transfer the patch as play or remove and improperly discard an irritating patch. Additionally, if a reasonable extraction method is developed in the illegal drug use community, the drug remaining in used patches would be of interest to drug abusers. Thus, we cannot assume that this dosage form has inherent resistance to misuse.

- **Concerns regarding exposure to heat**
  Postmarketing surveillance with other transdermal patches has demonstrated that external heat sources have contributed to increased drug absorption. School aged children are often exposed to sun and other hot conditions such as increased activity during recess, gym classes, and baths/showers. The Sponsor has conducted a heat study that shows that heat increases absorption of the product. This information is reflected both in the Precautions section of the labeling as well as the patient information.

- **Concerns with keeping the patch on during the day**
  We are concerned that this novel dosage form may not be appropriate for use in young children, as a child may not actually keep the patch on during the day. Children may play with the patch, remove the patch, and even possibly stick the patch on a friend. In addition, we are concerned that teenage patients may cut the patch in half and share one half with a friend, as the side effect profile shows insomnia, anorexia, and weight loss, all of which may be considered desirable effects in middle- and high-school aged patient populations.

- **Concerns with proposed time interval of application and removal**
  This patch differs with respect to the typical transdermal patches which are generally left on for a minimum of 24 hours and are labeled for release over 24 hours. However, this patch is labeled to be worn for nine hours with a release rate per hour. We are concerned that it would be difficult to educate users (healthcare professionals and caregivers) about this

[1] Risk Management Program, NDA 21-514; pg 1.

unique wear time requirement, which if ignored, could lead to excessive wear time and increased adverse events.

- **Concerns regarding patch identification after application**
  Because the MTS patch is translucent, we are concerned that it may be difficult to locate once applied to the child's skin. The name and strength of the product should be clearly visible on the patch after application so it can be readily identified, if needed, by emergency personnel, parents of children who arrive home wearing the patch and other people.

3.3 SYNOPSIS OF SPONSOR'S SAFETY CONCERNS

The Sponsor acknowledges that methylphenidate is a Schedule II controlled substance for which there is potential for abuse and diversion. Their observations from review of national trends of methylphenidate and stimulant abuse are that the most common forms of abuse of methylphenidate are swallowing intact pills and "snorting" or injection of crushed pills. They do not believe that the patch will be attractive to abusers or diverters because applying a patch will not produce the stimulant euphoria of pills that are swallowed or snorted.

The Sponsor has claimed that there are several populations of potential concern for abuse including patients, friends, and drug abusers and there are several potential avenues for diversion including occasional diversion of individual new or used MTS "locally" to friends, and mass diversion of new or used MTS to illicit drug dealers.

4 PROPOSED RISK MANAGEMENT PLAN

The Sponsor proposes several components of the risk management plan with the intent of reducing and detecting abuse and diversion.

4.1 PROPOSED RISKMAP

4.1.1 Targeted Education and Outreach

4.1.1.1 Supplemental Educational Materials

The Sponsor plans to provide supplementary educational materials to parents, teachers, school nurses, pharmacists, and prescribers. The objective of the supplementary educational materials is to educate these audiences by providing information and reinforcing messages about the abuse potential of MTS and available tools to help prevent misuse and abuse. The information will be distributed to doctors' offices and pharmacies. The Sponsor will also work with ADHD member organizations such as CHADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder) to make the materials available to a wider audience.

Comments:

- *The sponsor needs to provide a detailed description of these supplementary educational materials, including the key messages that will be conveyed, the format of materials (e.g. trifold brochure, 10 page booklet, compact disk, website), and the mechanism to distribute these to homes, schools, pharmacies and physicians offices (to reach the stated target*

audiences of "parents, teachers, school nurses, pharmacists and doctors"). An information sheet for parents and caregivers appears at the end of the professional product labeling. We suggest:

- *Add a section about how to use the administration chart for tracking patch application, removal, and disposal, which is part of the sponsor's proposed risk management program.*
- *Move the instructions for use to the end of this information sheet. The caregiver should first be informed of important safe use information before being told to apply the patch to their child.*
- *Highlight the importance of the 9-hour wear-time as a separate section or bullet and emphasize that longer wear times may increase side effects.*
- *Remove the following sections which are redundant and merely add length to the information: "How Does [Trademark] Work?" And "When Should [Trademark] be Used?"*
- *Remove the statement "'[redacted]", which implies safety.*

4.1.1.2 Sales Representative Training

Sales representatives will be trained and certified by written testing on issues surrounding potential abuse and diversion. The objective of sales representative training is to enable representatives to educate health care professionals on the possibility and nature of potential diversion and abuse.

4.1.2 Reminder Systems

4.1.2.1 Packaging and Charting System

The Sponsor proposes to include a chart in each package. The chart would be similar to what is used in a hospital setting; that is, each dose administered would be initialed, dated and timed. The time of removal will be indicated on the chart. The stated objectives of the charting system are to:

- Provide education on proper storage, disposal, and use of the charting system.
- Enable ready detection of removed MTS.
- Document administration, removal, and disposal of MTS.
- Provide the basis for engaging parents in the behavioral program.

Comments: The provided chart could be a very useful tool for parents/caregivers to document that all applied patches are returned (helping to assure that patches have not been transferred to others) and properly disposed. However, there should not be an expectation that this voluntary tool: (1) would be used by all parents/caregivers and (2) would serve as an accounting tool the firm could use to "document administration, removal and disposal of MTS" once it is in the patient's home. In addition, the chart should be mentioned in the submitted patient labeling (see section 4.1.1.1 above).

