PRODUCT MONOGRAPH

MYLAN-PINDOLOL

(Pindolol Tablets, USP)

5 and 10 mg

Antihypertensive/Antianginal Agent

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Date of Preparation:
August 19, 2010

Control#: 140702

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(Pindolol Tablets, USP)

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THERAPEUTIC CLASSIFICATION

Antihypertensive/Antianginal Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Pindolol is a 13-adrenergic-receptor-blocking agent which possesses partial agonist activity (intrinsic sympathomimetic activity - I.S.A.). It is used in the treatment of hypertension and/or the prophylaxis of angina pectoris.

Hypertension

The mechanism of the antihypertensive effect of pindolol has not been established. Among the factors that may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the 13-receptor sites in the heart, thus decreasing cardiac output

b) a reduction in total peripheral resistance

c) inhibition of the vasomotor centres

d) inhibition of renin release by the kidneys.

Angina pectoris

The mechanism of the antianginal effect of pindolol has not been established. Pindolol may reduce the oxygen requirement of the heart at any level of effort by blocking catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. However, oxygen requirements may be increased by such actions as increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period. When the net effect is beneficial in patients with angina, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks.

In man, orally-administered pindolol is rapidly and almost completely absorbed (95%). Because of negligible hepatic first pass effect, the bioavailability of oral pindolol is high and approaches 90% of the oral dose. Maximum plasma concentrations are reached one to two hours after oral administration and the plasma half-life is approximately 31/2 hours. The elimination rate of pindolol is not dose dependent. 40% of pindolol is bound to plasma proteins. Pindolol has a volume of distribution of 2-3 L/kg and a total clearance of 500 mL/min.

Pindolol is partially metabolized in the liver with approximately 40% of an oral dose being excreted unchanged in the urine. The remaining 60% is excreted in the urine and feces as inactive metabolites. The principal metabolites of pindolol are its conjugated glucuronide, and its phenolic derivative conjugated with sulfuric or glucuronic acid.

Approximately 80% of an oral dose is accounted for in the urine within 24 hours.

A summary of the results of comparative, randomized, crossover bioavailability studies of MYLAN-PINDOLOL (Pindolol) 5 and 10 mg tablets and the respective marketed Canadian products is presented below:

Geometric Mean
Arithmetic Mean (C.V.%)

Parameter	5 mg Tablets			10 mg Tablets		
	Test Product	Reference Product	Ratio of means	Test product	Reference Product	Ratio of means
AUC_t (ng•h/mL)	572.78	547.74	104.6	425.0	431.0	99.0
	587.49 (22.8)	563.83 (24.7)		437.9 (24.7)	442.3 (23.3)	
AUC_i (ng•h/mL)	604.38	577.78	104.6	454.4	458.1	99.2
	622.27 (24.6)	596.61 (26.2)		469.5 (26.3)	470.4 (23.9)	
C_{max} (ng/mL)	97.90	100.71	97.2	74.0	75.9	97.5
	100.17 (22.1)	103.23 (23.1)		76.5 (26.8)	78.5 (25.6)	
T_{max} (h)	1.35 (0.578)	0.96 (0.299)		1.05 (0.36)	1.22 (0.76)	
$T_{1/2}$ (h)	3.50 (0.620)	3.48 (0.626)		3.81 (0.64)	3.67 (0.48)	

For T_{max} and T arithmetic mean (standard deviation) are presented.

INDICATIONS AND CLINICAL USE

a) Hypertension

MYLAN-PINDOLOL (pindolol) is indicated for the treatment of mild to moderate hypertension. Pindolol is usually used in combination with other drugs, particularly a thiazide diuretic. However, it may be used alone as an initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a B-blocker rather than a diuretic.

The combination of pindolol with a diuretic and/or peripheral vasodilator has been found to be compatible and generally more effective than pindolol alone. Limited experience with other antihypertensive agents, including methyldopa, has not shown evidence of incompatibility with pindolol.

MYLAN-PINDOLOL is not recommended for the emergency treatment of hypertensive crises.

b) Angina Pectoris

MYLAN-PINDOLOL is indicated for the prophylaxis of angina pectoris.

