CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-724

PHARMACOLOGY REVIEW

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

Date:	**March 24, 2004**
To:	**Bob Rappaport, M.D., Director** **Division of Anesthetics, Critical Care and Addiction Drug Products** **(HFD-170)**
Through:	**Deborah B. Leiderman, M.D., Director** **Michael Klein, Ph.D., Team Leader** **Controlled Substance Staff (HFD-009)**
From:	**Katherine Bonson, Ph.D., Pharmacologist** **Controlled Substance Staff (HFD-009)**

Subject:	**Consult on abuse potential for NDA review**
	NDA 21-446, 21-723, 21-724, 21-725
	Lyrica (pregabalin)
	Treatment for (respectively) neuropathic pain associated with
	      diabetes, neuropathic pain associated with herpes zoster,
	      epilepsy,
	Sponsor: Pfizer, Inc.

Background:

The Division of Anesthetics, Critical Care and Addiction Drug Products (HFD-170) consulted CSS regarding the abuse potential of pregabalin (Lyrica). Pregabalin is a calcium channel blocker at the alpha-2-delta protein subunit that is being developed for the treatment of neuropathic pain associated with diabetes, neuropathic pain associated with herpes zoster, epilepsy, Some of the medications approved for the treatment of pain are controlled substances under the Controlled Substances Act (CSA). The Sponsor proposes that pregabalin not be controlled under the CSA, citing the results from non-clinical studies, clinical trials and human abuse potential studies as support for their position that pregabalin lacks abuse potential and should be approved for marketing as a non-scheduled drug.

Conclusions and Recommendations:

Based upon review of all the data provided by the Sponsor, CSS concludes that pregabalin has an abuse liability similar to that of diazepam, a Schedule IV substance under the CSA.

As required by the CSA (21 USC 811(c)), CSS is preparing an "Eight Factor Analysis", a document that evaluates pregabalin in terms of its potential for abuse. In this document, CSS will recommend that pregabalin be placed into Schedule IV of the CSA. The "Eight Factor Analysis" is transmitted to the Drug Enforcement Administration (DEA) under the signature of the Assistant Secretary for Health at the Department of Health and Human Services, with the concurrence of the FDA Commissioner and the National Institute on Drug Abuse.

The most salient findings for this conclusion are that pregabalin produced a high rate of euphoria (4.8-11.8%) relative to placebo (1.2%) in GAD clinical trials. This strongly suggests that pregabalin has reinforcing properties.

Additionally, in the clinical abuse potential study, conducted in sedative/alcohol-abusing subjects, subjective responses to "good drug effect", "high", "liking" and "liking (end of session)" for the 200 and 450 mg doses of pregabalin were similar to or greater than the responses to 15 and 30 mg of diazepam. These data strongly suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam.

Finally, pregabalin produced self-administration in rhesus monkeys at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug. This also demonstrates that the drug produces reinforcing effects.

In submitting the NDA application, the Sponsor agreed to not market the drug product, if FDA determined that the drug should be scheduled under the CSA, until the DEA has issued a final schedule ruling. FDA/CDER has initiated the drug scheduling process and has notified the DEA. However, the Sponsor and HFD-170 should be aware that scheduling actions by the DEA involve several federal agencies and multiple clearances, and therefore can take an unpredictable period of time before finalization occurs.

I. Summary of Data Related to Abuse Potential from Clinical Studies

A. Clinical Studies Assessing Safety and Efficacy of Pregabalin

Incidence of "Euphoria"

A high rate of euphoria was reported by Generalized Anxiety Disorder (GAD) patients taking pregabalin in clinical trials: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. In contrast, the placebo-treated rate of euphoria in GAD patients was 1.2%. No GAD patients who experienced euphoria had a history of drug or alcohol abuse. Since drugs are scheduled on the basis of behavioral effects suggestive of abuse potential, not on therapeutic indication, the presence of a high rate of euphoria in any clinical population suggests a safety issue with pregabalin.

In addition, the reported incidence of euphoria from pregabalin was 1.0-2.4% in neuropathic pain patients and 1.0-2.2% epilepsy patients, at doses of 150, 300 and 600 mg,

relative to the incidence in the placebo-treated groups (0.0% in neuropathic pain patients and 0.3% in epilepsy patients). It is noteworthy that the doses used in the GAD clinical trials that produced euphoria (200, 400 and 450 mg) were not tested in the neuropathic pain and epilepsy clinical trials. It is possible that the 200, 400 and 450 mg doses would produce euphoria if they were administered to other patient populations.

Additionally, in the clinical pharmacology (pharmacokinetic) studies, 43 of 440 healthy subjects (9.8%) experienced "euphoria" (28 mild, 14 moderate, 1 severe).