4.1.2.2 Disposal Methods

The Sponsor plans to educate caregivers and healthcare professionals on the proper disposal of MTS patches. They propose that patches should be folded and flushed to assure destruction.

Comment: This is consistent with disposal methods for other transdermal drug products of abuse and is acceptable to ODS.

4.2 PHARMACOVIGILANCE/SURVEILLANCE PLAN

4.2.1 School/Community Monitoring

The objective of the School/Community Monitoring component is to identify sentinel occurrences of drug abuse and misuse of MTS rapidly and in populations at greatest risk. The sponsor plans to develop a protocol and data analysis plan consistent with the CDC-developed guidance for disease outbreaks. They plan to begin data collection with the start of the 2005/2006 school year to garner baseline information prior to the introduction of MTS onto the marketplace.

Comment: It is unclear how, where, and by whom will the data collection be performed. We look forward to receiving the protocol and data analysis plan.

4.2.2 Internet Monitoring Program

The objective of the Internet Monitoring component is to identify potential sentinel occurrences of diversion, tampering, abuse, or misuse of MTS across the broad population which relays such information via the internet.

The internet will be broadly searched every 2 weeks for key words and for specific websites identified as "repositories of current information on the diversion, modification, tampering, and illicit manufacture of substances for abuse".

Comment: This seems like a viable information source to detect the perception of abusers regarding the desirability of the product and the likelihood of extraction from the patch at home.

4.2.3 News/Media Monitoring

The objective of news/media monitoring is to identify sentinel occurrences of drug abuse and misuse of MTS, and to detect potential regional issues.

A major public relations firm will scan the national media on a daily basis using key words related to the product and the product class as they relate to abuse and diversion. A report will be compiled monthly and submitted to Sponsors.

Comment: The Sponsor should include any media cases in their adverse event reporting obligation to the FDA.

4.2.4 Federal Surveys Monitoring

The objective of the Federal Surveys Monitoring is to detect potential regional issues and track trends of abuse and diversion across time, demography, and geography and provide rates of drug use in the target population.

Publication of survey findings will be tracked, published findings for individual surveys will be characterized, and an investigational protocol, the data analysis plan, and a final comprehensive report will be created.

4.2.5 Supply Chain Monitoring

An education system will be instituted to enhance the ability of critical elements within the distribution /supply chain to detect potential diversion of MTS. Education brochures will be developed for wholesalers and for pharmacists and doctors to enhance their awareness of tactics used for diversion purposes.

The objective of Supply Chain Monitoring is to more effectively detect unusual patterns of distribution and sales and thereby be better positioned to determine whether such patterns are indicative of potential inappropriate distribution and use.

Comment: The Sponsor should describe the mechanism (periodic, expedited) and timing of reports to FDA from all of the data sources.

4.3 OTHER

4.3.1 Risk Management Coordinator

The Sponsor plans to hire a risk management coordinator who will be the primary contact and project manager for all activities surrounding risk management

4.3.2 Toll Free Number

The Sponsor will institute a toll free number for use with the Risk Management Program. This number will be available to aid in detecting patterns of abuse.

Comment: The Sponsor needs to better describe the purpose for this toll-free number, how this purpose would be explained, and where the number would be found by potential users (e.g. professional labeling, patient labeling, supplemental materials, website, and or patch itself). A toll free number for a more generally described use, such as "for questions regarding Daytrana please call..." may be more appropriate. As with media monitoring, cases of abuse and diversion or incidental adverse event reports should be reported to FDA.

5 DISCUSSION

If approved, Daytrana® will be the first methyphenidate-containing transdermal product available in the U.S. The primary "risk" issue appears to be the potential for abuse and diversion in

children that may occur to a greater extent with this novel delivery system as opposed to the once-a-day oral methylphenidate formulations. Diversion via transfer of an "active" patch appears to be a concern that is unique to a transdermal delivery system for methylphenidate. Diversion may come in the form of simple compliance (i.e., child removes patch), sharing of patches, selling of patches, or forced removal of patch at the hands of a schoolyard bully.

The Sponsor has proposed to address the issue of abuse and diversion with a risk management program that focuses on surveillance and on the education of health care providers and consumers regarding safe storage, use, collection and disposal of the MTS. Although not stated as an objective, the Sponsor's Risk Management Submission states that, "risk management is [intended] to foster appropriate medical use while discouraging inappropriate use, abuse, and diversion..." Proper disposal of worn patches (by folding and flushing) is identified as a key element of risk management. Education of parents, pharmacists, and doctors and packaging are identified as the primary approaches to compliance with use as labeled.

This document conveys comments from the divisions in the Office of Drug Safety on the surveillance and education plan currently proposed by the Sponsors as well as additional recommendations to address the abuse/diversion potential (see below).

6 RECOMMENDATIONS TO SPONSOR

- We recommend the name and strength of the product be clearly visible on the patch after application so it can be readily identified, if needed, by emergency personnel, parents of children who arrive home wearing the patch and others.

- Regarding the Surveillance Plan:
  - The Sponsor should submit all serious outcome cases of abuse, misuse, or diversion on an expedited basis (15-day).
  - The Sponsor should summarize in a section of the Periodic report all cases of abuse, misuse, and diversion regardless of whether an adverse event occurred. Sources of such cases include, but are not limited to, the MTS toll-free line, the Internet Monitoring Program, News/Media monitoring, and the Sponsor's general information phone lines and direct emails to the Sponsor. In addition, the Sponsor should provide a summary in the Periodic report of all other surveillance monitoring data (e.g., from Federal Surveys, School/Community Monitoring, etc.).
  - The Sponsor should submit the School/Community Monitoring protocol and data analysis plan for FDA information.
  - The Sponsor needs to better describe the purpose for the toll-free number, how this purpose would be explained, and where the number would be found by potential users (e.g. professional labeling, patient labeling, supplemental materials, website, and or patch itself). A toll-free number for a more generally described use, such as "for questions regarding Daytrana please call..." may be more appropriate.

