PRODUCT MONOGRAPH

[Pr]APO-PINDOL

(Pindolol tablets U.S.P.)

Tablets 5, 10 and 15 mg

Antihypertensive/Antianginal Agent

APOTEX INC.
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Control No: 219137

DATE OF REVISION:
October 12, 2018

NAME OF DRUG

[Pr]APO-PINDOL

(Pindolol tablets U.S.P.)

Tablets 5, 10 and 15 mg

THERAPEUTIC CLASSIFICATION

Antihypertensive/Antianginal Agent

ACTIONS

APO-PINDOL (pindolol) is a β-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 β-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%) from the gastrointestinal tract. The mean absolute bioavailability after oral administration is about 87 to 92%. Plasma levels of 10 to 30 nanogram/mL are associated with its therapeutic efficacy. Following single dose administration 5 mg pindolol, the mean maximum plasma concentration (C_{max}) of pindolol was 33.1 ± 5.2 nanogram/mL (T_{max} 1 to 2 h). The elimination rate of pindolol is not dose dependent. The elimination half-life of Apo-Pindol* is 3 to 4 hours and the drug has a systemic clearance of between 400 and 500 mL/min. Approximately, 40% of pindolol is bound to plasma proteins. Pindolol is extensively and rapidly distributed throughout the body with a mean volume of distribution of 2 to 3 L/kg. The elimination kinetics has generally been described as a mono-exponential decay function using one compartment pharmacokinetics.

Pindolol is partially metabolized in the liver with approximately 30 to 40% of an oral dose being excreted unchanged in the urine. The remaining 60 to 70% of pindolol is metabolized in the liver forming inactive metabolites - hydroxylate, which is excreted via kidney and liver as glucuronides and ethereal sulfate. The inactive polar metabolites are excreted out with elimination half-life of 8 h. The fraction eliminated in bile is approximately 6 to 8%.

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

Bioavailability study was performed using normal volunteers, the rate and extent of absorption after a single oral dose of Visken 10 mg or APO-PINDOL 10 mg was measured and compared. The results can be summarized as follows:

	Visken 10 mg	APO-PINDOL 10 mg	% Diffr.
AUC 0-24 (ng-hr/mL)	325.0	301.4	-7.3
C_{max} (ng/mL)	51.79	49.58	-4.3
T_{max}	1.34	1.22	-9.0
$T_{1/2}$ (hrs)	3.9	3.9	+0.0

Peak plasma concentrations were observed in 0.5 to 3 hours.

INDICATIONS

A) Hypertension

APO-PINDOL (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 β 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.

APO-PINDOL is not recommended for the emergency treatment of hypertensive crises.

B) Angina Pectoris

APO-PINDOL (pindolol) is indicated for the prophylaxis (prevention) of angina pectoris.

CONTRAINDICATIONS

APO-PINDOL (pindolol) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation.

For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.

- Patients with bronchospasm, including bronchial asthma or severe chronic obstructive pulmonary disease (see PRECAUTIONS)
- Patients with congestive heart failure (see WARNINGS)
- Patients with right ventricular failure secondary to pulmonary hypertension
- Patients with Prinzmetal's Angina (variant angina)
- Patients with sinus bradycardia (<45 to 50 beats/minute)
- Patients with cardiogenic shock
- Patients with second or third-degree atrioventricular (A-V) block
- Patients with sick sinus syndrome
- Patients with severe peripheral arterial circulatory disturbances
- Patients with untreated pheochromocytoma
- Patients receiving anesthesia with agents which produce myocardial depression, e.g. ether

WARNINGS

A) Cardiac Failure:

Special caution should be exercised when administering APO-PINDOL (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 β-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 β-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 digitalization and diuretic therapy, APO-PINDOL should be immediately withdrawn.

B) Abrupt Cessation of Therapy with APO-PINDOL:

Patients with angina should be warned against abrupt discontinuation of APO-PINDOL. 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 ß-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of APO-PINDOL 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, APO-PINDOL therapy should be discontinued stepwise under very close observation.

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

C) Various skin rashes and conjunctival xerosis have been reported with β- 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 β-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. A switch to another therapeutic agent might be advisable.