Physical Dependence and Withdrawal Syndrome

When discontinuation-emergent symptoms are summed across short-term psychiatric studies with pregabalin at doses ranging from 150-600 mg/day, the most frequently observed adverse events compared to placebo were insomnia, headache, nausea, infection and diarrhea.

When a similar evaluation was conducted for long-term psychiatric studies with pregabalin, the rate for adverse events in pregabalin-treated subjects was greater than that seen in placebo-treated subjects for insomnia, nausea, headache, diarrhea and chills. These data are suggestive of the presence of a withdrawal syndrome in psychiatric patients, indicative of physical dependence.

In contrast, the rate of adverse events during discontinuation from pregabalin in the neuropathic pain study was similar to that of placebo.

An evaluation of the psychiatric studies using the Physician's Withdrawal Checklist showed significant differences in withdrawal scores between pregabalin and placebo. The withdrawal symptoms were experienced by patients at all doses of pregabalin, although not every dose of pregabalin showed significant differences from placebo in every psychiatric study.

A post-hoc analysis of two pharmacokinetic studies in which pregabalin was administered for either 2 or 4 weeks showed that the rate of discontinuation-emergent signs and symptoms was similar to placebo, although the profile was different. In the 2-week study, healthy volunteers received either placebo or a single pregabalin dose of 25-300 mg on Days 1 and 22 and multiple doses of 75, 300, 600 or 900 mg/day on Days 8-21. In the 4-week study, healthy volunteers received either placebo or 900 mg/day of pregabalin on Days 1-28 and a single 300 mg dose of pregabalin on Day 29. Pregabalin discontinuation produced such symptoms as headache, nausea and diarrhea, while placebo discontinuation produced accidental injury, infection, skin disorder and ventricular extrasystoles.

B. Clinical Abuse Potential Studies

In the clinical abuse potential study, subjective responses to "good drug effect", "high" "liking" and "liking (end of session)" for the 200 and 450 mg doses of pregabalin were similar to or greater than the those for 15 and 30 mg of diazepam. Subjects identified the 200 mg dose of pregabalin as a sedative while identifying the 450 mg dose as a sedative/stimulant. These data suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam, a Schedule IV drug. It is notable that the majority of subjects were alcohol users, with only a few subjects who were users of sedatives and/or sedatives plus alcohol. This suggests that individuals without sedative abuse histories may experience pregabalin as reinforcing.

C. Psychomotor Clinical Studies

In three separate clinical abuse potential studies, subacute administration of pregabalin was synergistic with oxycodone, lorazepam and ethanol in producing performance deficits in psychomotor tasks. In a separate clinical abuse potential study, subacute administration of pregabalin (alone) produced a similar degree of performance deficits in psychomotor tasks as alprazolam (alone).

II. Summary of Data Related to Abuse Potential from Preclinical Studies

A. Receptor Binding

Pregabalin does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the calcium channel. This is similar to the binding profile for gabapentin. The mechanism of action of pregabalin is not well understood.

B. Microdialysis in Rats

Morphine increased extracellular levels of dopamine in the nucleus accumbens, but pregabalin and saline did not. Pregabalin blocked the increase in dopamine following morphine administration. Since dopamine levels are increased by many, but not all, drugs of abuse, this suggests that pregabalin does not have the same reinforcing effects as morphine, as Schedule II drug.

C. Behavioral Studies

The preclinical behavioral studies with pregabalin are not valid for assessing abuse potential. Deficits in the studies include:

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* the use of different infusion rates in the methohexital-pregabalin and the pentobarbital-pregabalin self-administration studies, which can affect the apparent reinforcing properties of a drug (ie: faster infusion rates are more reinforcing)

* the use of different routes of administration for midazolam and pregabalin in the conditioned place preference study, which can affect the apparent reinforcing properties of a drug (ie: routes with fast onset are more reinforcing)

* the 5 hour time lag between drug training and saline training in the conditioned place preference study with rats may be inadequate, since monkeys in a separate study showed behavioral effects for longer than 5 hours after pregabalin administration

* the lack of data regarding the pharmacokinetics of pregabalin in animals, which will influence the choice of appropriate pretreatment times

* the lack of data regarding the plasma levels of pregabalin produced by the animal doses selected compared to those produced by proposed therapeutic doses

Despite inadequately designed preclinical studies, there are indications in the preclinical studies that pregabalin has abuse potential:

* pregabalin produced self-administration of >10 injections/day at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug, thus demonstrating that pregabalin produces reinforcing effects.