- Regarding the Educational Plan:
  - The Sponsor states that educational materials will be distributed at doctor's offices and will be available at pharmacies. The sponsor should also make sure to include the

information sheet for parents and caregivers that currently appears at the end of the professional labeling in the (10-count and 30 count) cartons or trays of the product to increase the likelihood that it would be received by the parent or caregiver.

- We also have the following suggestions regarding the information sheet:
  - Add a section about how to use the administration chart, which is part of the sponsor's proposed risk management program.
  - Move the instructions for use to the end of this information sheet. The caregiver should first be informed of important safe use information before being told how to apply the patch to their child.
  - Highlight the importance of the 9-hour wear-time as a separate section or bullet and emphasize that longer wear times may increase side effects.
  - Remove the following sections which are redundant and merely add length to the information: "How Does [Trademark] Work?" And "When Should [Trademark] be Used?"
  - Remove the statement "[redacted], which implies safety.
  - Any other educational materials aimed at patients, parents or caregivers developed by the sponsor should be written at a 6th-8th grade reading level to enhance the understanding by lower literacy populations.

MTS RMP Review Team

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Claudia Karwoski, PharmD, Scientific Coordinator, ODS IO /s/11-30-05
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Carol Holquist, RPh, Director, DMETS, HFD-420/s/11-28-05
Gerald DalPan, MD, MHS, Director, DSRCS, HFD- 410/s/11-28-05

_____

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety (ODS), HFD-400

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/s/

Mary Dempsey
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DRUG SAFETY OFFICE REVIEWER

Anne Trontell
12/2/2005 07:50:22 AM
DRUG SAFETY OFFICE REVIEWER

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

CLINICAL INSPECTION SUMMARY

DATE:	December 1, 2005
TO:	Richardae Taylor, Pharm.D., Regulatory Project Manager Robert Levin, M.D., Medical Officer Division of Psychiatric Drug Products, HFD-130
THROUGH:	Ni A Khin, MD, Chief, Good Clinical Practice Branch I (GCPB1, HFD-46) Division of Scientific Investigations (DSI)
FROM:	Roy Blay, Ph.D. Reviewer, GCPB1, DSI, HFD-46
SUBJECT:	Evaluation of Domestic Inspections
NDA:	21-514
APPLICANT:	Noven Pharmaceuticals Inc.
DRUG:	Methylphenidate Transdermal System (MTS)
PROTOCOLS:	SPD485-302, SPD485-201
THERAPEUTIC CLASSIFICATION:	Standard
INDICATION:	Treatment of pediatric Attention-Deficit/Hyperactivity Disorder (ADHD)
PDUFA GOAL DATE:	December 28, 2005

I. BACKGROUND

Noven Pharmaceuticals Inc., in collaboration with Shire Development Inc., is developing a transdermal system to deliver sustained levels of d, l-methylphenidate. The drug is delivered transdermally across intact skin by an adhesive patch.

In this NDA, the sponsor included the results from two pivotal clinical studies:

Protocol SPD485-302 entitled: "A Phase III, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo Controlled, Dose Optimization Study, Designed to Evaluate the Safety and Efficacy of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in Pediatric Patients aged 6- 12 with Attention-Deficit/ Hyperactivity Disorder".

The primary objective of this study was to evaluate, under controlled conditions, the safety and efficacy of SPD485 (MTS) as compared to placebo (PTS) and CONCERTA® , as determined by the change in the clinician completed Attention- Deficit/Hyperactivity Disorder–Rating Scale, Version IV (ADHD-RS-IV), in the symptomatic treatment of children (aged 6-12) diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders, 4th ed.–Text Revision (DSM-IV-TR) criteria.

Protocol SPD485-201 entitled: "A Phase II, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Dose Optimization, Analog Classroom, Crossover Study, Designed to Assess the Time Course of Treatment Effect, Tolerability and Safety of Methylphenidate Transdermal System (MTS) in Pediatric Patients aged 6-12 with Attention- Deficit/Hyperactivity Disorder (ADHD)".

Methylphenidate Transdermal System (MTS) is a Class II central nervous system stimulant that is under investigation for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children. Its active ingredient, methylphenidate (MPH), as an immediate or sustained release tablet, has been used in the treatment of ADHD for the past 30 years. MTS may offer certain advantages over immediate and long-acting oral formulations of MPH. These potential advantages could include greater convenience with once daily administration and the elimination of swallowing large extended release tablets which is problematic for small children.

The primary objective of this study was to evaluate, under controlled conditions (a simulated classroom) at multiple time points throughout the day, the behavioral effects, as measured by the Swanson, Kotkin, Agler, M- Flynn, and Pelham Rating Scale (SKAMP) deportment scale, of MTS compared to placebo in children (aged 6-12) diagnosed with Attention-Deficit/ Hyperactivity Disorder (ADHD) by DSM-IV-TR criteria.