D) Sinus bradycardia may occur with the use of APO-PINDOL due to unopposed vagal activity remaining after blockade of β_1-adrenergic receptors. However, due to its intrinsic sympathomimetic activity (ISA), pindolol causes less bradycardia at rest than some other β-adrenergic blocking agents. If excessive bradycardia occurs the dosage of APO-PINDOL should be reduced.

E) In patients with thyrotoxicosis, possible deleterious effects from long-term use of pindolol have not been adequately appraised. β blockage may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, these patients should be carefully monitored for thyroid function. Abrupt withdrawal of APO-PINDOL may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

F) **Concomitant use with calcium channel blockers:** Intravenous verapamil must not be administered to a patient already receiving treatment with APO-PINDOL due to the associated danger of cardiac arrest.

Oral calcium channel blockers (verapamil or dilitiazem) should not be given to patients receiving beta-blockers since the depressant effects on myocardial contractility, heart rate and A-V conduction may be additive. However, in exceptional cases when in the opinion of the physician, concomitant use is considered essential; such use should be instituted gradually in a hospital setting, under close medical supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

Verapamil and diltiazem give no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker. Then the calcium channel blocker may be started with the usual dose.

G) **Psoriasis:** Since beta-blockers may aggravate psoriasis, APO-PINDOL should only be prescribed after careful consideration of benefits and risks in patients with history of psoriasis.

PRECAUTIONS

A) Caution should be exercised in patients prone to non-allergic bronchospasm (e.g. chronic bronchitis, emphysema) since APO-PINDOL (pindolol) may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of β - receptors.

B) APO-PINDOL 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 β-blockers.

In these patients, the reaction may be more severe due to pharmacologic effects of the β-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 β-agonists, including parenteral salbutamol or isoproterenol, to overcome bronchospasm and norepinephrine to overcome hypotension.

C) APO-PINDOL 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. β-adrenergic-blockers may mask the premonitory signs and symptoms (e.g. palpitations, tachycardia, tremor) of acute hypoglycemia whereas sweating is not inhibited. The concurrent use of beta-blockers and antidiabetic medication should always be monitored to confirm that diabetic control is well maintained.

D) APO-PINDOL 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 β-adrenergic-blocking action of pindolol may produce an excessive reduction of sympathetic activity. APO-PINDOL should not be combined with other β-blockers.

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

G) The management of patients being treated with β-blockers and undergoing elective or emergency surgery is controversial. Although β-adrenergic-receptor-blockade impairs the ability of the heart to respond to β-adrenergically-mediated reflex stimuli, abrupt discontinuation of therapy with APO-PINDOL may be followed by severe complications (see WARNINGS).

Some patients receiving β-adrenergic-blocking agents have been subject to protracted

severe hypotension during anesthesia. Difficulty in re-starting and maintaining the heart beat has also been reported.

For these reasons, in patients with angina, undergoing elective surgery, APO-PINDOL 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 β-blockade are no longer present 48 hours after cessation of medication.

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

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

In patients with severe renal impairment, further impairment of renal function has been only rarely observed during therapy with pindolol.

I) **Anaphylactic reaction:** Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, especially non-selective beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers should be avoided in patients who are at increased risk for anaphylaxis.

J) **Phaeochromocytoma:** If patients with phaeochromocytoma are treated with a beta-blocker, an alpha-blocker should always be co-administered. (see CONTRAINDICATIONS)

K) **Usage in Pregnancy:** Since 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.

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

M) **Fertility:** In rats, pindolol did not cause any adverse effects on fertility or reproductive performance at a dose of 10 mg/kg, which is 17-times the human dose. While effects in animals are not always predictive of human effects, at dose levels of 30 mg/kg and greater, female rats were observed to mate less frequently than untreated animals (see TOXICOLOGY).

N) **Usage in Children:** Since there is no experience with pindolol in the treatment of pediatric age groups, pindolol is not indicated for paediatrics.

O) **Usage in Geriatric patients:** No evidence exists that geriatric patients require different dosages; however these patients should be treated cautiously. An excessive decrease in blood pressure or pulse rate may reduce blood supply to vital organs to inadequate levels.

P) Because dizziness or fatigue may occur during initiation of treatment with β-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 (see WARNINGS), 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, pruritis, 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.