APPENDIX A:
ABUSE POTENTIAL STUDIES WITH PREGABALIN

A. Clinical studies assessing safety and efficacy of pregabalin:

* euphoria
* physical dependence/withdrawal

B. Clinical abuse potential studies with pregabalin:

* clinical abuse liability study
* comparison to oxycodone for pharmacokinetics
* comparison to lorazepam in psychomotor tasks
* comparison to ethanol in psychomotor tasks
* comparison to alprazolam in psychomotor tasks

C. Summaries of preclinical studies:

* receptor binding
* in vivo microdialysis in rats
* behavioral studies:

    -- self-administration
    -- conditioned place preference
    -- drug discrimination
    -- spontaneous behavior
    -- locomotor behavior
    -- physical dependence/withdrawal

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Attachment A:
CSS Review of Pregabalin Pharmacology

Study Summaries:

A. Clinical Studies Assessing Safety and Efficacy of Pregabalin

Pregabalin has been tested up to 15,000 mg (15 gm) in clinical trials. This is 150-300 times the proposed therapeutic dose of 75 mg BID (oral) for neuropathic pain and epilepsy, and 100 mg BID (oral) for generalized anxiety disorder. Of particular interest is that the Sponsor states that adverse events were not clinically different from those at therapeutically recommended doses.

Incidence of "Euphoria"

In the Phase 2/3 studies (controlled and uncontrolled), a total of 423 of 8666 (4.8%) subjects experienced "euphoria" (263 mild, 146 moderate, 14 severe). Twenty-six subjects withdrew due to euphoria. None of the patients who experienced euphoria had a history of drug abuse or dependence. The average time to onset of euphoria was 1 day and duration was 7 days. Euphoria ceased while patients were still taking medication. This suggests that tolerance developed to euphoria during chronic administration. However, a week-long duration of euphoria can be considered a safety and abuse liability issue.

As depicted in **Table 1** (below), a high rate of euphoria was reported by Generalized Anxiety Disorder (GAD) patients taking pregabalin in clinical trials: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. No GAD patients who experienced euphoria had a history of drug or alcohol abuse. Drugs are scheduled on the basis of abuse potential, not on therapeutic indication. The presence of a high rate of euphoria in any clinical population is suggestive of an abuse potential in the general population.

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TABLE 1

Incidence of Euphoria in Clinical Trials :

Pregabalin Dose	Incidence of Reports of "Euphoria"		
	GAD	Epilepsy	Neuropathic Pain
150 mg	0.5%	0	1.0%
200 mg	**10.3%**		
300 mg	3.3%	2.2%	2.4%
400 mg	**4.8%**		
450 mg	**11.8%**		
600 mg	2.5%	1.0%	1.5%
all doses	4.5%	0.8%	1.4%
placebo	1.2%	0.3%	0

In contrast to GAD patients, the reported euphoria in the neuropathic pain and epilepsy clinical trials was never above 2.4%. However, the doses that produced euphoria in the GAD clinical trials were not tested in the clinical trials for these indications. This leaves open the possibility that these doses may produce euphoria if they are used in neuropathic pain or epilepsy patients.

In the clinical pharmacology (pharmacokinetic) studies, 43 of 440 subjects (9.8%) experienced "euphoria" (28 mild, 14 moderate, 1 severe).

Physical Dependence and Withdrawal Syndrome

When discontinuation-emergent symptoms are summed across short-term psychiatric studies (testing GAD, social phobia, panic disorder and acute mania) with pregabalin at doses ranging from 150-600 mg/day (n = 1851), the most frequently seen adverse events were insomnia (2.4%), headache (2.1%), nausea (1.8%), infection (1.7%) and diarrhea (1.4%). At the 300 mg dose, there was a higher incidence of insomnia (4.1%) and at the 200 mg dose, there was a higher incidence of headache (4.3%). The incidence in placebo-treated subjects (n = 817) was less than 1.5% for these symptoms.

When a similar evaluation was conducted for long-term psychiatric studies with pregabalin at 450 mg/day, the rate for adverse events in pregabalin-treated subjects (n = 429) was greater than that seen in placebo-treated subjects (n = 243): insomnia (5.2% vs. 0.8%), nausea (4.0% vs. 0.8%), headache (3.2% vs. 2.5%), diarrhea (2.8% vs. 0.8%) and chills (2.0% vs. 0.0%). These data demonstrate the presence of a withdrawal syndrome in psychiatric patients, indicative of physical dependence.

In contrast, the rate of adverse events during discontinuation from pregabalin in the neuropathic pain study was less than 1.0% for all symptoms.

An evaluation of the psychiatric studies using the Physician's Withdrawal Checklist showed significant differences in withdrawal scores between pregabalin and placebo. The withdrawal symptoms were experienced by patients at all doses of pregabalin, although not every dose of pregabalin showed significant differences from placebo in every psychiatric study.