Specifically, the SKAMP deportment scale (items 5, 6, 7, 8, 12, and 13 of the full scale) is a teacher Rating Scale that was used to evaluate the behavioral effects of MTS compared to placebo under controlled conditions. Measurements were taken at multiple time points throughout the day (pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours) during the double-blind, crossover, Analog Classroom visits (Visit 8 and Visit 9 End of

Study/Early Termination). The SKAMP was designed for independent observers to rate 13 items representing two factors of classroom behavior: attention and deportment. Each item is rated on a 7-point impairment scale (0=normal, 6=maximal impairment). This was a multi-center, placebo-controlled, crossover study with an open- label optimization phase, designed to assess the time course of treatment effect, tolerability and safety of MTS in pediatric subjects diagnosed with ADHD. Subjects visited the study site nine times during the course of approximately 14 weeks. Over 2 consecutive Saturdays, the "Analog Classroom" was designed to see how well a child performed in a simulated classroom.

II. RESULTS (by site):

NAME	CITY, STATE	Protocol	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
John Burnside, M.D.	San Antonio, TX	302	4 Aug 05	19 Oct 05	NAI/011653
John Turnbow, M.D.	Lubbock, TX	201	4 Aug 05	15 Nov 05	NAI/011671
Padilla Americo, M.D.	Miami, FL	302	4 Aug 05	15 Nov 05	VAI/011673

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. John Burnside, M.D. (Site # 59, 17 subjects enrolled, protocol #SPD485-302)
   ADHD Clinic of San Antonio
   3535 Jones Maltsberger Road
   San Antonio, Texas 78247

   a. 17 subjects were enrolled in the study with 14 subjects completing the study and three dropping out: one was lost to follow-up, one could not swallow the test article, and a third for non-compliance. There were no deaths or serious adverse events reported. All 17 patient files were reviewed for the presence of signed consent forms. 12 subject files were reviewed in depth for inclusion criteria, medical history, physical examinations, and submitted data was compared with source documents, raw data, and case report forms.

   b. There were no limitations to the inspection.

   c. A Form FDA 483, Inspectional Observations, was not issued at the end of inspection. No significant data discrepancies were noted.

   d. The data appear acceptable in support of the relevant indication.

2. John Turnbow, M.D. (Site #3, 35 subjects enrolled, protocol #SPD485-201)
   Behavioral Neurology
   3315 81st Street, Suite A
   Lubbock, Texas 79423

   a. 35 subjects were enrolled in the study with 31 subjects completing the study. There were no deaths or serious adverse events reported. All 35 subject files were reviewed for consent forms, laboratory and ECG results, SKAMP efficacy results PERMPS results, and KSADS data.

   b. There were no limitations to the inspection.

   c. A Form FDA 483, Inspectional Observations, was not issued at the end of inspection. No significant data discrepancies were noted.

   d. The data appear acceptable in support of the respective indication.

3. Padilla Americo, M.D. (Site # 34, 14 subjects enrolled, protocol SPD485-302
   7500 SW 87th Avenue
   Suite 202
   Miami, Florida 33173

   a. At this site, 18 subjects were screened; 14 subjects were randomized and 13 subjects completed the study. No deaths or SAEs were reported. Subject 34016 was listed as lost to follow up. An audit of six subjects' records was conducted.

   b. There were no limitations to the inspection.

   c. A Form FDA 483, Inspectional Observations, was issued at the end of inspection. The inspection noted two protocol deviations that were not granted waivers in a timely fashion. Subject 34006 had a positive drug screen for Ritalinic Acid. This subject did not go through a washout period, and a protocol deviation was not granted until approximately two months later. The ADHD-RS score for subject 34001 dropped by 11% to an unacceptable condition at visit 7. According to the protocol, this subject should have been withdrawn from the study. A protocol deviation was not granted until approximately three months later.

      The Form 483 also noted that the blood pressure reading for subject 34001 was revised from 121/073 to 118/078 without explanation. This revision in blood pressure was significant because the original reading would have excluded the subject from the study since the value is outside of the 95th percentile for this subject.

   d. The impact, if any, of the observations noted above for subjects 34001 and 34006, on the overall data analysis, should be considered.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Turnbow and Burnside did not identify any significant observations. The inspection of Dr. Padilla identified two subjects (34001 and 34006) who met exclusionary criteria but remained in the study. The review division should assess the impact of these observations on its overall data analysis for this site. Overall, the data appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Ni A. Khin
Branch Chief, Good Clinical Practice Branch I, HFD-46
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/s/

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12/1/2005 04:37:27 PM
CSO

Ni Aye Khin
12/1/2005 04:44:13 PM
MEDICAL OFFICER

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA# 21-514
Drug Name: methylphenidate transdermal system

1. Does the application reference a listed drug (approved drug)? YES X NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Ritalin (methylphenidate HCL) Tablets/ NDA 10-187

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO X

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO ☐
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in dosage form, from tablets to transdermal patch.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO X

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO X

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO X

10. Are there certifications for each of the patents listed for the listed drug(s)? YES X NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s): 2,507,631

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES X NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES X NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES X NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A X YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES X NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES X NO ☐

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 54,732 NO ☐

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES X NO ☐

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/s/

Richardae Taylor
12/1/2005 04:09:35 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: October 28, 2005

To: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
(HFD-120)

Through: Deborah Leiderman, M.D., Director
Silvia Calderon, Ph.D., Team Leader

From: Geoffrey Zeldes, M.D., Pharm.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: CSS Consultation regarding sponsor resubmission for NDA 21-514
(methylphenidate transdermal system)
Indication: treatment of attention deficit hyperactivity disorder
Application Due Date: December 28, 2005
Sponsor: Noven Pharmaceuticals

Background

New Drug Application (NDA) 21-514 was submitted by Noven Pharmaceuticals, Inc. (Noven) on 27 June 2002 for the Methylphenidate Transdermal System (MTS) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients. MTS contains a mixture of *d*- and *l*-methylphenidate, an approved agent for the treatment of ADHD, in a multi-polymeric adhesive platform, as a means of delivering methylphenidate transdermally during the period of patch wear.

