PRODUCT MONOGRAPH

NTP-CLOBAZAM

(clobazam)

Tablets

Anticonvulsant

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THERAPEUTIC CLASSIFICATION

Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY

Clobazam is a 1,5-benzodiazepine with anticonvulsant properties.

In general, the mode of anti-epileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neurotoxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors.

Regarding the mechanism of action it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neuro-transmitter underlie the pharmacological effects of the benzodiazepines. Electrophysiologic studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced by the interaction of GABA with its receptors is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain.

The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete. The time to peak concentration ranges from 1 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption. The drug is highly lipophilic and is rapidly distributed in fat and cerebral grey matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The volume of distribution is large.

A comparative, two way single dose bioavailability study was performed on two clobazam 10 mg tablet formulations, NTP-CLOBAZAM and Frisium®. The pharmacokinetic data calculated for clobazam in the NTP-CLOBAZAM and Frisium® tablet formulations is tabulated below:

	Geometric mean Arithmetic mean (C.V.)		
	NTP-CLOBAZAM 2x10 mg	Frisium®** 2x10 mg	Ratio (%) Geometric Means
AUC_T (ng•h/mL)	7406 7706 (28)	7480 7758 (28)	99
$AUC_{(0-72)}$ (ng•h/mL)	6768 6956 (23)	6836 7004 (22)	99
C_{max} (ng/mL)	354 359 (16)	379 381 (10)	94
T_{max}* (h)	2.27 (1.3)	1.73 (1.0)	-
$T_{1/2}$* (h)	22.6 (8.0)	22.7 (7.9)	-
*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation). **Frisium® 10 mg Tablets (Hoechst-Roussel Canada Inc., Canada)			

Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam forms a number of metabolites with N-desmethylclobazam being the most important.

The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36 to 46 hours) than for clobazam (mean 18 hours; range 10 to 30 hours). N-desmethylclobazam reaches higher serum levels, especially with long-term administration of clobazam.

The half-life increases with the patient's age. The drug is about 85% protein-bound; hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethylclobazam to clobazam efficacy.

Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50 to 300 ng/mL with the corresponding range for N-desmethylclobazam being from 1000 to 4000 ng/mL. The serum levels at which anticonvulsant effects can be expected are not yet known but it can be assumed that the therapeutic range lies in the order of the figures given above. Since N-desmethylclobazam blood levels are 10 to 20 times higher than those for clobazam, and this metabolite also has anti-epileptic effects, it may be more important to the anti-epileptic efficacy of clobazam than the parent compound itself.

After oral administration of ^{14}C-labeled clobazam to man, approximately 90% of the radioactivity was recovered in urine.

Seven double-blind studies have been reported in which clobazam was given as adjunctive therapy versus placebo within an established antiepileptic regimen; clobazam was shown to be significantly superior to placebo.

INDICATIONS AND CLINICAL USE

Clobazam has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

CONTRAINDICATIONS

Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow-angle glaucoma.

WARNINGS

Geriatrics:

Clobazam should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose (see Precautions).

Potentiation of Drug Effects:

Patients should be cautioned about the possibility of additive effects when clobazam is combined with alcohol or other drugs with CNS depressant effects. Patients should be advised against consumption of alcohol during treatment with clobazam (see Precautions).

Physical and Psychological Dependence:

Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer clobazam to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance. Signs and symptoms of withdrawal may follow discontinuation of use of clobazam; thus it should not be abruptly discontinued after prolonged use (see Precautions).

Pregnancy and Lactation:

Clobazam should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with clobazam is indicated should cease breast-feeding, since clobazam passes into breast milk.

Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If clobazam is prescribed to a woman of childbearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant.

Anterograde Amnesia:

Anterograde amnesia is known to occur after administration of benzodiazepines.

Patients with Depression or Psychosis:

Clobazam is not recommended for use in patients with depressive disorders or psychosis.

PRECAUTIONS

Occupational Hazards:

Clobazam possesses a mild CNS depressant effect; therefore, patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy.

Geriatrics:

Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions.

Dependence Liability:

Clobazam should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines.

These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, clobazam should be withdrawn gradually.

Tolerance: Loss of part or all of the anticonvulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development.

The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment, but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur.

Mental and Emotional Disorders:

It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay.

Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, clobazam should not be used in patients suspected of having psychotic tendencies.

Patients with Impaired Renal or Hepatic Function:

Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if clobazam is used in patients who may have some impairment of renal or hepatic function. It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged therapy with clobazam is indicated, blood counts and liver function should be monitored periodically.