Post- Market Adverse Drug Reactions
The following adverse drug reactions are, in most cases, mild and transient in nature and necessity for interruption of pindolol therapy is rarely observed (see WARNINGS and PRECAUTIONS).

These adverse drug reactions (table 1) have been derived from post-marketing experience with Apo-Pindol. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions (frequency not known)

Psychiatric disorders
Sleep disorders, depression, hallucinations
Nervous system disorders
Tremor, dizziness, headache
Cardiac disorders
Bradycardia, conduction disorder, cardiac failure
Vascular disorders
Hypotension, symptoms of peripheral vascular disorders (peripheral coldness), Raynaud's-like symptoms
Respiratory, thoracic and mediastinal disorders
Bronchospasm, dyspnea
Gastrointestinal disorders
Gastrointestinal disorders (nausea, vomiting, abdominal pain and diarrhea)
Skin and subcutaneous tissue disorders
Skin reaction, hyperhidrosis, worsening of psoriasis
Musculoskeletal and connective tissue disorders
Muscle cramps
General disorders and administration site conditions
Fatigue

DRUG INTERACTIONS

Table 2 – Established or Potential Drug-Drug Interactions

Product	Ref	Effect	Clinical comment
Monoamine oxidase (MAO) inhibitors	C,T	Combining these medications may increase the risk of hypotension, orthostasis, bradycardia, and heart failure due to excessive reduction of sympathetic activity. Possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the MAO inhibitor	Monoamine oxidase (MAO) inhibitor may potentiate the pharmacologic effects of beta-blockers, which are thought to competitively antagonize catecholamines at cardiac and other peripheral adrenergic neurons. Concurrent use with beta-blockers is not recommended.
Antidiabetic agents	T	Beta-blockers may interfere with the usual hemodynamic response to hyperglycaemia and produce a rise in blood pressure associated with severe bradycardia.	Beta-blockade reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs. Beta-blockers should be avoided in unstable diabetic patients (patients who experience wide and unpredictable fluctuations of blood glucose values and/or difficulty in stabilizing blood glucose levels) prone to episodes of hypoglycemia (see WARNINGS and PRECAUTIONS).
Calcium-channel blocking agents (e.g. verapamil, diltiazem)	CT (Carruthers 1991)	Because of their potential effect on the cardiac conduction system and contractility, the i.v. route must be avoided. Oral treatment, if judged absolutely necessary, requires careful monitoring, especially when the beta-blocker is combined with a verapamil-type calcium antagonist.	Use with great care with any other calcium antagonists, particularly diltiazem hydrochloride or diltiazem maleate. The combination of non-dihydropyridine calcium channel blockers (verapamil and diltiazem) and β-blockers warrants caution since additive effects on myocardial contractility,