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine monoamines into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer.

The methylphenidate transdermal system, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

On 10 October 2003, the Agency issued an approvable letter detailing the deficiencies of NDA 21-514. The Agency requested the Sponsor to address the high incidences of insomnia, anorexia, and significant weight loss noted in the short term studies. The FDA expressed concern that these adverse events could result in growth retardation or other serious adverse consequences with

chronic long term treatment with MTS. The Agency suggested that decreasing the wear time of the MTS patch might decrease insomnia, anorexia, and significant weight loss to acceptable levels. The Agency also requested a Risk Management Program be developed for the product.

CSS has been asked to review and comment on the resubmission.

Submission Review

The NDA can be found in the electronic document room (EDR). Data on the product submission was obtained utilizing the EDR and DFS. Sections on chemistry, pharmacokinetics, labeling (including abuse / dependence) and risk management were reviewed.

Product Description

The sponsor proposes 4 patch dosage sizes including 12.5 cm^2 (27.5 mg), 18.75 cm^2 (41.3 mg), 25 cm^2 (55 mg), and 37.5 cm^2 (82.5 mg). The actual amount of MPH delivered by the different patch strengths over 9 hours ranges from 10 mg for the smallest patch to — ng for the largest. MPH is contained in the adhesive formulation utilizing — ransdermal technology, consisting of an acrylic adhesive, a silicone adhesive and methylphenidate. Release of active drug from the adhesive — ; constant over time, with no rapid release component when the patch is initially applied. The total amount of drug absorbed transdermally is determined by the surface area (size) of the patch (ie. amount of adhesive/methylphenidate exposed to the skin).

All 4 patch sizes of this product contain 1 ½ times more methylphenidate then Concerta®, the controlled release oral formulation utilized by the sponsor to compare safety and efficacy. Comparable Concerta® dosages include 18 mg, 27 mg, 36 mg, & 54 mg. (See Synopsis Table VII on next page)

Table 1 and Table VII are taken from the Sponsor submission. The data indicates that for "comparable" dosing, the patch results in doubling of the mean 9 hour plasma concentration of *d*-MPH when compared to Concerta®. This level is sustained at a steady state until the patch is removed and then decreases over a 2-3 hour period.

TABLE 1

Mean ± SD Plasma *d*-Methylphenidate (Sample taken at 9 hrs after application)

Pharmacokinetic Parameters After Repeated 9-Hour Applications of [TRADEMARK] for 7 Days

Parameters	12.5 cm^2 (N = 7)	18.75 cm^2 (N = 32)	25 cm^2 (N = 27)	37.5 cm^2 (N = 8)
C_{max} (ng/mL)	20.0 ±11.1	23.9 ±8.9	30.5±16.0	46.5 ±27.3
T_{max} (hrs)*	7.1 (4.3 – 8.8)	8.0 (5.7-11.8)	8.8 (5.8 –11.7)	8.8 (7.3 – 10.3)
AUC_{0-t} (ng·hr/mL)	139±95.2	171 ±78.1	225 ±139.0	332 ±254.0

* Median (range)

The patch contains a racemic mixture of *d*-MPH and *l*-MPH. Concerta® contains only *d*-MPH. In addition to the already mentioned doubling of *d*-MPH levels, there is also a significant plasma concentration of *l*-MPH which results from application of the patch. The following table taken from the submission illustrates this:

Synopsis Table VII: Mean (SD) 9 hour plasma *d*- and *l*-MPH concentrations (ng/mL) for MTS and CONCERTA

Patch Size	*d*-MPH	*l*-MPH	Capsule Strength	*d*-MPH	*l*-MPH
12.5cm2	12.7	6.87	18mg	8.65	0.00
(N=5)	(7.42)	(4.09)	(N=3)	(1.75)	(0.00)
18.75cm2	20.1	10.0	27mg	11.0	0.852
(N=14)	(15.3)	(7.08)	(N=13)	(9.48)	(2.31)
25cm2	38.6	20.2	36mg	20.1	0.178
(N=20)	(17.0)	(8.64)	(N=23)	(9.77)	(0.322)
37.5cm2	47.0	28.6	54mg	23.2	0.337
(N=33)	(27.1)	(20.6)	(N=41)	(13.2)	(0.618)

Abuse Potential

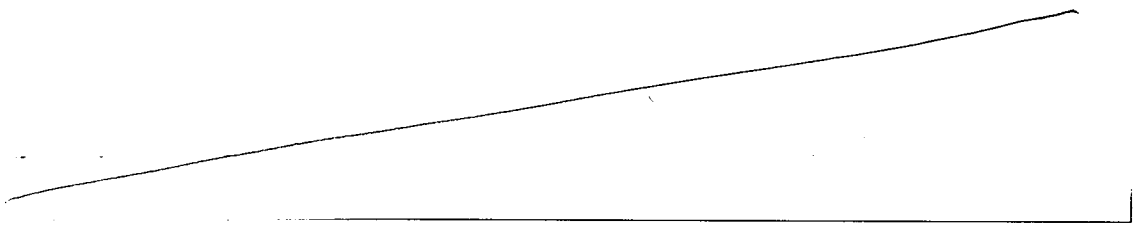
There is no initial rapid release component of the patch. Onset of action is 2-3 hours after transdermal application of the patch as prescribed. Theoretically, this may make this product less of an attraction to an abuser because there would be no "rush" from applying the patch. Similarly, "sharing" a patch would entail a 2-3 hour delay before the 2nd user would perceive any drug effect, while the initial user would not have the patch available to maintain a drug effect.