A post-hoc analysis of two pharmacokinetic studies in which pregabalin was administered for either 2 or 4 weeks showed that the rate of discontinuation-emergent signs and symptoms was similar to placebo, although the profile was different. In the 2-week study, healthy volunteers received either placebo or a single pregabalin dose of 25-300 mg on Days 1 and 22 and multiple doses of 75, 300, 600 or 900 mg/day on Days 8-21. In the 4-week study, healthy volunteers received either placebo or 900 mg/day of pregabalin on Days 1-28 and a single 300 mg dose of pregabalin on Day 29. Pregabalin discontinuation produced such symptoms as headache, nausea and diarrhea, while placebo discontinuation produced accidental injury, infection, skin disorder and ventricular extrasystoles.

B. Clinical Abuse Potential Studies

Subjective Response Study

#1008-098
Abuse liability of pregabalin in recreational sedative/alcohol users
(Study conducted by

This is a crossover study in which subjects were randomized to one of five treatment sequences that included pregabalin (200 and 450 mg), diazepam (15 and 30 mg) and placebo. All study medication was given orally in a total of six capsules per session. Each treatment session was separated by a washout period of at least 5 days.

Fifteen subjects completed the study. All subjects were recreational sedative users (experienced with sedatives at least six times in lifetime) or moderate alcohol users (12 drinks per week for the past year). Ten subjects met alcohol criteria, two met sedative criteria and three met both criteria. Inclusion of volunteers with different drug histories may be inappropriate, since social drinkers and those who use sedatives for non-medical reasons may not have the same subjective responses to sedative administration. Exclusionary criteria included dependence on any drug except for nicotine.

Unusually, the investigators do not have a concluding statement concerning the abuse potential of pregabalin, based on the present clinical abuse potential study.

Physiological Measures

The only physiological measure that was responsive to drug administration was an increase in heart rate in the diazepam 30 mg group. The Sponsor attributes this to subjects falling asleep and then being startled when awakened for hourly assessments.

Subjective Measures (D = diazepam, P = pregabalin, PL = placebo; dose as number)

A variety of subjective measures from the POMS, ARCI and VAS were collected. Those specifically related to abuse potential assessment are presented below in **Table 2**:

TABLE 2

Comparison of Subjective Response to Pregabalin and Diazepam
(D = diazepam, P = pregabalin, PL = placebo; dose as number)

Good Drug Effects (VAS) -- increased by D30 > **P450** > **P200** > D15

High (VAS) -- increased by D30 = **P450** > D15 = **P200**

Liking (VAS) -- increased by D30 = D15 = **P450** = **P200**

Liking (End of Session) -- **P450** > D30 = D15 = **P200**

These data show that both doses of pregabalin produce good effects, high, and drug liking that are equivalent to or greater than at least one dose of diazepam. Notably, the 450 mg dose of pregabalin was liked in the end of session questionnaire better than either dose of diazepam or the lower dose of pregabalin. Since diazepam is a known drug of abuse, these results suggest that pregabalin has similar abuse potential to diazepam.

The data in **Table 3** (below) show that both drugs at the doses tested produce effects that are recognized as sedative effects by subjects. Of interest is that the 450 mg dose of pregabalin is recognized as a both a sedative and stimulant by subjects both during the study (VAS questionnaire) and after the study (Drug Identification Question). However, the ARCI subscale for stimulants (BG scale) did not register this dose of pregabalin as a stimulant.

TABLE 3

Drug Identification Question (End of Session):

	Placebo	Sedative	Stimulant
Placebo	73%	20%	7%
D15	40%	53%	7%
D30	0	87%	13%
P200	0	73%	27%
P450	20%	40%	40%

Sedated (VAS) -- increased by D30 > D15 = **P200** > **P450**

Stimulated (VAS) -- increased by **P450**

Stimulant-Like (BG Scale of ARCI) -- no change from any drug

Multiple Choice Procedure:

The Sponsor notes that this procedure was developed to assess reinforcing effects with results that are similar to self-administration procedures. Previously, benzodiazepines have been shown to have higher crossover points than placebo. However, in the present study, there were no significant drug effects.

The Sponsor states that, "Individuals tended to always choose drug when the alternative was the loss of money, but they chose money even at the lowest level. Although the cross-over value was lower for placebo ———) than the drug conditions (all averaged around ⌐ these differences were not significant." The Sponsor acknowledges that it is unexpected that diazepam did not produce crossover effects, but does not provide any explanation.

Studies Investigating Effect of Pregabalin on Task Performance

<u>#1008-078</u>
Evaluation of potential pharmacodynamic interaction between pregabalin and oxycodone administered orally to healthy volunteers
(Study conducted by ⸺⸺⸺⸺⸺)

This is a randomized, partial double-blind crossover study. Each of 12 subjects received all four treatments, in randomized order. Subjects did not have experience with drugs of abuse. There were seven days between the start of each treatment phase. The four oral treatments include:

1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with
     10 mg oxycodone
2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with
     placebo
3) placebo every 12 hrs for three doses -- third dose is given with
     10 mg oxycodone
4) placebo every 12 hrs for three doses -- third dose is given with placebo

Pregabalin was in capsules with matching placebos, but that oxycodone was in tablets that did not match either the pregabalin or the oxycodone placebo tablets. This accounts for the "partial double-blind" statement about design.

Blood was drawn for PK measurements at appropriate times. Oxycodone did not interfere with pregabalin pharmacokinetics. There was no clinical significant reduction in respiration rate or tidal volume from pregabalin alone or with oxycodone.

The pregabalin side effect profile alone included sleepiness, dizziness and asthenia. These effects increased slightly with oxycodone in combination with pregabalin.

A variety of psychomotor tasks were used in this study, including: simple reaction time, choice reaction time, digit vigilance, numeric working memory, immediate word recall, delayed word recall, word recognition, picture recognition, tracking, critical flicker fusion, body sway, and self-rated alertness.

Pregabalin increased reaction times for almost all tests and increased time for task completion. Oxycodone alone did not reduce task performance. The combination of oxycodone and pregabalin produced similar decrements, but these were of greater magnitude than pregabalin alone. However, pregabalin did improve task performance on two tests: improving accuracy on choice reaction time and tracking.

<u>#1008-076</u>

Evaluation of potential pharmacodynamic interactions between pregabalin and lorazepam administered orally to healthy volunteers

This is a randomized, double-blind, placebo-controlled crossover study in 12 healthy volunteers. Treatments were given orally, 7 days apart and included:

1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with 1 mg lorazepam
2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with placebo
3) placebo every 12 hrs for three doses -- third dose is given with 1 mg lorazepam
4) placebo every 12 hrs for three doses -- third dose is given with placebo

Blood was drawn for PK measurements at appropriate times. Lorazepam did not interfere with pregabalin pharmacokinetics, and pregabalin did not alter lorazepam pharmacokinetics. There was no clinical significant reduction in respiration rate or tidal volume from pregabalin alone or with lorazepam.

Dizziness, nausea and headache were reported more frequently after subjects received pregabalin with lorazepam than from pregabalin alone.

A variety of psychomotor tasks were used in this study, including: word recognition, immediate word recall, delayed word recall, simple reaction time, choice reaction time, digit vigilance, numeric working memory, picture recognition, visual tracking, critical flicker fusion, body sway, and Bond-Lader VAS.

Pregabalin alone reduced task performance in simple and choice reaction times, working memory, word recall, tracking, body sway and self-rated alertness. Lorazepam alone produced a greater degree of interference with performance than pregabalin on most tasks. The combination of pregabalin and lorazepam produced deficits in task performance that appeared to be synergistic in response, rather than additive. Reaction times, performance speed and sway were especially affected by the drug combination.

<u>#1008-079</u>

Double-blind crossover study to evaluate potential pharmacodynamic interactions between pregabalin and ethanol administered orally to healthy volunteers
(Study conducted by ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯ .)

This is a randomized, double-blind, placebo-controlled crossover study in 11 healthy volunteers. Note that the main question was how pregabalin changes ethanol responses, rather than the other way around. Treatments were given orally, 7 days apart and included:

1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given 30 min prior to 0.7 g/kg ethanol
2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given 30 min prior to placebo-equivalent ethanol (0.4%)
3) placebo every 12 hrs for three doses -- third dose is given 30 min prior to 0.7 g/kg ethanol
4) placebo every 12 hrs for three doses -- third dose is given 30 min prior to placebo-equivalent ethanol (0.4%)

Blood was drawn for PK measurements at appropriate times. Ethanol did not interfere with pregabalin pharmacokinetics, nor did pregabalin interfere with ethanol pharmacokinetics. There was no clinical significant reduction in respiration rate or tidal volume from pregabalin alone or with ethanol.

Dizziness, nausea and headache were reported more frequently after subjects received pregabalin with ethanol than from pregabalin alone.

A variety of psychomotor tasks were used in this study, including: word recognition, immediate word recall, delayed word recall, simple reaction time, choice reaction time, digit vigilance, numeric working memory, picture recognition, visual tracking, critical flicker fusion, body sway, and Bond-Lader VAS.

The combination of pregabalin and ethanol prolonged reaction time for simple reaction time and choice reaction time tasks and increased body sway. For all other tasks, pregabalin did not alter the effects from ethanol alone. Interestingly, pregabalin reduced the detrimental effects of ethanol on: accuracy in choice reaction time, speed of digit vigilance, accuracy of immediate word recall and alertness.

Pregabalin alone had no significant effects on task performance. The Sponsor acknowledges this is different than results from other cognitive studies with pregabalin, but provides no explanation. The results are indeed unusual, given that the same dose of pregabalin in other abuse liability studies did produce detriments in task performance.

#1008-097
Investigation into the effects of pregabalin, alprazolam and placebo on cognitive and psychomotor function, car driving ability and sleep
(Study conducted by ⎯⎯⎯⎯⎯⎯⎯⎯

This is a randomized, double-blind, 3-way crossover study with treatments administered three times a day (TID). Drug treatments were: pregabalin 150 mg (450 mg/day; 75 mg capsules used), alprazolam 1 mg (3 mg/day; 0.5 mg capsules used), and placebo, with seven day washout inbetween treatments. In each treatment period, subjects were treated for three days, followed by placebo on Day 4.

There were a total of 24 subjects, with 8 subjects each randomized to each of three treatment sequences. Subjects were excluded if they had "clinically significant use of psychotropic medication in the last 3 months".

Critical Flicker Fusion -- P = A > PL -- shows impairment of information processing

Hick's Choice Reaction Time -- A > P = PL -- A impaired motor, recognition and total reaction time.

Compensatory Tracking Task -- A > P > PL -- sensory motor coordination impaired by A more than by P

Line Analog Rating Scale -- A > P > PL on sedation; A = P > PL for uncoordination; no significant effects in anxiety or depression

Rapid Visual Information Processing -- A > P = PL

Sternberg Memory Scanning Task -- A > P > PL -- no serious memory impairment

Leeds Sleep Evaluation Questionnaire -- A = P > PL -- good sleep on both

Sleep EEG -- P > PL > A -- P increased slow wave sleep, A decreased it; overall sleep parameters were improved by both

Wrist Actigraphy -- no difference

Brake Reaction Time -- A > P > PL

Side Effect Profile: P produced dizziness, headache, sleepiness. A produced sleepiness, abnormal gait and asthenia.

Conclusion: Pregabalin produces mild impairments in motor behavior and information processing

C. Summaries of Preclinical Studies

Receptor Binding Studies

The Sponsor submitted two charts with Ki (inhibitory constant) values for various binding sites in the brain.

The first chart compared Ki values between pregabalin and gabapentin for GABA sites, opioid sites, dopamine transporter, NMDA sites, 5HT1 and 5HT2 sites. Neither drug

produced Ki values in the nanomolar range for any site except for the gabapentin binding site.

The second chart presented Ki values for a full binding profile of CNS neurotransmitter sites. The only sites that showed Ki values in the nanomolar range were the "gabapentin site", commonly known as alpha2-delta1 and alpha2-delta2 sites of the calcium channel.

These data demonstrate that pregabalin does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the calcium channel.

In Vivo Microdialysis with Rats

Summary data were submitted. Microdialysis was conducted in rat brains, with cannulae extended into the nucleus accumbens for detection of dopamine. Rats were injected (s.c.) with saline, morphine (0.75 mg/kg), pregabalin (10 mg/kg) or a combination of morphine and pregabalin (no doses given), with pregabalin administered 40 min before the morphine.

Morphine significantly increased extracellular levels of dopamine in the nucleus accumbens over an 80 min collection period. Pregabalin and saline had no effect on dopamine. Pretreatment with pregabalin blocked the increase in dopamine levels following morphine administration.

Behavioral Studies with Animals

No information is provided by the Sponsor concerning the plasma levels of pregabalin produced by the animal doses selected compared to the plasma levels of pregabalin produced by proposed therapeutic doses in humans.

Thus, it is impossible to evaluate the validity of the animal studies in terms of abuse potential of pregabalin.

Self-Administration (Pregabalin vs. Methohexital)

Monkeys (n = 4) were used in the study, but only 3 of the animals received each dose of the drug. The fourth animal was unable to receive the highest dose because of solubility problems, given that this was the largest monkey of the group.

Monkeys were trained to receive IV injections of methohexital (0.1 mg/kg/injection), following the presentation of a red light and 10 bar presses by the monkey. Monkeys were then offered pregabalin at 1.0, 3.2, 10 and 18 mg/kg/injection. No information is

provided to justify the doses of drugs selected. All experimental sessions lasted 130 min
(2 hr, 10 min).

The Sponsor notes that because of the solubility problems with pregabalin, the drug had
to be infused over a 25 sec period. However, the methohexital and saline were infused
over a 5 sec period. The narrative states that methohexital and saline were also made
available in a 25 sec infusion rate, but no data are presented with this designation. It is
well known that infusion rate can have a critical impact on the reinforcing effects of a
drug, with slower infusions producing lesser reinforcing effects. Thus, comparisons
between methohexital given at an infusion rate 5 times faster than that of pregabalin are
not valid.

In the summary of abuse potential data, but not in the study summary itself, the Sponsor
states that "positive reinforcement" was defined as 10 inj/day for 7 days. This definition
is not included in the study summary itself. This may be because the 3.2 mg/kg/infusion
produced 14 injections/day and 10 mg/kg/infusion produced 11 injections/day, indicating
that these two doses produced positive reinforcement.

The Sponsor notes that evaluation of individual rate data (not submitted) showed that
monkeys had a high rate of self-administration of pregabalin during initial exposure to
the drug that then declined with further drug availability.

In the conclusion, the Sponsor states that pregabalin produces an inverted U-shaped
curve, which is characteristic of drugs of abuse. But the Sponsor interprets this as
meaningless since the methohexital self-administration was greater than pregabalin.
However, comparisons are not valid between the drug conditions because of the
difference in infusion rates. It is clear from the data in this study that pregabalin is self-
administered by monkeys, at a rate greater than the 10 injections/day criteria for
reinforcement, indicating that pregabalin may have abuse potential.

The Sponsor concludes that pregabalin has "no reinforcing effects" at doses of 1-18
mg/kg/infusion. However, individual and mean data show that animals do self-
administer pregabalin above the 10 injections/day criteria set for a reinforcing response
during the first week. The Sponsor emphasizes that this self-administration diminished
the following week, but this does not obviate the interpretation that pregabalin is
reinforcing during initial exposure to the drug.

Given that there is no information submitted in the NDA concerning the development of
tolerance with pregabalin, it is possible that tolerance to pregabalin can account for the
reduction in self-administration during the second week of access to the drug.

| | methohexital | saline | | pregabalin (mg/kg) | | |
	0.1 mg/kg		1	3.2	10	18
Mean	65 + 9	7 + 1	5 + 1	14 + 2	11 + 3	7 + 3

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Self-Administration (Pregabalin vs. Pentobarbital)

Monkeys (n = 4) who had previously been trained to self-administer drugs of abuse, including pentobarbital, were used in the study. Monkeys first received IV saline, and when daily injections were 10 or less, the animals received IV injections of pentobarbital (1.0 mg/kg/injection) until the daily intake was 16 injections per day. Saline was then offered for several days until daily injections returned to 10 or less. Monkeys were then offered pregabalin at 1, 2, 4, and 8 mg/kg/injection. Note that these doses are less than the doses of pregabalin (1.0, 3.2, 10 and 18 mg/kg/injection) used in the self-administration study with methohexital. No information is provided to justify the doses of drugs selected, nor why these differ from the methohexital study. All experimental sessions lasted for 24 hr, compared to the 130 min (2 hr, 10 min) sessions used in the methohexital study. Positive reinforcement was defined as 10 injections/day or greater.

Pentobarbital, pregabalin and saline were infused at a rate of 1 ml/23 sec, with an injection volume of 0.25 ml/kg. No information is provided about the weight of each animal. Thus, it is likely that each monkey received session drugs under varying infusion rates that could be up to or greater than one minute in duration. It is well known that infusion rate can have a critical impact on the reinforcing effects of a drug, with slower infusions producing lesser reinforcing effects. Thus, although there is equivalence in infusion rate between drug conditions for each animal, comparisons of group means from each drug condition are not valid.

The Sponsor concludes that pregabalin has "no reinforcing effects" at doses of 1-8 mg/kg/infusion. However, individual and mean data show that animals do self-administer pregabalin above the 10 injections/day criteria set for a reinforcing response during the first week. The Sponsor emphasizes that this self-administration diminished the following week, but this does not obviate the interpretation that pregabalin is reinforcing during initial exposure to the drug. Given that there is no information submitted in the NDA concerning the development of tolerance with pregabalin, it is possible that tolerance to pregabalin can account for the reduction in self-administration during the second week of access to the drug.

Conditioned place preference

Study 1

Rats were tested to see if morphine (0.1, 0.3, 1.0, 2.0 and 3.0 mg/kg, s.c.) or pregabalin (3, 10, 30 mg/kg, p.o.) induced a conditioned place preference (CPP). The results suggest that morphine induced CPP at all but the lowest dose, but that no dose of pregabalin induced a CPP.

Study 2

Pregabalin was tested for its ability to block the development of CPP with morphine. Rats received either pregabalin (1, 3, 10, 30 mg/kg, p.o.) or saline 60 min prior to administration of a submaximal dose of morphine (0.75 mg/kg, s.c.). The 10 mg/kg dose of pregabalin was found to block the development of CPP from morphine.

Study 3

CPP was established in rats with morphine. Pregabalin (10 mg/kg, p.o.) was given 60 min prior to testing to see if it would influence morphine-induced CPP. Pregabalin blocked the maintenance of morphine CPP. Rats were re-tested without further pregabalin administration on the following two days, but morphine CPP returned in the absence of further pregabalin administration.

There are many flaws in the CPP studies. The routes of administration are different between the two drug conditions. It is very unusual to use oral dosing with CPP, and its use makes comparison between the two drug conditions invalid since morphine was administered subcutaneously. The pretreatment time is not given in one study. The separation time between training sessions with drug or saline was only 5 hours. This may not be adequate, given that the behavioral effects of pregabalin were present in monkeys past the 5 hour mark.

Drug discrimination

Study 1

Monkeys (n = 4) were trained to discriminate 0.56 mg/kg midazolam (s.c., pretreatment time not given) under a stimulus-shock termination schedule. Challenge sessions with pregabalin (30, 100, 180, 300 mg/kg) were conducted with the drug administered orally 4 hr prior to placement in the test cage. All doses of pregabalin were indistinguishable from saline (ie: percent responding on the midazolam lever of less than 7%).

Study 2

Monkeys (n = 3) were treated daily with a combination of diazepam (5.6 mg/kg, p.o., administered 3 hr prior to session) and flumazenil (0.32 mg/kg, s.c., administered immediately prior to session). Thus, the discriminative cue is the effect of flumazenil in producing a benzodiazepine withdrawal syndrome. Monkeys were then tested with pregabalin (30, 100, 180 mg/kg, p.o., administered 4 hr prior to the session) and flumazenil (0.00032 - 0.32 mg/kg, s.c., administered immediately prior to session).

A dose of 0.01 and 0.032 mg/kg of flumazenil in placebo-treated monkeys produced full generalization to the flumazenil cue in diazepam-dependent monkeys. No data are shown from the diazepam/flumazenil trials for comparison. The results with pregabalin-treated

animals showed that pregabalin/flumazenil could produce full generalization to the flumazenil cue, although the dose of flumazenil necessary to produce this effect was larger than that at the 300 mg dose of pregabalin compared to placebo treatment. This indicates that pregabalin does not prevent the development of benzodiazepine withdrawal.

The Sponsor interprets this as indicating that "pregabalin might attenuate some aspects of benzodiazepine withdrawal" but the data do not support this contention.

There are many flaws in the drug discrimination studies. No data are shown from the diazepam/flumazenil trials for comparison. The routes of administration are different in some studies, and the pretreatment times are different in other studies.

Study 3

A published paper was submitted from a study where rats were trained to discriminate morphine (30 mg/kg, s.c., 30 min pretreatment). Gabapentin (1-100 mg/kg, s.c.) did not generalize to morphine and instead generalized to the saline cue. No data are shown in the paper to support this.

Spontaneous behavior in monkeys

Monkeys (n = 6) received IV pregabalin at doses of 4, 16, 32 and 64 mg/kg. The volume of injection was 0.24, 0.8, 1.6, and 3.2 ml/kg (respectively). Since the infusion rate was 1 ml/23 sec, the speed of injection for the lowest dose was significantly different from that of the highest dose. Animals were observed for 5 hr after pregabalin administration.

The Sponsor notes that animals manifested gross behavioral signs 5 hr after administration of the drug, so for the two final sessions, animals were observed for 24 hr. Since doses of the drug were administered on a randomized basis, not all animals were observed for 24 hr for each dose. Raters were blind to the drug condition in each session.

No gross behavioral changes were seen at 4 mg/kg and retching was seen in one monkey at 16 mg/kg. Two monkeys exhibited tremors at 32 mg/kg. At 64 mg/kg, 3 of 4 monkeys showed slowed motion, ataxia and 2 of 4 animals showed hypoactivity, asthenic posture, frequent drinking, sitting position with fixed eyeball movement, grasping movements. Some of these behaviors were present after 5 hr.

Locomotor behavior in rats

Pregabalin (3, 10, 30 mg/kg, i.p.), gabapentin (10, 30, 56, 100 mg/kg, i.p.) or saline was administered to rats 45 min prior to administration of cocaine (10 mg/kg, i.p.), amphetamine (0.5 mg/kg, i.p.) or saline. Locomotor behavior was measured in a n Omnitech chamber.

The locomotion induced by cocaine was blocked by all doses (10-100 mg/kg) of gabapentin but only at the 30 mg/kg dose of pregabalin. The locomotion induced by amphetamine was blocked by the highest doses of gabapentin (56 mg/kg) and pregabalin (30 mg/kg).

Physical Dependence / Withdrawal

Rats received pregabalin (100-400 mg/kg, i.p.) or pentobarbital (up to 900 mg/kg, i.p.) for 12 days. The doses chosen were based on minimum effective dose 40 times that for anxiolysis/analgesia.

The withdrawal signs that were counted included changes in body weight and hyperexcitability. Weight loss during drug discontinuation showed a 3% loss in placebo group, a 14% loss in the pentobarbital group, at a 10-11% loss in the pregabalin group.

Another measure was "cumulative signs in 96 hr", with the vehicle group showing a score of 1, the pentobarbital group at score of 14, and the pregabalin group a score of 4-6.

These data show a mild withdrawal syndrome following discontinuation of pregabalin.