Product	Ref	Effect	Clinical comment
			heart rate, AV conduction or on blood pressure (e.g. pronounced bradycardia, sinus arrest, and heart failure) have been observed. Close medical supervision and ECG monitoring, particularly at the beginning of treatment, is recommended (see WARNINGS) Severe reduction in blood pressure and heart failure upon the concomitant administration of dihydropyridine derivatives such as nifedipine with pindolol in patients with latent cardiac insufficiency is possible.
Anti-adrenergic agents	T	Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers, which may lead to postural hypotension.	When therapy is discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blockers should be gradually discontinued several days before clonidine is discontinued, in order to reduce the potential risk of a clonidine withdrawal hypertensive crisis (rebound effect). Monitoring of blood pressure is recommended during the anti-adrenergics withdrawal.
Non-steroidal anti-inflammatory drugs (NSAIDs)	T	Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker, may decrease its antihypertensive effect, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by NSAIDs.	Anti-hypertensive effects of beta-blockers may be decreased by non-steroidal anti-inflammatory drugs, which may lead to uncontrolled hypertension. Monitoring is required.
Phenothiazines	CT	Concurrent administration of pindolol and thioridazine is reported to result in a moderate increase in the serum levels of thioridazine and two of its metabolites, as well as higher than expected serum pindolol levels.	Concurrent use with beta-blockers with phenothiazines results in an increased plasma concentration of either drug, which may lead to hypotension, ventricular tachycardia, and pigmentary retinopathy. Monitoring is required.
Sympathomimetic drugs	T	Concomitant administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine phenylpropanolamine, or xanthine derivatives with a non-selective beta-blocker may enhance the pressor response resulting in severe hypertension due to antagonistic effects.	Pindolol may antagonize the effects of sympathomimetic drugs and xanthine derivatives which may lead to severe hypertension. Monitoring is required.
Anesthetic agents	CT	Beta-blockers and certain anaesthetics may be additive in their cardio-depressant effect and may lead to protracted severe hypotension (see WARNINGS and PRECAUTIONS).	Anaesthetic agents causing myocardial depression, such as cyclopropane and trichloroethylene, are best be avoided.
Anti-arrhythmic agents	CT	Concomitant administration of beta-blockers with class I anti-arrhythmic agents such as disopyramide, tocainide, flecainide or amiodarone have a potentiating effect on atrial-conduction time and induce negative inotropic effect, which may lead to myocardial depression, cardiac failure, hypotension, bradycardia, AV block and asystole.	Although this potentiation effect is weak for pindolol, the possibility of interactions with anti-arrhythmic agents can not be eliminated. Monitoring is required.
Digitalis glycosides	T	Beta-blockers and digitalis glycosides may be additive in their depressant effect on myocardial conduction, particularly through the atrioventricular node.	Concomitant administration of digitalis glycosides may induce serious bradycardia or heart block and thus should be avoided.
Ergot alkaloid	T	Administration with beta-blockers may enhance the vasoconstrictive effect of ergot alkaloids.	Concomitant administration with beta-blockers with ergot alkaloid may enhance the vasoconstriction, which leads to

Product	Ref	Effect	Clinical comment
			hypertension.
Cimetidine	CT	Cimetidine is a moderate inhibitor of multiple cytochrome enzymes such as CYP2D6, CYP3A4, CYP2C19, CYP2E1, CYP2C9, and CYP1A2. Concomitant administration of cimetidine may inhibit the hepatic metabolism of pindolol resulting in increased plasma concentrations of pindolol, which may lead to hypotension.	Monitoring is required.
Fingolimod	CT	Bradycardia	Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

SYMPTOMS AND TREATMENT OF OVERDOSAGE

An overdosage of beta-blocker may lead to pronounced bradycardia, hypotension, cardiac failure, cardiogenic shock, conduction abnormalities, cardiac arrest, dyspnea, bronchospasm, vomiting, hypoglycemia, depressed levels of consciousness, generalized convulsions, coma and death. In rare circumstances, overdose of beta-blockers with intrinsic sympathomimetic activity (ISA), like Apo-Pindol, may present with tachycardia and hypertension. Concomitant ingestion of alcohol, antihypertensives, antidepressants, or antiarrhythmic may aggravate the signs and symptoms of overdose.

If overdosage occurs, in all cases therapy with APO-PINDOL (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 APO-PINDOL 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 APO-PINDOL. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

A) Hypertension

APO-PINDOL (pindolol) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic but may be used alone (see INDICATIONS).

APO-PINDOL should be taken with meals.

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

APO-PINDOL 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 APO-PINDOL 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 APO-PINDOL (pindolol).

B) Angina Pectoris

The dosage of APO-PINDOL must always be adjusted to the individual requirements of the patient.

In angina, APO-PINDOL should be administered on a three or four times per day dosing regimen. APO-PINDOL 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.

Special populations:

Patients with impaired renal function/hepatic function

Patients with impaired renal or hepatic function may usually be treated with normal doses. Only in severe cases may a reduction of the daily dose be necessary (see PHARMACOLOGY –Special Populations).

Pediatric patients

Since the efficacy and safety of APO-PINDOL has not been established in children, APO-PINDOL is not indicated for paediatrics.

Geriatric patients

No evidence exists that geriatric patients require different dosages; however these patients

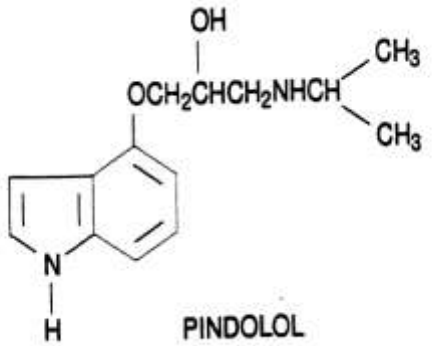
should be treated cautiously. (see PRECAUTIONS and PHARMACOLOGY – Special Populations)

PHARMACEUTICAL INFORMATION

Trade Name: Apo-Pindol

Proper Name: pindolol tablets U.S.P.