The total amount of methylphenidate in each patch appears large when compared to oral dosing forms of MPH (IR forms contain up to 20 mg and ER forms up to 54 mg). However, the matrix formulation of the patch prevents easy access to this total drug content and lessens the risk of the drug being accessible for dissolution and injection or for rapid release. This decreases the safety concerns associated with misuse and abuse of the intact product. The method in which the methylphenidate is contained in the adhesive portion of the patch requires complex chemical extractions to obtain an abusable form of the drug. This procedure would be lengthy and expensive and most likely not worth the time or trouble by an abuser, due to the small yield of drug from a patch. The sponsor indicates that exposing the patch to alcohol does release from the product but not at levels which would be abusable or raise safety issues. Similarly, it would be unlikely that an abuser would want to cut and chew the patch due to the relatively small total amount of drug contained in the patch. The greater abuse concern would be diversion of this product. For example, a patient might share a single patch with someone else, unlike an oral dosage form, which can only be ingested by one person.

Drug Dependence

The risk associated with abuse, misuse, or addiction (substance or drug dependence) from the methylphenidate transdermal patch will likely be similar to other formulations of methylphenidate.

The following is the black box warning statement contained in the proposed drug labeling:



A similar black box warning appears in the Ritalin label:

> **Drug Dependence**
>
> Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.
>
> Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

Because the proposed warning is based on information obtained from an older drug product, it includes out-of-date terminology and concepts, and fails to address current issues regarding the safety of this drug.

If the sponsor includes information in the black box warning specifically mentioning the possibility of severe depression if the drug is withdrawn, then this issue needs to be addressed specifically in both the Risk Management Program and the labeling / patient information. In view of the recent FDA warning regarding Strattera® and suicide, the black box warning for this product should be updated, with this issue addressed.

Risk Management Program

The Risk Management Program was also reviewed. The goal of the Program as stated on the first page of the document is to provide a comprehensive approach towards reducing and detecting abuse and diversion of the product. No mention is made of risks regarding the safety of the product, such as overdose or misuse.

The Risk Management Program contains sections on packaging and the charting system printed on the package, disposal methods, school/community monitoring, internet monitoring program, news/media monitoring, federal surveys monitoring, supply chain monitoring, supplementary educational materials, sales representative training, risk management coordinator, and providing a toll free number. These sections are described generically, and have varying degrees of importance for risks associated with a stimulant type drug. Most of the sections describe a method to collect data, but do not indicate how this data will be used to promote the safe use of the product.

This Program was compared to the actual labeling section containing "Information for Parents or Caregivers". Although a section of the Risk Management Program defines a Charting System to be printed on the packaging as a method of tracking individual patch use, no instructions are provided in the labeling explaining how a parent is to utilize the chart.

The Risk Management Program describes the creation of a Risk Management Coordinator position, but does not clearly define the role of this person in relationship to reporting data between the sponsor and the FDA.

Conclusions

The abuse potential of the methylphenidate patch should be similar to other MPH formulations. The abuse potential of an individual patch, due to the relatively small of amount of drug in each patch, compared to reported amounts utilized by abusers, and the difficulty of extracting that drug into an abusable form, is not a large cause for concern. Diversion of the intact product would have a higher risk of abuse potential. While easy to share a patch, the long delay in reaching peak drug effect, would make this type of abuse less likely.

Recommendations

Label

The black box warning concerning Drug Dependence needs updating. It is copied from the Ritalin package insert, which is out of date, and does not address specific product properties. For example, "Frank psychotic episodes can occur, especially with parenteral abuse," is not relevant as this product can not be administered parenterally.

Sponsor should specify or study how drug release and absorption is affected by heat (internal or external), exercise and activity level and adhesion problems. Several safety issues were raised in a previous CSS consult (4/3/03), which have yet to be addressed by the current labeling. These involve varying patch properties while being worn by the patient. For example, will a patch applied to a child with a fever release a higher amount of drug? Similarly, how does physical activity, such as after school sports or physical education during school affect the amount of drug which is released? If a patch seems to be loose, what action does the sponsor recommend? If an occlusive dressing is recommended, how will this effect the drug release properties of the patch?

Labeling for the Patient

A section must be added to the labeling for the patient, where instructions are given on how to utilize the tracking chart provided on the side of the box in which the product will be dispensed. It would also be helpful to track the use of the product by having the sponsor collect the completed box charts from the parent, when the box is empty, perhaps as a requirement to obtain another box.

The labeling for the patient should also include clear instructions on the 9 hour recommended wear time for the product. This could be accomplished by providing instructions to write down time of application and at the same time "calculate" and write down the removal time.

Risk Management Program

The proposed risk management program is broad and general in scope, designed to address issues of abuse and diversion, but not of drug safety, specifically the risks of misuse and potential overdose. Further clarification is needed regarding how the various components of the program will actually impact the risk of this product. For example, the role of the risk management coordinator, a liaison position to interface with the various stakeholders, must be clearly defined,

including method and frequency of reporting data to the FDA. Specific educational programs must be developed for both the physician and the patient (and families) to address the safety concerns of using a stimulant chronically.