Patients with Acute, Severe Respiratory Insufficiency:

In patients with acute, severe respiratory insufficiency, respiratory function should be monitored.

Laboratory Tests:

If clobazam is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable.

Drug Interactions:

Most studies of the potential interactions of clobazam with other antiepileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur.

Alcohol may also significantly increase plasma clobazam levels. Several of the established anti-epileptic agents: carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin.

Toxicologic Studies:

In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were 3 malignancies: 2 (male and female) in the thyroid and 1 (female) in the liver. The relevance of these findings to man has not been established.

ADVERSE REACTIONS

From 19 published studies of clobazam use in epileptic patients, the overall incidence of side effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side effects.

The incidence of side effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%): $p<0.05$, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side effects occurred at

incidences of greater than 1% [ataxia (3.9%), weight gain (2.2%), dizziness (1.8%), nervousness (1.6%), behavior disorder (1.4%), hostility and blurred vision (1.3%)] while other effects occurred at a less than 1% incidence.

Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with clobazam and when higher doses are used. Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability.

After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients; it sometimes persisted for some length of time.

Occupational Hazards:

Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol.

As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

Isolated cases of skin reactions such as rashes or urticaria have been observed.

SYMPTOMS AND TREATMENT OF OVERDOSE

The cardinal manifestations are drowsiness, confusion, reduced reflexes, increasing sedation and coma.

Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off.

Treatment

Immediate gastric lavage may be beneficial if performed soon after ingestion of clobazam. Given the route of excretion, (see Pharmacology) forced diuresis by short-acting loop diuretic may be useful some hours post-ingestion. If respiratory depression and/or coma are observed, the presence of other CNS depressants should be suspected. Respirations, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of i.v. fluids started. Hypotension and CNS depression are managed by the usual means.

DOSAGE AND ADMINISTRATION

As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind.

In patients with impaired liver and kidney function, clobazam should be used in reduced dosage.

Adults:

Small doses, 5 to 15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary.

Children:

In infants (<2 years), the initial daily dose is 0.5 to 1 mg/kg/day. The initial dose in children (2 to 16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day.

As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that clobazam be gradually reduced in dose before treatment is discontinued.

Administration: If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night.

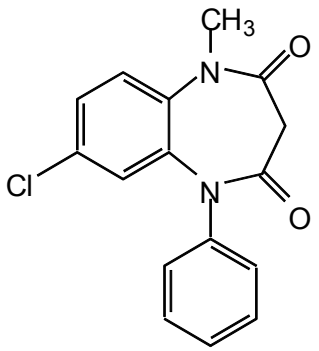
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Clobazam

Chemical Name: 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)dione

Structural Formula:



Molecular Formula: $C_{16}H_{13}O_2N_2Cl$ Molecular Weight: 300.7

Description: White, odorless, crystalline powder. Soluble in chloroform and methanol. Very slightly soluble in water. Melting range of 182 - 3°C.

Non-Medicinal Ingredients:

Each 10 mg tablet contains: colloidal silicon dioxide, lactose, magnesium stearate, sodium starch glycolate, starch and talc

STABILITY AND STORAGE RECOMMENDATIONS: Unit dose strips and blister packs should be stored between 15°–25°C and protect from high humidity.

AVAILABILITY OF DOSAGE FORMS

NOVO–CLOBAZAM (clobazam) is available as:

10 mg: White to off white, round, scored tablet engraved **N** on one side and **1|0** on the other side.

Supplied in blister packs of 30.

PHARMACOLOGY

Pharmacologic studies in animals have shown that clobazam can suppress seizures induced by a variety of experimental procedures. With respect to electro-shock induced seizures in the mouse, clobazam is more effective than valproic acid but less effective than clonazepam.

Although comparison with diazepam and phenobarbital produced inconsistent results in this model, the anticonvulsant effects of all three substances can probably be regarded as similar.

The anticonvulsant effect of clobazam in acoustically induced seizures in the mouse were less marked than those of clonazepam and diazepam as shown by ED_{50}. In most cases however, in particular with chemically induced seizures, clobazam was more potent than the other antiepileptic agents: phenytoin, phenobarbital, carbamazepine and valproic acid (Table 1).