CONTRAINDICATIONS

MYLAN-PINDOLOL (pindolol) should not be used in the presence of:

1. sinus bradycardia
2. second and third degree AV block
3. right ventricular failure secondary to pulmonary hypertension
4. congestive heart failure (see **WARNINGS)**
5. cardiogenic shock
6. anesthesia with agents which produce myocardial depression, e.g. ether
7. bronchospasm, including bronchial asthma or severe chronic obstructive pulmonary disease (see **PRECAUTIONS).**

WARNINGS

a) Cardiac Failure

Special caution should be exercised when administering MYLAN-PINDOLOL (pindolol) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with 13-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Pindolol may reduce but does not abolish the inotropic action of digitalis on the heart muscle. However, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of pindolol when the two drugs are used concomitantly. The effects of 13-blockers and digitalis are additive in depressing AV conduction. In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac

failure. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalised and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalisation and diuretic therapy, MYLAN-PINDOLOL should be immediately withdrawn.

b) Abrupt Cessation of Therapy with MYLAN-PINDOLOL

Patients with angina should be warned against abrupt discontinuation of MYLAN-PINDOLOL. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of B-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of MYLAN-PINDOLOL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be observed carefully. The same frequency of administration should be maintained. In situations of greater urgency, MYLAN-PINDOLOL therapy should be discontinued stepwise under very close observation.

If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with MYLAN-PINDOLOL be reinstituted promptly, at least temporarily.

c) Various skin rashes and conjunctival xerosis have been reported with B-blockers, including pindolol. A severe oculo-muco-cutaneous syndrome, whose signs include

conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis, has occurred with the chronic use of one B-adrenergic-blocking agent (practolol). This syndrome has not been observed with pindolol. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

d) Sinus bradycardia may occur with the use of MYLAN-PINDOLOL due to unopposed vagal activity remaining after blockade of B_1-adrenergic receptors. However, due to its intrinsic sympathomimetic activity (ISA), pindolol causes less bradycardia at rest than some other B-adrenergic blocking agents. If excessive bradycardia occurs, the dosage of MYLAN-PINDOLOL should be reduced.

e) In patients with thyrotoxicosis, possible deleterious effects from long-term use of pindolol have not been adequately appraised. B-blockade may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, abrupt withdrawal of MYLAN-PINDOLOL may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

PRECAUTIONS

a) Caution should be exercised in patients prone to non-allergic bronchospasm (e.g. chronic bronchitis, emphysema) since MYLAN-PINDOLOL (pindolol) may block

bronchodilation produced by endogenous and exogenous catecholamine stimulation of 13-receptors.

b) MYLAN-PINDOLOL should be administered with caution to patients with allergic rhinitis prone to bronchospasm.

There may be increased difficulty in treating an allergic type reaction in patients on 13-blockers.

In these patients, the reaction may be more severe due to pharmacologic effects of the 13-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm.

Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of B-agonists, including parenteral salbutamol or isoproterenol, to overcome bronchospasm and norepinephrine to overcome hypotension.

c) MYLAN-PINDOLOL should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes)

who are receiving insulin or oral hypoglycemic agents. B-adrenergic-blockers may mask the premonitory signs and symptoms (tachycardia, tremor) of acute hypoglycemia.

d) MYLAN-PINDOLOL dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see **DOSAGE AND ADMINISTRATION).**

e) Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored because the added 13-adrenergicblocking action of pindolol may produce an excessive reduction of sympathetic activity. MYLAN-PINDOLOL should not be combined with other B-blockers.

f) Appropriate laboratory tests should be performed at regular intervals during long-term treatment.

g) The management of patients being treated with 13-blockers and undergoing elective or emergency surgery is controversial. Although B-adrenergic-receptorblockade impairs the ability of the heart to respond to B-adrenergically-mediated reflex stimuli, abrupt discontinuation of therapy with MYLAN-PINDOLOL may be followed by severe complications (see **WARNINGS).**

Some patients receiving B-adrenergic-blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

For these reasons, in patients with angina undergoing elective surgery, MYLAN-PINDOLOL should be withdrawn gradually following the recommendation given under "Abrupt Cessation of Therapy" (see **WARNINGS).** According to available evidence, all clinical and physiological effects of B-blockade are no longer present 48 hours after cessation of medication.