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/s/

Geoffrey Zeldes
11/4/2005 10:45:25 AM
MEDICAL OFFICER

Silvia Calderon
11/4/2005 10:51:08 AM
CHEMIST

Deborah Leiderman
11/7/2005 10:58:06 AM
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Research and Evaluation
Office of Drug Evaluation III
Division of Dermatology and Dental Drug Products

Tel 301-796-1019
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From: Brenda Carr, M.D./Medical Officer, Dermatology

Via: Markham Luke, M.D., Ph.D./Dermatology Team Leader
Stanka Kukich, M.D./Deputy Division Director, DDDP

To: Russell Katz, M.D./ Division Director, HFD-120
Division of Neurology Products

HFD-540 Consult #: 753

Subject: NDA 21-514 resubmission

Material Reviewed: Results from contact sensitization study

Date: September 20, 2004

Background: NDA 21-514 was submitted to the Division of Neuropharmacological Drugs (HFD-120; now Division of Neurology Products) on June 27, 2002 by Noven Pharmaceuticals for their product, Methylphenidate Transdermal System (MTS; ——— ® system). The product was developed for the once-daily treatment of Attention Deficit Hyperactivity Disorder (ADHD) by a patch delivery system.

In support of the NDA, the applicant conducted a combined skin sensitization and irritation study (N17-008), with the complete study report submitted to the NDA. Study N17-008 revealed the applicant's product to be an irritant, and the product's role as a potential sensitizer could not be excluded (see HFD-540 consult #360).

On April 25, 2003, the review division issued a Not-Approvable letter citing numerous clinical, chemistry and biopharmaceutics deficiencies. Pertinent to this consult is what was reported to the applicant as Clinical Issue #4:

"Our Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6-week duration would be helpful in investigating this potential signal."

On June 28, 2005, the Division of Neurology Products received a resubmission from the applicant in response to the Not-Approvable action. Results from a topical safety study were included in the resubmission, and the Division of Dermatologic and Dental Drug Products has been requested to review those study results.

****

SKIN SENSITIZATION TESTING OF NOVEN. METHYLPHENIDATE TRANSDERMAL SYSTEM (Protocol No. N17-020)

Design: single-center, randomized, evaluator-blind

Number of subjects: The study enrolled 194 subjects.

Methods:

The three test articles listed below were tested simultaneously:

Treatment Code	Patch Type	Concentration	Method and Quantity of Application of Patch
A*	N/A	55.0 mg/ 25 cm^2	One Noven Methylphenidate Transdermal System (MTS) to the back
B*	N/A	0 mg/ 25 cm^2	One Placebo Transdermal System (TS) to the back
C	Occluded**	Neat	0.2 ml Saline applied via occlusive patch to the back

*Initial MTS and Placebo TS size was 110.0 mg / 50 cm2 and 0.0 mg / 50 cm2. respectively.

Two controls were included in the study to help distinguish irritation reactions from possible sensitization reactions:

- A placebo patch (B), containing no active drug, functioned as a control for the irritation or sensitization elicited by the patch itself.
- Saline (C), a negative, non-sensitizing control with low irritation potential, functioned as an indicator of each subject's inherent reaction to occlusive study conditions.

On each test day, the saline patch was prepared according to the specification above. A 50 cm^2 MTS and TS were applied to the back per original protocol on Induction Day 1 (48 hr application period). Prior to Induction Day 2, the 50 cm^2 MTS containing 110.0 mg of methylphenidate and the Placebo TS patch were cut in half and applied to the previous test site. Halving the MTS reduced the test article to 50.0 mg/ 25 cm^2. The original dose was halved due to a high incidence of adverse events early in the study.

Comment: The reviewer does not consider that halving the MTS patch compromised the conduct of the study.

Induction

The induction applications were made three times a week for three successive weeks. Each test article was applied to sites on the skin of the paraspinal region for a contact period of 48 (± 4) hours on Monday and Wednesday and 72 (+ 8) hours on Friday. Test articles were applied once for 48 (± 4) hours during the challenge and re-challenge phases.

Reactions were evaluated 48 (±4) or 72 (±8) hours after each induction application. Evaluations for irritation were conducted 30 minutes to 1 hour after patch removal.

All induction applications for an individual test article were made to the same site unless reactions become so severe as to make this inadvisable. In cases of severe reactions, subsequent applications of the offending test article were made to an adjacent area.

Comment: The induction phase also allows for evaluation of irritancy of the test articles.

Rest Period

An approximate 2-week rest period followed the final induction application. No test articles were applied during the rest period.

Challenge Phase

Following the rest period, a 48 (±4) hour challenge application of the test articles was made to naïve sites on each subject. The sites were scored 48 (±4) and 96 (±8) hours after patch application.

Re-challenge Phase

If the Investigator deemed a reaction to be possibly indicative of contact sensitization, one 48 (±4) hour patch application of test article(s) was made to a naïve site to further define the reactions. The sites were scored 48 (±4) and 96 (±8) hours after patch application.

Comment: The study was of appropriate design for one intended to evaluate the irritation and sensitization potential of the test articles.

RESULTS

A total of 194 subjects were enrolled in the study. A total of 131 subjects completed the induction and challenge phases of the study. Two additional subjects participated in the challenge phase; however, one did not receive induction application 9, and a second subject only had a 48-hour evaluation at challenge. Thus, the number of subjects evaluable for sensitization evaluation was 133.

Comment: For a sensitization study, it is generally recommended that enrollment be sufficient to allow for at least 200 evaluable subjects. However, for the applicant's product, the results revealed that the numbers of subjects was adequate to permit conclusions regarding the sensitization potential of their product.