Table 1

Anticonvulsant activity of antiepileptic drugs in mice (chemically induced seizures)

(ED_{50} [mg/kg orally])

	Pentetrazol	Picrotoxin	Bicuculline	Isoniazid	Nicotine	Strychnine
	125 mg/kg	15 mg/kg	5 mg/kg	600 mg/kg	1.5 mg/kg	1.2 mg/kg
Clobazam	1.7	4.7	16.2	10.7	2.3	10.4
Diazepam	0.41	4.1	10.0	2.8	0.80	4.9
Clonazepam	0.038	2.3	1.0	0.075	0.14	>5
Phenobarbital	6.7	12.2	20.5	18.7	7.6	46.9
Phenytoin	7.6	3.6	10.4	21.8	19.8	>100
Carbamazepine	11.2	7.3	16.2	25.0	18.1	>100
Valproate	158	75.4	362	494	168	>800

Although the ED_{50} is an important index, it is not a measure of the therapeutic value, since it has the disadvantage of not reflecting any undesired effects of the drug which might limit its subsequent use. The protective index (PI) is a more reliable indicator in this regard. The PI is equal to the quotient TD_{50}/ED_{50} where the TD_{50} is the dose at which 50% of the animals in the Rota rod test show signs of ataxia. Hence, if the PI > 1, anticonvulsant effects occur before the undesired ataxic effects. The greater the PI, the wider is the margin between the desirable anticonvulsant effect and the undesired ataxic effect. Comparing this index, clobazam was superior to diazepam, clonazepam, phenobarbital and valproic acid. Carbamazepine and phenytoin were sometimes inferior and sometimes superior to clobazam in the respective tests (Table 2).

Table 2

Protective indices of clobazam and other antiepileptics in tests on anticonvulsant activity in mice

	Electro-convulsive Seizures	**Pentetrazol (tonic)**	**Pentetrazol (clonic)**	**Picrotoxin**	**Bicuculline**	**Isoniazid**	**Nicotine**	**Strychnine**
Clobazam	4.9	23.1	17.1	8.4	2.4	3.7	17.1	38
Diazepam	0.9	12.2	10.0	1.2	0.5	1.8	6.3	1.0
Clonazepam	0.6	9.0	7.1	0.2	0.3	4.5	2.4	<0.1
Phenobarbital	3.4	7.0	3.0	3.9	2.3	2.5	6.2	1.0
Phenytoin	14.6	13.3	<1	28.1	9.7	4.6	5.1	<1.0
Carbamazepine	12.6	9.1	<1	14.0	6.3	4.1	5.6	<1.0
Valproate	1.8	3.0	1.8	6.3	1.3	1.0	2.8	<1.0

Finally, the anxiolytic, sedative and myorelaxant effects of clobazam (a 1,5-benzodiazepine) were compared with those of 10 different 1,4-benzodiazepines. The ratios of specific effect to anticonvulsant effects showed that clobazam is a highly specific anticonvulsant.

Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. For serum concentrations between 0.05 and 10 mg/mL, the binding to serum proteins is shown in Table 3.

Table 3

Binding of ^{14}C clobazam to serum proteins

Species	% Binding	Range Measured
rat	66 ±2	0.05-10 mg/mL
dog	83 ±2	0.05-10 mg/mL
monkey	76 ±3	0.05-10 mg/mL
human	85 ±3	0.05-10 mg/mL

After oral administration, absorption of clobazam was practically complete in all three animal species. Data are given in Table 4 which shows also maximum blood levels for the total concentration in the animal species examined and the times at which they were reached. Total concentration refers to clobazam and its metabolites.

Table 4

Blood levels after oral administration of ^{14}C clobazam

Species	n	Maximum Total Concentration (mg/mL)	Time (H after application)	Dose (mg/kg)
Rat	6	0.046 ± 0.012	0.5	0.52
Dog	5	0.24 ±0.043	2-4	0.5
Monkey	2	0.67 ±0.82	0.5;1	2.5

Both after a single oral and intravenous dose, more than two-thirds of the drug associated radioactivity is found in the faeces; dogs, however, excreted about 3/4 of the radioactivity with the urine, irrespective of the route of administration. In monkeys, the excretion also occurred mainly in the urine; in all three species, renal excretion was just as rapid as that from blood or plasma (Table 5). Elimination was almost completed after 48 hours in all species.

Table 5

Excretion after administration of ^{14}C-clobazam to different animal species

Species	Route of Administration	Dose mg/kg	Excretion (% administered dose)		
			Urine	Faeces	Balance
Rat	Intravenously	0.1	27 ±1	73 ±6	100 ±6
Rat	Orally	0.52	29 ±6	71 ±7	100 ±1
Dog	Intravenously	0.10	78 ±9	28 ±4	106 ±2
Dog	Orally	0.50	74 ±5	28 ±2	102 ±3
Monkey	Orally	2.5	61 ±14	N.D.	

The two most important chemical changes of clobazam during metabolism are dealkylation and hydroxylation. Dealkylation at nitrogen-1, particularly pronounced in the dog, does not differ between the 1,4- and 1,5-benzodiazepines. However, hydroxylation at the 3-position which occurs with 1,4-benzodiazepines such as diazepam, does not occur with clobazam and may be a characteristic of 1,5-benzodiazepines in general.

In several studies clobazam exhibited activity against seizures with doses usually ranging below those that cause disorders in motor activity (see ACTION AND CLINICAL PHARMACOLOGY and Table 2). This separation is evident also with N-desmethylclobazam. The advantage of clobazam compared with 1,4-benzodiazepines lies mainly in the fact that motor activity is influenced only after very high doses, these doses being markedly above those required to induce tranquilizing and anti-aggression activities. In animal studies, clobazam had no marked effect on the cardiovascular system, respiration or excretion.

TOXICOLOGY

Acute Toxicity

In mice, the oral LD_{50} was 640-1101 mg/kg, the intraperitoneal toxicity, 289-615 mg/kg, and the subcutaneous toxicity, 2250- 2500 mg/kg. In rats, the oral LD_{50} was 6000 mg/kg, the intraperitoneal LD_{50}, 740-1526 mg/kg, and the subcutaneous toxicity, > 5000 mg/kg. In rabbits, the oral LD_{50} was 320 mg/kg whereas in guinea pigs it was 109 mg/kg. Signs exhibited during acute toxicity testing included somnolence, prostration, reduction in spontaneous motility, irregular breathing, ataxia, tremors, convulsions, loss of righting reflexes and reduction in body temperature. These were the most frequently observed signs in lethally poisoned animals.

Chronic Toxicity

Clobazam was administered to rats in the diet or by gavage at doses of 0, 4, 12, 20, 25, 35, 100, 200, 400 and 600 mg/kg for periods ranging from 6 to 18 months. At 100 mg/kg for 6 months a transient slight growth retardation in males and in females a transient mild anemia and

leucocytosis were observed. Reduction in spontaneous activity, piloerection, lateral position, fall in body temperature, depression and death were observed in 4 treated with 100 mg/kg, in 3 treated with 400 mg/kg and in one control animal during the treatment period. Animals treated with 100 mg/kg for 2 weeks and subsequently changed to 200 mg/kg for up to the 36th week and then 600 mg/kg for the duration of the 18-month study showed dose-dependent increases in liver and thyroid and microscopic lesions, consisting of eosinophilic inclusions in the proximal convoluted tubules of the females and yellow granules in the livers of both males and females. The eosinophilic inclusions were accompanied by proliferation of the smooth endoplasmic reticulum.

Clobazam was administered to Beagle dogs at doses of 0, 2.5, 5, 10, 20, 40 and 80 mg/kg for periods ranging from 6 to 12 months. Dose-dependent symptoms were noted and consisted of sedation, ataxia tremors, somnolence, emesis, seizures and progressive rise in serum alkaline phosphatase. At the 80 mg/kg dose for 6 months a significant increase in the weight of the liver was observed in males and females. In the 12-month study using 0, 5, 10 and 40 mg/kg a dose-dependent increased accumulation of pigments in hepatocytes and Kupffer cells was observed in the 5 mg/kg group. In another 12-month study where 0, 2.5 and 5 mg/kg doses were used there were yellow granules in the epithelial cells of the proximal convoluted tubules in the 5 mg/kg group at one year. The studies have shown that convulsions were observed on the second and third day after abrupt discontinuation of the drug.

In the one year study where 0, 5, 10 and 40 mg/kg of clobazam were used and in the 6-month study were 0, 5, 20 and 80 mg/kg were used, deaths occurred (9 and 2, respectively), but the

exact cause could not be ascertained. However, the animals experienced convulsive seizures with foaming at the mouth during the treatment period.

In a special study clobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 and 40 mg/kg daily for 16 months. Withdrawal symptoms were assessed beyond the fourth month of treatment following the interruption of medication on several occasions for 1 to 9 days. The incidence and the severity of the withdrawal symptoms were related to the duration of treatment and the greater susceptibility of the female than the male dog.

The withdrawal symptoms consisted of tremors, accelerated respiration, violent tonic-clonic convulsions, abundant salivation, frothing at the mouth, ptosis, sedation, ataxia stereotyped movements, gasping for breath, biting of the tongue. The symptoms usually subsided following reinstitution of medication.

N-desmethylclobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 and 40 mg/kg daily for 12 months.

After 48 hours of drug withdrawal, symptoms occurred and consisted of short tonic clonic convulsions and of relatively persistent tremor in the male dog whereas the female dog exhibited only a relatively persistent tremor.

Clobazam was administered to Rhesus monkeys by gavage at doses of 0, 2.5, 7.1 and 20 mg/kg for 52 weeks. There was a slight reduction in heart rate at 2.5 and 7.1 mg/kg. In addition, at 7.1 mg/kg sedation was observed. One male died in coma.

Signs of withdrawal appeared on the second day and these were aggression, piloerection, restlessness, little appetite and an unusual supine position. These withdrawal signs disappeared after readministration of clobazam.

Reproduction and Teratology

Clobazam was administered orally in the diet to rats and mice at doses up to 200 mg/kg/day for 60 days, during pairing, throughout pregnancy and for 21 days of postnatal development of the offspring. No impairment of fertility in males and females and no effects on pregnancy or course of labour were noticed which could be attributed to the drug. In rats, the offspring developed normally and their behaviour during the lactation period was unremarkable. In mice, litter sizes were normal, but a dose-dependent death rate of fetuses was observed in the highest dose group (200 mg/kg). In these litters, the dams did not bite through the umbilical cords and did not clean or nurse the offspring. This abnormality in the dams could have been compound induced after parturition. Liver weights were increased at the highest dose (200 mg/kg).

Teratologic studies were performed in mice, rats and rabbits treated in the diet with clobazam at doses of up to 400 mg/kg of body weight/day.

In rats and mice, no teratogenic effects were noted. In the fetuses and in the neonatal animals, there were no differences between the test groups and the control group with regard to number of implantations, resorptions, number of live and dead fetuses, placental weight, crown-rump length of fetuses, and sex ratio in the live fetuses, nor were there any external, visceral or skeletal malformations or anomalies attributable to clobazam. In the reared fetuses of the dams treated with clobazam during pregnancy, no retardation in post-natal growth and no external malformations and no visceral or skeletal abnormalities were observed except for four cases of cleft palate occurring at a dose of 100 mg/kg/day.

In rabbits, the rate of fetal resorption was higher in animals treated with 100 mg/kg than in the controls. In the group treated with 4 mg/kg, one unilateral exophthalmus, one exencephalus combined with ceolosomy and syndactyly of the front legs were observed, whilst in the 20 mg/kg group, one hydrocephalus with umbilical hernia was noted; these malformations were thought not to be drug related.

Carcinogenicity

Carcinogenic studies were conducted in mice and in rats.

Clobazam was administered daily in the diet at doses of 0, 4, 20, and 100 mg/kg to groups of 60 male and 60 female CD-1 mice for 80 weeks.

Because of fighting in the group of males, male animals of the 100 mg/kg/day group were supplemented with a subgroup of 43 spare animals. Nine weeks after initiation of study, it was necessary to add a second subgroup of 42 spare animals.

The males of the supplemented subgroup treated with 100 mg/kg/day had more (8.3%) neoplastic changes (hepatomas) than the controls (1.7%) and the other treated male mice.

Clobazam was administered daily in the diet at doses of 0, 4, 20 and 100 mg/kg/day to groups of 60 male and 60 female CD rats for 104 weeks.

Gross lesions identified at necropsy consisted of liver pallor and thyroid gland enlargement in males dosed at 100 mg/kg/day. The non-neoplastic histopathologic changes associated with treatment included an increased incidence of endometrial hyperplasia, cystic endometrial hyperplasia, and endometrial polyps and polypoid areas in females treated with 100 mg/kg/day. Thyroid changes included an increase in follicular cell adenomas in males (21.7% vs 5.7% in controls) treated with 100 mg/kg/day, and there was follicular carcinoma in one male (1.7%) of this group.

One male rat in the 100 mg/kg/day group (1.7%) and one female rat in the 20 mg/kg/day (1.7%) group had squamous cell carcinomas in the thyroid gland. In the liver, changes included an increase in focal hyperplasia in females treated with 20 (11.7%) or 100 (6.7%) mg/kg/day. Nodular hyperplasias were increased in females treated with 100 mg/kg/day (3.3% vs 1.7% in

controls). Hepatocellular carcinoma was found in one decedent female (1.7%) treated with 20 mg/kg/day.

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