In emergency surgery, since MYLAN-PINDOLOL is a competitive inhibitor of 13-adrenergic-receptor agonists, its effects may be reversed by sufficient doses of such agonists as isoproterenol or levarterenol.

h) **Impaired Renal or Hepatic Function:** B-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on pindolol clearance, but poor hepatic function may cause blood levels of MYLAN-PINDOLOL to increase substantially.

i) **Usage in Pregnancy:** Since MYLAN-PINDOLOL has not been studied in human pregnancy, the drug should not be given to pregnant women. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against possible hazards. Pindolol crosses the placental barrier.

j) **Lactating Women:** Pindolol passes in small quantities into breast milk.

k) **Usage in Children:** There is no experience with MYLAN-PINDOLOL in the treatment of pediatric age groups.

l) Because dizziness or fatigue may occur during initiation of treatment with B-adrenoreceptor blocking drugs, patients driving vehicles or operating machinery should exercise caution until they have determined their individual response to treatment.

ADVERSE REACTIONS

Cardiovascular

Congestive heart failure, severe bradycardia (see **WARNINGS),** may occur. Syncope, lightheadedness and postural hypotension. Lengthening of PR interval, second degree AV block, palpitation, chest pains, cold extremities, Raynaud's phenomenon, claudication, hot flushes. Very rarely arrhythmia, coronary insufficiency.

Central Nervous System

Insomnia, nightmares, vivid dreams, fatigue, drowsiness, weakness, dizziness, vertigo, tinnitus, headache, mental depression, nervousness. The following adverse reactions have been reported rarely: aggressiveness, motor disorders, confusion.

Gastrointestinal

Diarrhea, constipation, flatulence, heartburn, nausea and vomiting, abdominal pain and dry mouth.

Respiratory

Shortness of breath and/or dyspnea, wheezing, bronchospasm.

Allergic, Dermatological (see **WARNINGS)**

Exanthema, sweating, pruritus, psoriasiform rash.

Eyes

Itching, burning, grittiness, dryness.

Miscellaneous

Muscle cramps, appetite stimulation, weight gain, urinary frequency.

Clinical Laboratory

On rare occasions, changes in the following parameters were noted: elevated transaminases, alkaline phosphatase, LDH, serum uric acid, reduced bilirubin.

SYMPTOMS AND TREATMENT OF OVERDOSE

The most common signs to be expected with overdosage of a B-adrenergic-blocking agent are congestive heart failure, bradycardia, hypotension, bronchospasm, or hypoglycemia.

If overdosage occurs, in all cases therapy with MYLAN-PINDOLOL (pindolol) should be discontinued and the patient observed closely. If required, the following therapeutic measures are suggested:

1. Bradycardia: atropine or another anticholinergic drug.
2. Heart block (second or third degree): isoproterenol or transvenous cardiac pacemaker.
3. Congestive heart failure: conventional therapy.
4. Hypotension: (depending on associated factors) epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis (see **PRECAUTIONS** concerning the use of epinephrine).
5. Bronchospasm: aminophylline or isoproterenol.
6. Hypoglycemia: intravenous glucose.

It should be remembered that pindolol is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of MYLAN-PINDOLOL. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

a) Hypertension

MYLAN-PINDOLOL (pindolol) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic but may be used alone (see **INDICATIONS AND CLINICAL USE).**

MYLAN-PINDOLOL should be taken with meals.

The dosage of MYLAN-PINDOLOL must always be adjusted to the individual requirements of the patients in accordance with the following guidelines:

- MYLAN-PINDOLOL therapy should be initiated with doses of 5 mg in the morning with breakfast and 5 mg with the evening meal. If an adequate response is not achieved after one to two weeks, the dose should be increased to 10 mg twice a day.

- If after one to two additional weeks an adequate response is not observed, dosage may be increased to 15 mg twice a day (30 mg/day).

- Doses greater than 30 mg daily must be given on a t.i.d. schedule.

- Patients who show a satisfactory response to MYLAN-PINDOLOL at daily doses of 10 to 20 mg may be maintained by giving the required total dose once daily in the morning with breakfast.

- The usual maintenance dose is within the range of 15 to 45 mg daily which should not be exceeded. However, during long-term therapy, some patients may be maintained on smaller doses of MYLAN-PINDOLOL.

b) Angina Pectoris

The dosage of MYLAN-PINDOLOL must always be adjusted to the individual requirements of the patient.

In angina, MYLAN-PINDOLOL should be administered on a three or four times per day dosing regimen. MYLAN-PINDOLOL therapy should be initiated with doses of 5 mg three times a day taken with meals. If after one to two weeks an adequate response is not observed, dosage may be increased. The usual maintenance dose is 15 mg up to the maximum of 40 mg per day.

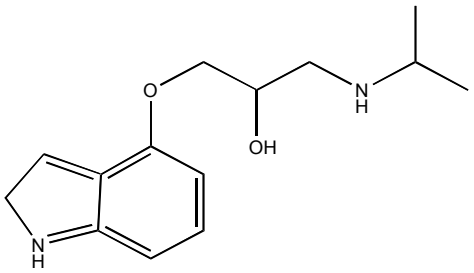
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Pindolol, USP

Chemical Name: 4-(2-hydroxy-3 -isopropylaminopropoxy)-indole

Structural Formula:



Molecular Formula: $C_{14}H_{20}N_2O_2$

Molecular Weight: 248.3

Pindolol is a white, odourless powder practically insoluble in water, slightly soluble in methanol and very slightly soluble in chloroform. The melting point is 169-173°C. MYLAN-PINDOLOL (pindolol) is the free base of pindolol.

Stability and Storage Recommendations

Store at 15-30°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

MYLAN-PINDOLOL (pindolol) tablets are available as:

5 mg: White, biconvex round tablets with a "G" on one side and "P5" on the other side. Bottles of 100 and 500.

10 mg: White, biconvex round tablets with a "G" on one side and "P10" on the other side. Bottles of 100 and 500.

PHARMACOLOGY

Effects on the Cardiovascular System

Pindolol, in the non-anesthetized dog, produced a 70% inhibition of tachycardia and changes in blood pressure induced by isoproterenol at doses of 0.05 mg/kg i.v. and 2 mg/kg i.v., respectively. Complete antagonism was observed following pindolol at doses of 0.1 to 5 mg/kg i.v. In the anesthetized dog, 0.2 to 2.0 mg/kg i.v. produced dose dependent decreases in blood pressure; heart rate changes were unrelated to dose and were reduced by 12% after a dose of 0.2 mg/kg i.v. and 4% after i.v. injection of 2 mg/kg.

In the anesthetized dog, 0.2 to 1 mg/kg i.a. antagonized the vasodilation induced by isoproterenol, whereas transient 25 to 40% reductions in vascular resistance were observed after intra-arterial doses of 50 and 200 mg/kg. Intravenous doses of 2 mg/kg of pindolol elicited peripheral vasodilation and an associated reduction in total peripheral resistance.

In vivo studies on the guinea pig atrium showed that pindolol produced dose dependent antagonism of epinephrine-induced positive inotropy and chronotropy.

In five healthy volunteers given a single oral dose of 10 mg of pindolol, antagonism of isoproterenol-induced tachycardia and changes in blood pressure and heart rate were observed 30 minutes after ingestion and persisted for 24 hours.

In ten hypertensive patients receiving pindolol for 16 months in divided doses of 20 to 40 mg, blood pressure reduction was associated with statistically significant reduction in forearm and total systemic vascular resistance at rest and during stress testing. Venous tone was significantly reduced during and after exercise. No significant change was reported in cardiac output following prolonged used (see **ACTIONS AND CLINICAL PHARMACOLOGY).**

Pindolol has little membrane stabilizing activity being approximately 1/12 that of quinidine in prolonging the relative refractory period of cardiac cells in the isolated guinea pig atrium. A concentration of up to 5% pindolol was devoid of local anesthetic effects when applied to the cornea of the eye.

Pindolol possesses partial agonist (intrinsic sympathomimetic) activity. Long-lasting increases in myocardial activity manifested by positive chronotropic actions were observed following i.v. infusions of pindolol at doses of 0.16 mcg/kg to 2.5 mg/kg in the reserpinized, adrenalectomized and vagotomized cat.

Pindolol decreases the basal rate of myocardial oxygen consumption and blocks increases mediated by increased sympathetic nervous system activity.

Pindolol has antiarrhythmic activity. At doses of 8 mg/kg in the anesthetized dog, pindolol increased the dose of ouabain required to produce ventricular arrhythmia. In

guinea pigs and dogs, it delayed the onset of ouabain-induced ventricular arrhythmia and in the dog produced reversion to sinus rhythm.

Pindolol has been reported to reduce plasma renin activity in some patients. However, plasma renin may remain unchanged or increase following treatment. There does not appear to be any significant relationship between the antihypertensive activity of pindolol and changes in plasma renin activity.

Effects on Pulmonary Function

In a study of 58 hypertensive patients with normal respiratory function who received oral doses of 15, 30 or 60 mg of pindolol, no significant changes were observed in forced expiratory volume (FEV), maximum voluntary ventilation rate, maximum expiratory flow rate and maximum mid-expiratory flow rate.

Decreased FEV_I has, however, been reported in other studies.

Other Effects

Electroencephalography changes, following oral doses of 5 and 10 mg in healthy volunteers, consisted of theta and fast beta and decreases in alpha activity. In rats given 5.2 mg/kg s.c., pindolol blocked tetrabenazine-induced ptosis but not catalepsy. In mice at doses of 1 to 30 mg/kg i.v., pindolol antagonized reserpine-induced hypothermia.

TOXICOLOGY

a) Acute Toxicity

Species	Route	LD_{50} (mg/kg)
Mouse	i.v.	29 ± 1.2
Mouse	p.o.	200 ± 22
Rat	i.v.	35 ± 1.7
Rat	p.o.	260 ± 36
Rabbit	i.v.	10 ± 0.9
Rabbit	p.o.	650 ± 102
Dog	p.o.	≥ 30

b) Subacute

Species	Strain	Sex M	Sex F	# of Groups	# of Animals/ Group	Dose mg/kg/ day	Route	Duration of Study	Toxic Effect
Rats		40	40	4	10M, 10F	0, 16, 66, 246	p.o.	13W	At 246 mg/kg/day there was a mortality rate of 20%. Arrest of spermatogenesis in males and hypoplastic uteri in females were observed at doses of 66 and 246 mg/kg/day. Doses of 16, 66 and 246 mg/kg/day slightly to moderately increased SGPT levels, and reduced food intake, the efficiency of food utilization and organ and body weights. Treated animals had a slightly higher incidence of infection than controls. Granular inclusions in liver and adrenal cells and increased numbers of fat droplets in renal tubule cells were seen at doses of 246 mg/kd/day. Similar but less prominent changes were found at 66 mg/kg/day. There were isolated incidences of thymus involution, contraction of the seminal vesicles and prostatic atrophy. Green discolouration of the urine was observed.
Rats		40	40	4	10M, 10F	0, 5, 25, 130	p.o.	26W	At 130 mg/kg/day, decreased body weight and cyanosis were observed.
Dogs	Beagle	8	8	4	2M, 2F	0, 5, 20, 80 6 days/ week	p.o.	13W	At 80 mg/kg/day, convulsions, GI disturbances, mydriasis, erythema secondary to cutaneous vasodilation were observed. Food intake and body weight were reduced.
Dogs	Beagle	12	12	4	3M, 3F	0, 5, 15, 45	p.o.	26W	At 45 mg/kg/day, the mortality rate was 50%. Hepatocyte swelling, and the presence of intracellular hyaline droplets and lipochrome pigment in hepatocytes and Kupffer cells were seen at 15 and 45 ,g/kg/day and a few single sporadic degenerating liver cells were observed. Green discolouration of the urine was seen at 15 and 45 mg/kg/day. One dog in each group given 5, 15 and 45 mg/kg/day showed transient increases in alkaline phosphatase. In the 45 mg/kg/day group, convulsions, GI disturbances, arrest of spermatogenesis, weight loss and reduced adrenocortical lipids were observed.
Rats		30	30	3	10M, 10F	0, 1, 3	i.v.	4W	None
Dogs	Beagle	2	2	1	2M, 2F	0	i.v.	4W	---
		4	4	2	2M, 2F	1.5	i.v.	4W	Erythema secondary to cutaneous vasodilation.
Rats		5	5	1	5M, 5F	0	i.m.	4W	---
		10	10	1	10M, 10F	5	i.m.	4W	Slight irritant effect at injection site.

h) Chronic Toxicity

Rats		120	120	4	30M, 30F	0, 2, 14, 98	p.o.	2Y	Green discolouration of the urine at 98 mg/kg/day. At 2, 14 and 98 mg/kg/day, deposition of a greenish brown pigment in Kupffer cells of the liver.
Dogs	Beagle	16	16	4	4M, 4F	0, 2, 6, 18	p.o.	2Y	Tachycardia of 1 week duration. Erythema secondary to cutaneous vasodilation which was not dose dependent. Emesis and soft stools.
Monkeys	Rhesus	9	9	3	3M, 3F	0, 2.5, 25	p.o.	1Y	At 2.5 mg/kg/day, heart rate was slowed 15-20%. Bradycardia was seen at 25 mg/kg/day. Green discolouration of the urine at 25 mg/kg/day.

d) Deposition of Pigment

Oral administration of pindolol to rats at a dose of 200 mg/kg/day for 26 weeks resulted in the deposition of a melanin-like pigment in the liver, spleen, adrenal gland and subcutaneous tissue. Partial disappearance of this pigment from Kupffer cells in the liver occurred within four weeks following discontinuation of pindolol.

In dogs given oral doses of 5, 15, and 45 mg/kg/day for 26 weeks, dose related increases in hepatocyte lipid content were observed.

However, despite the pigment deposition and increased lipid content, all tests done for hepatic, splenic and adrenal function were normal. The significance of pigment and lipid changes is unknown.

e) Teratology and Reproduction Studies

i) Teratology

The parameters studied in the rat and rabbit teratology studies were the following: total number of pregnancies, implantations, viable fetuses, dead fetuses, total prenatal deaths, abnormal fetuses in % of living fetuses.

There was significantly greater mortality in the offspring of females treated with 100 mg/kg/day in the first four-day postpartum period and in pups of females receiving 30 mg/kg/day during the 4 to 21-day postpartum interval. This increased mortality may be a

consequence of deficits in maternal rearing behaviour, inhibition of lactation or the presence of the drug in maternal milk.

Rat:

Doses of 30 and 100 mg/kg were administered orally to groups of 20 pregnant rats on days 7-16 of gestation. Treatment with pindolol did not adversely affect any of the parameters studied.

Rabbit:

Doses of 8, 23 and 80 mg/kg were administered orally to groups of respectively, 13, 16 and 15 pregnant rabbits on days 6-18 of gestation. None of the parameters studied was significantly affected.

ii) Reproduction

Rat:

Doses of 10, 30 and 100 mg/kg were administered orally to groups of 15 male and 30 female rats. Males were treated for 70 days prior to and during the mating period. The females were treated for up to 15 days prior to mating, during mating, and throughout the gestation and lactation period to 21 days postpartum, with an interim sacrifice at Day 13 of gestation.

Spermatogenesis and fertility were reduced at doses of 30 but not 100 mg/kg/day. Tubular atrophy in the testes was found in male rats treated with doses of 30 and 100 mg/kg/day.

f) Carcinogenicity Studies

Mouse:

Pindolol was administered to 50 male and 50 female mice at dietary levels of approximately 124 mg/kg/day for 82 weeks, with an equal number of mice serving as controls. The incidence of nodules and masses observed at necropsy were comparable in the treated and control groups. This strain of mice was previously shown to be susceptible to chemical carcinogenesis.

Rat:

Pindolol was administered to 50 male and 50 female rats at a mean dose of 50 mg/kg/day for 83 weeks. A similar group of 100 rats served as a control. Mortality and incidence of tumour were comparable in the treated and untreated groups. This strain of rat was previously shown to be susceptible to chemically (2AAF) induced carcinogenesis.

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