Comparative Irritation

Applicant Table (Sec. 10.4.1.2)

	Irritation Analysis		Irritation Analysis	
	MTS	**Placebo TS**	**MTS**	**Negative Control - Saline**
Mean Irritation Score	2.06	1.62	2.06	0.78
Std. Dev.	0.56	0.65	0.56	0.57
N	145	145	145	145
Adjusted Difference	0.03 (n=145)		1.08 (n=145)	
95% Upper Confidence[1]	0.1536[2]		1.2047[2]	

[1]MTS is equivalent to the comparator (placebo or control) if 95% upper confidence bound is less than or equal to zero.
[2]MTS is more irritating than the placebo and the control.

Comment: MTS was more irritating than the placebo TS and the negative control (saline). The irritation analysis reflected scoring of dermal responses such as erythema, edema, papules, and vesicles.

Contact Sensitization

A total of 36 of 133 subjects participated in the re-challenge phase, and 18 of these subjects (13.5%) were considered to have manifested sensitization (based on the challenge and/or re-challenge periods). For 3 additional subjects, irritation was the assessment following re-challenge; however, sensitization could not be excluded, and the applicant considered that a second re-challenge might have been helpful in elucidating the nature of the reaction. Eight subjects had readings at challenge that could have indicated sensitization but were not re-challenged. Thus, there were 11 subjects for whom re-challenge (8 subjects) or a second re-challenge (3 subjects) might have proven helpful. If it is considered that these 11 subjects were indeed sensitized, the rate of sensitization increases to 21.8%. Thus, under the conditions of study, the rate of sensitization ranged from 13.5% to 21.8%.

Adverse Events

Of 194 subjects who were treated with the test articles, 183 reported at least one adverse event. Of the 63 subjects discontinued from the study, 33 discontinued due to adverse events. The majority of adverse events were considered to be mild or moderate in intensity. There were no deaths during the study.

There were two serious adverse events reported during the study: one subject was hospitalized with severe diarrhea and chest pain, considered possibly related to MTS; another subject was hospitalized with severe abdominal pain, which was considered unlikely to be related to MTS. The most common adverse events were insomnia (80.6%), headache (49.0%), anorexia (30.9%), nervousness (29.4%), dry mouth (27.8%), asthenia (24.7%), nausea (23.7%), hyperkinesia (19.6%), tachycardia (15.5%), dyspepsia (10.8%), pain (9.8%), paresthesia (8.8%), and dizziness (8.2%). Most symptoms were believed to have been due to methylphenidate.

Comment: Per the draft package insert (Clinical Pharmacology section), " [redacted]

Since application times in this study were from 48 to 72 hours, conditions of use were not comparable to those proposed for the clinical setting (9 hour application time). Any irritancy at the patch site might also have allowed for increase systemic exposure, since the local inflammation could have allowed for increased percutaneous absorption of the methylphenidate. Rate of adverse events in this study may therefore not be predictive of what might be expected when the product is used under the more conservative recommended dosing conditions (9 hour application time and applying to alternate hip daily).

Conclusions: The applicant has provided sufficient information to inform labeling regarding the potential for their product to cause skin irritation and contact sensitization. Study N17-020 reaffirmed previous work that the applicant's product can cause irritancy. The study also allows a conclusion that there is significant potential for the applicant's product to induce contact sensitization. The proposed conditions of use in the clinical setting (9-hour application times with a daily change in the site of application) may decrease the potential for irritancy; it is unclear to what extent the potential for sensitization might be impacted.

Recommendations: It is recommended that labeling reflect the potential for the product to cause irritancy and sensitization and describe the results from the skin sensitization study, N17-020. Recommended changes to the applicant's proposed package insert are attached. (Note: Recommended labeling changes from the consulting division are highlighted for ease of identification. Other marked changes are by a different author.)

Please do not hesitate to contact the Division of Dermatology and Dental Drug Products with any additional questions or concerns.

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29 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

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/s/

Brenda Carr
10/24/2005 02:12:39 PM
MEDICAL OFFICER

Markham Luke
10/24/2005 02:23:41 PM
MEDICAL OFFICER
Consult reply from dermatology regarding Methylphenidate Patch.

Stanka Kukich
10/26/2005 08:18:59 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-514

Noven Pharmaceuticals, Inc.
Attention: Jeff Dow, Esq.
Director, Regulatory Affairs
11960 SW 144th St.
Miami, Fl 33186

Dear Mr. Dow:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for methylphenidate transdermal system.

At a June 30, 2005 meeting of the Pediatric Advisory Committee, a concern was raised about reports of psychiatric adverse events occurring in patients being treated with various drug products for ADHD. The reports considered at that meeting were for the drug Concerta, but it was acknowledged that similar reports have been made for other ADHD products. Although some psychiatric adverse events are already mentioned in the labeling for various ADHD products, there was general support for the view that labeling may need to be enhanced to better characterize these events. However, there was also agreement that such labeling changes should await a more comprehensive review of psychiatric events for ADHD products. In order to facilitate this more comprehensive review, we are requesting psychiatric adverse event data for various products approved for the treatment of ADHD and for products with pending NDA applications under review for the treatment of ADHD.

Please find below a request for psychiatric adverse event data for methylphenidate transdermal system. This same request is being sent to the manufacturers of all products approved for the treatment of ADHD and for products with pending NDA applications under review for the treatment of ADHD.

We ask that you respond to this request by December 1, 2005. The details of the request are provided below.

Safety Review of Drug Therapies for ADHD
Psychiatric Adverse Effects
Analysis Plan and Safety Data Request

1. Cumulative review of postmarketing spontaneous or literature reports for psychiatric events of interest received by sponsor after January 1, 2000: