

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-397**
21-423
21-424

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-397 (capsules)/ 21-423 (tablets)/ 21-424 (solution)

Review number: 1

Sequence number/date/type of submission: NDA 21-~~937~~³⁹⁷/August 7, 2001/Orig. NDA submission
NDA 21-~~937~~/December 20, 2001/BZ
NDA 21-~~937~~/January 14, 2002/BZ
NDA 21-~~937~~/February 11, 2002/BZ
NDA 21-423/August 14, 2001/Orig. NDA submission
NDA 21-424/August 14, 2001/Orig. NDA submission

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Parke Davis Pharmaceuticals Lmted.

Manufacturer for drug substance: Parke Davis Pharmaceuticals Lmted.

Reviewer name: Timothy J. McGovern, Ph.D.

Division name: Anesthetic, Critical Care and Addiction Drug Products

HFD #: 170

Review completion date: May 21, 2002

Drug:

Trade name: Neurontin

Generic name (list alphabetically): gabapentin

Code name: CI-945

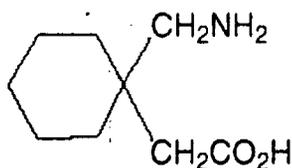
Chemical name: 1-(aminomethyl) cyclohexane acetic acid

CAS registry number: NA

Mole file number: NA

Molecular formula/molecular weight: C₉H₁₇NO₂/171.24

Structure:



Relevant INDs/NDAs/DMFs: NDAs 20-235, 20-882, 21-129, 21-216 for the treatment of epilepsy; IND 28,454

Drug class: derivative of inhibitory neurotransmitter gamma-aminobutyric acid (GABA)

Indication: _____

Executive Summary

I. Recommendations

- A. Recommendation on Approvability: These applications are approvable from a non-clinical perspective with the suggested label modifications (see section IX).
- B. Recommendation for Nonclinical Studies: None.
- C. Recommendations on Labeling: The sponsor's proposed labeling related to non-clinical information is acceptable with a minor modification in the "Pregnancy" section. The sections "Carcinogenesis, Mutagenesis, Impairment of Fertility", and "OVERDOSAGE" are identical to those previously approved. Reviewers in HFD-120 suggested that some wording in the "Pregnancy" section be updated to reflect current standard language for this section. New information in the section "CLINICAL PHARMACOLOGY: Mechanism of Action" that discusses the efficacy of gabapentin in relation to the proposed indication is supported by studies submitted by the sponsor or referenced literature publications. Minor modifications were incorporated. See section IX for specific details.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Acute toxicity studies at doses up to 8000 mg/kg in rats and mice and up to 5000 mg/kg in monkeys produced no deaths; observed clinical signs included ataxia, sedation, reduced grip strength, irregular or labored breathing, mild diarrhea, high stepping gait, cringing or creeping posture, and ptosis. Repeat dose studies (oral) of up to one-year duration were performed in rats and monkeys, up to 6 months in dogs and 3 months in mice. The kidney and liver were identified as target organs of toxicity in the rat. Findings included hyaline droplets in proximal tubules and higher kidney-to-brain weight ratios, glomerulonephrosis and granular cysts in outer medulla, increased liver weight, reversible hepatocellular cytomegaly, and foci of hepatocyte necrosis with an associated increase in liver enzymes. It was concluded that the human kidney would not be similarly affected. The liver was also identified as a target organ in dogs; findings included mild increases in ALAT and AP, which were correlated with hepatocellular hydropic enlargement, liver weight increase, kupfer cell granulomas accompanied by siderosis and periportal infiltration of lymphocytes and histiocytes. Liver findings were more severe in dogs than in rats due possibly to a unique metabolite produced by dogs. No significant toxicity was observed in monkeys or mice at the highest doses tested (500 mg/kg and 2000 mg/kg, respectively).

B. Pharmacologic Activity

Gabapentin penetrates the blood brain barrier but does not interact with GABA receptors, nor is it converted metabolically to GABA or a GABA antagonist. Its molecular site of

action has not been determined. Studies with radiolabeled gabapentin reveal a specific binding site in brain but not in other tissues. In vitro and in vivo biochemical studies indicate that gabapentin caused no significant changes in GABA concentrations in whole brain or synaptosomal fractions, electrically induced release of GABA or glutamate from brain slices, high affinity GABA uptake, activity of the GABA degradative enzyme GABA transaminase, prostaglandin and thromboxane production caused by seizures in rat brain, calcium influx into cultured neocortical neurons caused by activation of NMDA-type glutamate receptors. In vivo, gabapentin increases GABA turnover in the substantia nigra, a brain region involved in seizure activity. It also decreases inhibition of electrically-evoked potentials in the hippocampus, suggesting an interaction with the GABA system in that structure. In vitro, gabapentin decreases electrically-stimulated overflow of dopamine and serotonin and decreases glutamine content. Gabapentin also modulates responses mediated by NMDA-type glutamate receptors, but modulation is by a different mechanism than those of competitive, MK-801-like or glycine-site NMDA antagonists. Gabapentin demonstrated activity in various anticonvulsant models in rats and mice.

In more recent studies, gabapentin has demonstrated inactivity at various receptor sites including GABA_b, monoamine neuronal sites and cannabinoid receptors. Gabapentin reduced the hyperalgesia response in various animal models including the late phase response in the formalin footpad test and the carageenan paw pressure test. No effects were noted in the rat tail flick test and acetic acid writhing test, as well as the early phase of the formalin footpad test, indicating the gabapentin is not useful for treatment of rapid-onset acute pain. In addition, gabapentin reduced hyperalgesia and allodynia in numerous rodent models of neuropathic pain including nerve ligation. Gabapentin had no to mild effects on locomotor activity in rats and mice. Gabapentin prevented development of conditioned place preference to morphine and reduced cocaine- and amphetamine-induced increased locomotor activity. In addition, gabapentin showed inconsistent effects related to modulation of voltage gated channels, showing no effects in some studies but inhibiting calcium conductance in others. Gabapentin inhibited the release of norepinephrine, dopamine and 5-HT from brain slices under stimulated conditions.

C. Nonclinical Safety Issues Relevant to Clinical Use: There are no non-clinical safety issues relevant to clinical use.

III. Administrative

A. Reviewer signature: Timothy J. McGovern, Ph.D.

B. Supervisor signature: -- Concurrence - Timothy J. McGovern, Ph.D.

C. cc: list:

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:..... 1

II. SAFETY PHARMACOLOGY:..... 7

III. PHARMACOKINETICS/TOXICOKINETICS: 8

IV. GENERAL TOXICOLOGY:..... 9

V. GENETIC TOXICOLOGY:..... 10

VI. CARCINOGENICITY: 10

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:..... 11

VIII. SPECIAL TOXICOLOGY STUDIES: 11

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:..... 12

X. APPENDIX/ATTACHMENTS: 14

**APPEARS THIS WAY
ON ORIGINAL**

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Numerous pharmacology studies were performed and reviewed under NDA 20-235 and are summarized below under "Pharmacology summary". Additional studies were also performed to provide non-clinical evidence of activity related to neuropathic pain.

Primary pharmacodynamics: None.

Mechanism of action: The mechanism of action of gabapentin has not been fully elucidated. In recent investigations, gabapentin has demonstrated inactivity at various receptor sites including GABA_b, monoamine neuronal sites and cannabinoid receptors (Table 1).

Table 1: Receptor binding studies.

Study No. /Authors	Test model	Test result
740-03548	Cannabinoid receptor binding	Gabapentin exhibited no activity up to 1 mM for the human CB ₁ and rat cortex CB receptors
740-03547	GABA _b receptor binding	Gabapentin exhibited no affinity up to 1 mM for GABA _b receptors at both human cloned membrane receptors and "buffy coat" rat cortex membranes.
Ng et al, 2000	GABA _b receptor binding	Agonist activity at the GABA _b gb1a-gb2 heterodimer coupled to Kir 3.1/3.2 inwardly rectifying K ⁺ channels in <i>Xenopus laevis</i> oocytes. Practically inactive at the human gb1b-gb2 heterodimer.
740-03545	Monoamine neuronal reuptake affinities	Gabapentin exhibited no affinity up to 1 mM for inhibition of dopamine, norepinephrine and 5-HT neuronal reuptake sites.

Drug activity related to proposed indication: Gabapentin reduced the hyperalgesia response in various animal models (Table 2) including the late phase response in the formalin footpad test and the carageenan paw pressure test. However, no effects were noted in the rat tail flick test and acetic acid writhing test, as well as the early phase of the formalin footpad test, indicating the gabapentin is not useful for treatment of rapid-onset acute pain.

**APPEARS THIS WAY
ON ORIGINAL**

Table 2: Effects of gabapentin in animal models of analgesia

Study No. /Authors	Test model	Test result
4188-0412	Rat tail flick	Gabapentin showed no analgesic effect at 250 mg/kg i.g., but increased the analgesic effect of morphine (2.5 mg/kg, sc) when administered 70 min. prior to morphine.
740-03479	Mouse acetic acid-induced writhing test and formalin foot pad test	No activity in acetic acid-induced writhing test (30-300 mg/kg, po). No effect in early phase of formalin foot pad test; inhibition of late phase response (ED ₅₀ =113 mg/kg). Sedation noted at doses of 100 or 300 mg/kg.
770-0297	Rat formalin foot pad test Carageenan induced thermal hyperalgesia	Dose-dependent reduction of late phase formalin response (10-300 mg/kg, sc); minimum effective dose (MED) = 30 mg/kg. Naloxone did not affect response. Antagonism of the carageenan thermal response and blocking of mechanical hyperalgesia; MED = 30 and 10 mg/kg, sc, respectively. Intrathecal gabapentin (1-100 µg/animal) blocked mechanical hyperalgesia; MED of 100 µg Doses of 3-300 mg/kg failed to show antinociceptive action in transient pain models.
Carlton and Zhou, 1997	Rat formalin foot pad test	No effect on early phase response at 6 or 60 µg, intraplantar, but reduced response at 600 µg. All doses reduced late phase flinching response but not lifting/licking response.
Cesena and Calcutt, 1999	Rat (control and diabetic) formalin (5 or 0.5%) foot pad test	Suppressed flinching in early and late phase to 5% formalin at 50 mg/kg, ip in control and diabetic rats.
Dixit, Bhargava and Kaur, 1999	Rat formalin (5%) foot pad test	No effect at 10 mg/kg sc; 30 and 90 mg/kg produced dose-dependent reduction in pain score. 90 mg/kg gabapentin produced similar results as 3 mg/kg morphine, sc.
Shimoyama, Shimoyama, Davis, Inturrisi, Elliot, 1996	Rat formalin (5%) foot pad test	Dose-dependent (6-200 µg/rat, intrathecal) reduction up to 73-89% of the late phase response. No effect on tail flick response.
Yoon and Yaksh, 1999	Rat formalin (5%) foot pad test	Reduction of late phase response following intrathecal administration of 300 µg; no effect on early phase.
Kaneko et al, 1999	Rat formalin (0.25-2.5%) foot pad test	Dose-dependent (30 or 100 µg, intrathecal) decrease in late phase response; no effect on early phase. Pretreatment with 100 µg gabapentin did not decrease Fos-LI neurons evoked by 0.5% formalin; same dose decreased numbers of Fos-LI neurons in laminae I-II and VII-X in rats receiving 1.25% formalin, uniformly decreased numbers of Fos-LI neurons in all laminae of rats receiving 2.5%.
Boyce et al, 1998	Rat carageenan paw pressure test	Inhibition of carageenan-induced hyperalgesia; ID ₅₀ =5 mg/kg, po.
770-0296	Rat surgical pain model	Gabapentin dose-dependently prevented thermal hyperalgesia and tactile allodynia (MED = 30 and 10 mg/kg, SC, respectively) when administered 1 hour before surgery. 30 mg/kg completely inhibited both responses for 3 days after surgery.
Cheng et al, 2000	Rat surgical pain model	Gabapentin dose-dependently prevented mechanical allodynia (10-100 µg, intrathecal; ED ₅₀ =51 µg) when administered 2 hours after surgery. Synergistic effect with clonidine (ED ₅₀ = 9 µg).
Partridge et al, 1998	Rat Substance P-induced thermal hyperalgesia	Dose-dependent reduction of thermal hyperalgesia following IP (10-300 mg/kg, 60 min prior to Sub P) or intrathecal (3-300 µg, 15 min prior to Sub P) administration; ED ₅₀ =60 mg/kg IP or 50 µg IT.

Jun and Yaksh, 1998	Rat thermal footpad injury hyperalgesia	Reduced response following intrathecal pretreatment (100 or 300 μ g (ED10= 192 μ g). No change in thermal escape latency with non-injured footpad.
Jones and Sorkin, 1998	Rat thermal footpad injury tactile allodynia	Anti-allodynic effect of gabapentin (0-300 mg/kg, ip) occurred within 30-60 min. MED was 100 mg/kg; 300 mg/kg completely inhibited the injury-induced decrease in mechanical withdrawal time.
760-00177	Streptococcal Cell wall induced reactivation arthritis in rats	Gabapentin (10-100 mg/kg, oral) reduced edema but not neutrophil accumulation. Reduced thermal hyperalgesia in the arthritic limb.

In addition, gabapentin reduced hyperalgesia and allodynia in numerous rodent models of neuropathic pain including nerve ligation (Table 3).

**APPEARS THIS WAY
ON ORIGINAL**

Table 3: Animal models of neuropathic pain.

Study No. /Authors	Test model	Test result
770-0295	Streptozocin model of neuropathic pain in rats	Reduced static allodynia following streptozocin treatment at 10-100 mg/kg, po; MED =10 mg/kg. Dose-dependently blocked maintenance of dynamic allodynia; MED = 30 mg/kg. Intrathecal administration (1-100 µg) blocked maintenance of static and dynamic allodynia (MEDs = 10 and 1 µg, respectively); intraplantar administration (1-100 µg) had no effect.
Gillin and Sorkin, 1997	Chemotherapy model of neuropathic pain in rats	Reduced anti-GD2-gangliosides-induced tactile allodynia at doses of 30 and 100 mg/kg, IV; no effect at 10 mg/kg or less. Maximal percent analgesic effect was 76% and 93% at 30 and 100 mg/kg.
Takasaki et al, 2001	Acute herpes simplex infection mouse model	Reduced herpes simplex-induced tactile allodynia; MED of 10 mg/kg po, complete reduction at 100 mg/kg. Hyperalgesia also reduced by gabapentin. No effect noted in uninfected paw. Similar findings with intrathecal administration (30 and 100 µg). Intraplantar, intracisternal, and intracerebroventricular administration (1-100 µg) had no effect.
Hulsebosch et al, 2000	Spinal cord damage in rats	IP doses of 10 or 30 mg/kg reduced allodynia; 30 mg/kg completely prevented pain-related vocalization in response to blunt probing.
Hao et al, 2000	Spinal cord damage in rats	Repeated doses of 100 mg/kg IP reduced cold allodynia but produced sedation and motor impairments. 30 mg/kg had no effect after first administration but produced gradually increasing anti-allodynic effect with repeated dosing.
Abdi et al, 1998	Nerve ligation in rats	50 mg/kg, IP increased threshold for mechanical allodynia within 30 min and for up to 1 hour but did not influence the rate of continuing discharges of injured afferent fibers.
Pan et al, 1998	Nerve ligation in rats	Cumulative doses of 30-90 mg/kg, IV attenuated allodynia and inhibited ectopic discharge activity of 15 injured sciatic afferent nerve fibers. No effect on normal afferent fibers.
Xiao and Bennett, 1996	Nerve ligation in rats	10-75 mg/kg IP reduced heat hyperalgesia and mechanoallodynia in dose-related manner up to 4 hours; no effect on mechanohyperalgesia. Intrathecal administration (7.5-75 µg/kg) produced reduced heat hyperalgesia for up to 4 hr. IT injections up to 150 µg failed to affect mechanohyperalgesia where reduced heat hyperalgesia and mechanoallodynia were noted
Chen et al, 2000	Nerve ligation in rats	10-100 µg, intrathecal, produced dose-dependent increase in withdrawal threshold to mechanical stimulation; ED ₅₀ =45.9 µg; peak effect at 45 min. Strong synergistic interaction with 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX).
Hunter et al, 1997	Nerve ligation in rats	30-300 mg/kg, IP, reversed cold allodynia (ED ₅₀ =103 mg/kg) 1 hour post-dose; reversed tactile allodynia (ED ₅₀ =34 mg/kg). Increased tail flick response latency by 20%. Demonstrated dose-dependent anti-convulsant effect with ED ₅₀ =17.3 mg/kg in maximal electroshock seizure test.
LaBuda and Fuchs, 2000	Nerve ligation in rats	Decreased mechanical hyperalgesia at 10-90 mg/kg, SC, and attenuated escape/avoidance behavior.
Hwang and Yaksh, 1997	Nerve ligation in rats	10-1000 µg, subarachnoid injection, increased tactile threshold within 30 minutes with max. response to 100 and 300 µg.

Secondary pharmacodynamics: Gabapentin had no to mild effects on locomotor activity in rats and mice (Table 4).

Table 4: Gabapentin effects on locomotor activity.

Study No. /Authors	Test model	Test result
740-03472	Locomotor activity and inverted screen test in rats and mice	Oral administration of 3-300 mg/kg had no effect on locomotor activity or screen fall off.
770-01317	Beam walking test in rats	Increased time to cross beam and number of foot slips (MED=100 mg/kg, oral). 10-20% fell of beam at 300 mg/kg.

Gabapentin prevented development of conditioned place preference to morphine and reduced cocaine- and amphetamine-induced increased locomotor activity (Table 5).

Table 5: Gabapentin effects related to addiction.

Study No. /Authors	Test model	Test result
770-00320	Rats; Drug discrimination/Place preference	Prevented development of conditioned place preference to morphine following 100 mg/kg SC dose.
740-03441	Rats; stimulant-induced locomotor activity	Oral dosing (10-100 mg/kg) reduced cocaine- or amphetamine-induced increase in locomotor activity

In addition, gabapentin showed inconsistent effects related to modulation of voltage gated channels (Table 6), showing no effects in some studies but inhibiting calcium conductance in others.

Table 6: Influence of gabapentin on voltage gated channels.

Study No. /Authors	Test model	Test result
Stefani et al, 2001	Ligand- and voltage gated currents in isolated cortical neurons	Gabapentin (50 and 150 μ M) did not modify glutamate currents, produced slight reduction of GABA responses, negligible inhibition of sodium, but consistent inhibition of high voltage-activated calcium conductance.
740-03554	Voltage gated currents in isolated rat neocortex	Gabapentin (100 μ M) had no modulatory effect on calcium channels
Stefani et al, 1998	Voltage gated currents in isolated rat central neurons	Up to 34% inhibition of calcium currents in neurons isolated from pyramidal neocortical cells (IC ₅₀ =4 μ M).
Alden and Garcia, 2000	Neuronal and muscle calcium channel activity	In dorsal root ganglia, gabapentin reduced whole cell calcium current amplitude at positive membrane potentials but did not reduce low-voltage activated calcium current. In skeletal myotubules, gabapentin attenuated calcium current at positive membrane potentials but had no effect on cardiac myocytes.

Gabapentin inhibited the release of norepinephrine, dopamine and 5-HT from brain slices under stimulated conditions (Table 7).

Table 7: Gabapentin influence on neuronal amine release.

Study No. /Authors	Test model	Test result
740-03489	Rat neocortical and striatal slices	Gabapentin decreased K ⁺ -evoked neocortical [³ H]-norepinephrine release in a concentration dependent manner; IC ₅₀ =8.9 μM. Electrically-evoked [³ H]-dopamine release from striatal slices was inhibited (23%) by 100 μM gabapentin; no effect on K ⁺ -evoked release.
Pugsley et al, 1998	Rat hippocampal slices	Gabapentin 30-100 mg/kg, IP) inhibited DAP-stimulated norepinephrine, dopamine and 5-HT neurons. No effect on amine synthesis when administered alone.

Pharmacology summary: Gabapentin penetrates the blood brain barrier but does not interact with GABA receptors, nor is it converted metabolically to GABA or a GABA antagonist. Its molecular site of action has not been determined. Studies with radiolabeled gabapentin reveal a specific binding site in brain but not in other tissues. Specific binding activity is highest in the superficial layers of the neocortex and dendritic layers of the hippocampus, with low levels of binding in white matter and brainstem. Valproate, phenytoin, carbamazepine, phenobarbital, diazepam, ethosuximide, glutamate, glycine or glutamine do not prevent gabapentin binding. In vitro and in vivo biochemical studies indicate that gabapentin caused no significant changes in many parameters including GABA concentrations in whole brain or synaptosomal fractions, electrically induced release of GABA or glutamate from brain slices, high affinity GABA uptake, activity of the GABA degradative enzyme GABA transaminase, prostaglandin and thromboxane production caused by seizures in rat brain, calcium influx into cultured neocortical neurons caused by activation of NMDA-type glutamate receptors, and receptor binding at a wide variety of commonly-studies drug or neurotransmitter receptors and voltage-activated ion channels of brain tissue including GABA, glutamate glycine receptors of several types. In vivo, gabapentin increases GABA turnover in the substantia nigra, a brain region involved in seizure activity. It also decreases inhibition of electrically-evoked potentials in the hippocampus, suggesting an interaction with the GABA system in that structure. In vitro, gabapentin decreases electrically-stimulated overflow of dopamine and serotonin and decreases glutamine content. Gabapentin also modulates responses mediated by NMDA-type glutamate receptors, but modulation is by a different mechanism than those of competitive, MK-801-like or glycine-site NMDA antagonists. Gabapentin demonstrated activity in various anticonvulsant models in rats and mice.

No analgesic efficacy in the phenylquinone writhing and heat-induced tail flick tests was demonstrated up to 250 mg/kg po. There was slight evidence for an additive effect to tilidine in the writhing test and to morphine in the tail flick test.

In more recent studies, gabapentin has demonstrated inactivity at various receptor sites including GABA_b, monoamine neuronal sites and cannabinoid receptors. Gabapentin reduced the hyperalgesia response in various animal models including the late phase response in the formalin footpad test and the carageenan paw pressure test. No effects were noted in the rat tail flick test and acetic acid writhing test, as well as the early phase of the formalin footpad test, indicating the gabapentin is not useful for treatment of rapid-onset acute pain. In addition, gabapentin reduced hyperalgesia and allodynia in numerous rodent models of neuropathic pain including nerve ligation. Gabapentin had no to mild effects on locomotor activity in rats and mice. Gabapentin

prevented development of conditioned place preference to morphine and reduced cocaine- and amphetamine-induced increased locomotor activity. In addition, gabapentin showed inconsistent effects related to modulation of voltage gated channels, showing no effects in some studies but inhibiting calcium conductance in others. Gabapentin inhibited the release of norepinephrine, dopamine and 5-HT from brain slices under stimulated conditions.

Pharmacology conclusions: The mechanism of action has not been fully elucidated and receptor binding studies show limited activity at the various receptor types evaluated. Studies with radiolabeled gabapentin reveal a specific binding site in brain but not in other tissues. Gabapentin reduced the hyperalgesia response in various animal models including the late phase response in the formalin footpad test and the carageenan paw pressure test and reduced hyperalgesia and allodynia in numerous rodent models of neuropathic pain including nerve ligation.

II. SAFETY PHARMACOLOGY:

Safety pharmacology studies were performed and reviewed under NDA 20-235. Results are summarized below.

Safety pharmacology summary: The most prominent behavioral symptoms of gabapentin in conscious rodents were mild ataxia and impairment of motor function, delayed righting response, decreased spontaneous locomotor activity, and decreased abdominal muscle tone at doses in the range of 38-400 mg/kg PO or IP. Gabapentin did not reduce aggressiveness of fighting mice at a dose of 400 mg/kg ip and did not alter open-field behavior of mice at 10-1280 mg/kg po. Gabapentin increased the duration of catalepsy induced by halperidol at doses of 1 mg/kg and above and increased sleeping time from hexobarbital (3x longer at 400 mg/kg PO). Decreased breathing, exophthalmous, and ptosis were observed at doses of 800-1000 mg/kg. Reflexes in anesthetized cats were not affected by IV doses of 1-16 mg/kg. Gabapentin produced minor effects in anesthetized dogs following IV administration. Plasma levels in dogs that were 25x the therapeutic levels in monkeys produced mild changes (< 20% from baseline) in BP, HR, and dP/dt. A solution of 100 μ M gabapentin had no effect on HR, coronary flow, dP/dtmax or left ventricular pressure in an isolated, perfused guinea pig heart model. 1000 or 2000 μ M gabapentin had no effect on platelet aggregation induced by collagen or adenosine triphosphate. No CV effects were performed in rats or cats.

Safety pharmacology conclusions: Studies with gabapentin demonstrate the potential for behavioral effects. No significant cardiovascular effects were noted.

APPEARS THIS WAY
ON ORIGINAL

III. PHARMACOKINETICS/TOXICOKINETICS:

Kinetic studies in mice, rats, dogs and monkeys were performed and reviewed under NDA 20-235. Results are summarized below.

PK/TK summary: The pharmacokinetics are not gender specific. The maximum plasma concentration of gabapentin was reached within 2 hours in all species tested. Linear dose proportionality was not achieved due to an apparent lack of absorption at high doses (~ 100 mg/kg or more). Repeated dosing did not affect steady-state plasma levels. The elimination half-life is 1.5-3 hours in the species studied. The table below summarizes comparative kinetics across species after 14 days of dosing:

Species	Dose (mg/kg)	Cmax (µg/ml)	AUC (0-24)	T1/2 (hr)
Rat	2000	110	2070	nc
Dog	2000	197	1380	3
Monkey	500	40	346	10.5
Human	36	8.5	159	6

The drug was rapidly absorbed. Oral bioavailability was 40% in monkeys and 80% in dogs and rats. Trace amounts of gabapentin were found in brains and spinal cords of rats given labeled drug. The blood/brain ratios were 0.72 and 0.93 in rats and 0.35 to 0.87 in monkeys. In monkeys, CSF levels were 10-20% of plasma levels at 12 hours after a dose of 24 mg/kg. The pancreas of mice and rats, but not monkeys, was found to concentrate gabapentin. Levels in rat pancreas were about 6x higher than in rat blood. Protein binding is approximately 3% at plasma levels of 1-10 µg/ml in humans, rats and monkeys. Radioactivity was found in fetal tissue after dosing of pregnant rats, and the levels were slightly higher than in the mothers, although clearance was just as rapid from fetuses as from dams. Gabapentin is excreted in rat and monkey urine in an essentially unchanged state. Less than 2% is recovered in a form that is not identical to the parent compound, although dogs form N-methylgabapentin, which comprises 35% of the radioactivity excreted in urine. No other metabolites have been observed in mice, rats, dogs or monkeys. Excretion is largely renal in all species tested. The bile is not a pathway of elimination and radioactivity detected in feces was unchanged indicating a lack of absorption from the digestive tract. Intravenous dosing in dogs and rats results in >99% elimination in urine.

PK/TK conclusions: Gabapentin is rapidly absorbed with an oral bioavailability of 40% in monkeys and 80% in rats and dogs. The drug is concentrated in the pancreas of rats and mice but not monkeys. The compound is not highly metabolized; dogs form N-methylgabapentin, which comprises 35% of the radioactivity excreted in urine. Drug was distributed to the fetus following dosing of pregnant rats. Excretion is primarily through the urine.

APPEARS THIS WAY
ON ORIGINAL

IV. GENERAL TOXICOLOGY:

The Division of Neuropharmacologic Drug Products reviewed general toxicology studies assessing gabapentin during the development program for NDA 20-235.

Toxicology summary: Acute toxicity studies were performed in rats, mice and monkeys. Doses up to 8000 mg/kg in rats and mice and up to 5000 mg/kg in monkeys produced no deaths. Observed clinical signs included ataxia, sedation, reduced grip strength, irregular or labored breathing, mild diarrhea, high stepping gait, cringing or creeping posture, and ptosis.

Seven repeat-dose studies in rats up to one-year duration were performed. In a 4-week study, only soft feces were noted at the high dose of 900 mg/kg. The liver and kidney were identified as target organs in males in a 7-week study. Doses of 1000 and 2000 mg/kg resulted in hyaline droplets in proximal tubules and higher kidney-to-brain weight ratios. Similar findings were observed in a 13-week study at doses up to 3000 mg/kg. Increased liver weight was also noted in high-dose animals. The kidney findings were reversible in the 13-week study. A six-month study also identified kidney toxicity in males as evidenced by a reversible, dose-related, increased severity of hyaline droplet change in proximal renal tubules at 300 and 1500 mg/kg. An increased incidence of non-reversible glomerulonephrosis and granular cysts in outer medulla were also noted in males at 1500 mg/kg. A one-year study (up to 2000 mg/kg) again identified the kidney and liver as target organs with similar markers as identified previously. Similar kidney toxicity in hydrocarbon neuropathy could be due to inhibition of the hydrolysis of resorbed α -2 μ -globulin, a male rat specific protein. Whether a similar mechanism accounts for gabapentin-induced toxicity is unknown. However, kidney tissue from rats treated with gabapentin for 14 days was associated with a larger peak co-eluted with exogenous α -2 μ -globulin compared to control animals. It was concluded that the human kidney would not be similarly affected. Reversible hepatocellular cytomegaly was found in high-dose males of the 6-month study. Foci of necrosis in hepatocytes of males were not reversible. There was an association of between high levels of liver enzymes and the more severe cases of necrosis.

Five-week and 26-week oral studies were performed in dogs. The no effect dose was 125 mg/kg. The high dose of 2000 mg/kg was associated with mild increases in ALAT and AP, which were correlated with hepatocellular hydropic enlargement, and liver weight increase. Kupfer cell granulomas were reported at all doses, accompanied by siderosis at the high dose and periportal infiltration of lymphocytes and histiocytes. Liver findings were more severe in dogs than in rats due possibly to a unique metabolite produced by dogs.

Four-week and 52-week oral (gavage) toxicity studies were performed in monkeys. No significant toxicity was observed at the highest dose of 500 mg/kg, the highest feasible dose due to saturation of absorption. Soft stool or diarrhea were observed at the high-dose. In addition, thyroid weights were slightly increased and pituitary weights were slightly decreased.

A 13-week oral study in mice produced no effects at doses up to 2000 mg/kg.

Toxicology conclusions: The target organs of toxicity in the rat were identified as the kidney and liver. In dogs, findings in the liver were more severe due possibly to a unique metabolite. No target organs were identified in monkeys or mice.

V. GENETIC TOXICOLOGY:

Genotoxicity studies assessing gabapentin were reviewed during the development program for NDA 20-235 by the Division of Neuropharmacologic Drug Products.

Genetic toxicology summary: Gabapentin did not demonstrate mutagenic or genotoxic potential in three in vitro and four in vivo assays. It was negative in the Ames test and the in vitro HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay; it was negative in the in vivo chromosomal aberration assay and in the in vivo micronucleus test in Chinese hamster bone marrow; it was negative in the in vivo mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

Genetic toxicology conclusions: Gabapentin did not exhibit any potential for mutagenic or clastogenic activity in the seven studies performed.

Labeling recommendations: The currently approved labeling describing the genotoxic potential of gabapentin is acceptable.

VI. CARCINOGENICITY:

Carcinogenicity studies assessing gabapentin were reviewed during the development program for NDA 20-235 by the Division of Neuropharmacologic Drug Products.

Carcinogenicity summary: Full 2-year dietary studies were conducted mice and rats. In mice, dosing was up to 2000 mg/kg (0.3 to 3 times the maximum recommended human dose (MRHD) of 3600 mg on a mg/m² basis. No drug-related toxicities or neoplastic changes were observed. In rats, dosing was up to 2000 mg/kg (0.9 to 7.4 times the MRHD on a mg/m² basis; ~ 10 times the MRHD on a plasma concentration basis). A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was observed in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg (peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day). The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive.

Carcinogenicity conclusions: No evidence of carcinogenic potential was observed in mice following dietary administration of up to 2000 mg/kg/day. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was observed in male rats following dietary dosing up to 2000 mg/kg/day. The no effect level for this finding was the mid-dose of 1000 mg/kg/day.

Recommendations for further analysis: None

Labeling Recommendations: The currently approved labeling for the carcinogenic potential of gabapentin is acceptable.

Addendum/appendix listing: Not applicable

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive toxicity studies assessing gabapentin were reviewed during the development program for NDA 20-235 by the Division of Neuropharmacologic Drug Products.

Reproductive and developmental toxicology summary: A fertility and general reproduction study in rats (0, 500, 1000, 2000 mg/kg), teratology studies in rats (0, 60, 300, 1500 mg/kg), rabbits (0, 60, 300, 1500 mg/kg) and mice (0, 500, 1000, 2000, 3000, 40000 mg/kg), and a perinatal and postnatal study (0, 500, 1000, 2000 mg/kg) in rats were performed with gabapentin. All studies included oral gavage administration. Maternal toxicity was not noted in rats and mice but dose-selection was considered to be acceptable due to saturation of absorption in rats and the maximum feasible dose was used in mice. Substantial toxicity was noted in dams at the high dose in the rabbit study. Gabapentin was fetotoxic in rodents as determined by underossification (bones in skull, vertebrae, forelimbs, hindlimbs) in mouse and rat studies at human therapeutic dose levels. Dilatation of the renal pelvis (hydronephrosis) and blockage of the ureter (hydroureter) were increased in rat pups of primarily high-dose groups, but seen in lower dose groups to some extent. An increase of post-implantation losses was also seen in all treated groups of the rabbit segment II study. Gabapentin was approved with a Pregnancy Category C classification.

Reproductive and developmental toxicology conclusions: Gabapentin has been shown to delayed ossification of several bones in mice and rats at 1-7 times the MRHD (mg/m²); an increased incidence of hydroureter and/or hydronephrosis in rats at 2-7 times the MRHD and an increased incidence of postimplantation fetal loss in rabbits at 0.3-7 times the MRHD.

Labeling recommendations: The currently approved labeling concerning the potential for reproductive toxicity is acceptable.

VIII. SPECIAL TOXICOLOGY STUDIES:

Special toxicology studies assessing gabapentin were reviewed during the development program for NDA 20-235 by the Division of Neuropharmacologic Drug Products.

Conclusions: Gabapentin hydrochloride, when mixed with canine or human plasma, caused precipitation that appeared to be pH dependent, with maximum precipitation occurring when the pH of the solution was ~ 4.5. Gabapentin had no effect on purified bovine pancreatic trypsin activity in vitro at concentrations ranging from 0.001 to 10 mg/ml. No reactions were observed in rabbits following intraarterial, IV or ocular administration. Following intramuscular administration, creatine phosphokinase was mildly to moderately elevated for at least 48 hours; gross and microscopic examination of muscle tissue was unremarkable. A number of anticonvulsants, including phenytoin, carbamazepine, phenobarbital and valproate, were less well tolerated when given in combination with gabapentin (400 mg/kg, i.g.) than when administered alone. The combination of gabapentin and clonazepam showed no difference in toxicity, while haloperidol was tolerated better when given with gabapentin.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The sponsor has referred to their non-clinical database for Neurontin performed previously for their program for the indication of epilepsy to support their development program for treatment of _____ . Adequate and supportive studies were performed in addition to numerous pharmacology studies, which demonstrate the activity of Neurontin in the treatment of _____. Thus, the non-clinical program supports the approval of the marketing applications for Neurontin for the treatment of _____ .

General Toxicology Issues: None.

Recommendations: These applications are approvable from a non-clinical perspective.

Labeling with basis for findings: New information in the section "CLINICAL PHARMACOLOGY: Mechanism of Action" that discusses the efficacy of gabapentin in relation to the proposed indication is supported by studies submitted by the sponsor or referenced literature publications. Following input by HFD-120, the section should be modified as follows with proposed changes underlined:

First paragraph:

"The mechanism by which gabapentin exerts its _____ , analgesic actions is unknown, but in animal models of analgesia, gabapentin prevents allodynia, (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g., spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

Second paragraph:

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants.

Third paragraph:

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify GABA_A or GABA_B radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 µM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic, muscarinic or nicotine, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

Fourth paragraph:

~~_____~~

~~_____~~

The sponsor's proposed labeling related to non-clinical information is acceptable. The sections "Carcinogenesis, Mutagenesis, Impairment of Fertility", and "OVERDOSAGE" are identical to those previously approved.

The sponsor's proposed labeling for the "Pregnancy" section is identical to that previously approved. However, following input by HFD-120, the last paragraph of the "Pregnancy" section should be modified to reflect standard pregnancy category C wording as follows: "In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. _____ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

X. APPENDIX/ATTACHMENTS:

Addendum to review: None.

Other relevant materials (Studies not reviewed, appended consults, etc.): None.

Any compliance issues: None.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Timothy McGovern
5/21/02 10:10:17 AM
PHARMACOLOGIST

**APPEARS THIS WAY
ON ORIGINAL**