Structural Formula:



PINDOLOL

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

Molecular Weight: 248.3 g/mol

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

Description: APO-PINDOL is the free base of pindolol. It is a white, odourless powder soluble in methanol and acetic acid.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-PINDOL Tablets:
5 mg: Round, white tablet with bevelled edges. Scored and engraved APO over P5 on one side.
10 mg: Round, white tablet with bevelled edges. Scored and engraved APO over P10.
15 mg: Round, white tablet with bevelled edges. Scored and engraved APO over P15 on one side.

APO-PINDOL is available in bottles of 100 and 500, in unit dose packages of 100 (10x10), and Apotex long-term care unit dose packages (Apo-LTC Paks) of 620 (20x31) and 700 (20x35).

Non-medicinal Ingredients
Tablets 5 mg, 10 mg and 15 mg: Croscarmellose Sodium**,** Lactose Hydrous (Spray dried), Magnesium Stearate and Microcrystalline Cellulose.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C. Protect from moisture. Protect from light.

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 use (see ACTIONS).

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_1 has, however, been reported in other studies.

Other Effects
Electroencephalographic 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 tetrabenzine-induced ptosis but not catalepsy. In mice at doses of 1 to 30 mg/kg i.v., pindolol antagonized reserpine-induced hypothermia.

Special populations

Geriatrics
The elderly population may show higher plasma concentrations of pindolol as a combined result of a decreased metabolism of the drug in elderly population, a decreased hepatic blood flow and a decreased renal elimination.

Pregnancy
The elimination half-life of pindolol does not differ significantly between pregnant and non-pregnant patients. (see PRECAUTIONS).

Transplacental distribution of pindolol is not stereoselective. Pregnancy may alter the pharmacokinetic disposition of pindolol, suggesting an increase in the distribution volume and total clearance.

Patients with hepatic / renal impairment
Patients with impaired renal or hepatic function may usually be treated with normal doses. Only in severe cases may a reduction of the daily dose be necessary. The plasma half-life of pindolol is increased up to 11.5 hours, depending on severity, in patient with renal impairment and is increased up to 30 hours, depending on severity, in patients with liver cirrhosis.

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/F	No. of groups	N/group	Dose mg/kg/day	Route	Duration	Toxic Effects
Rat	40/40	4	10 M/10 F	0, 16, 66, 246	Oral	13 weeks	At 246 mg/kg 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. Doses of 16, 66 and 246 mg/kg 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/kg. Similar but less prominent changes were found at 66 mg/kg. There were isolated incidences of thymus involution, contraction of the seminal vesicles and prostatic atrophy. Green discolouration of the urine was observed.

b) Subacute (cont'd)

Species/ strain	Sex M/F	No. of Groups	N/group	Dose mg/kg/day	Route	Duration of Study	Toxic Effects
Rats	40/40	4	10 M/10 F	0, 5, 25, 130	oral	26 weeks	At 130 mg/kg/day, decreased body weight and cyanosis were observed.
Dogs/ Bealgle	8/8	4	2 M/2 F	5, 20, 80 (6 days/week)	oral	13 weeks	At 80 mg/kg/day, convulsions, gastrointestinal disturbances, mydriasis, erythema secondary to cutaneous vasodilation were observed. Food intake and body weight were reduced.
Dogs/ Beagle	12/12	4	3 M/3 F	0, 5, 15, 45	oral	26 weeks	At 45 mg/kg, 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 mg/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, gastrointestinal disturbances, arrest of spermatogenesis, weight loss and reduced adreno-cortical lipids were observed.

b) Subacute (cont'd.)

Species/ strain	Sex M/F	No. of groups	N/group	Dose mg/kg/day	Route	Duration	Toxic Effects
Rats	30/30	3	10 M/ 10 F	0, 1, 3	I.V.	4 weeks	None
Dogs/ Beagle	2/2 4/4	1 2	2 M/2 F 2 M/2 F	0 1.5	I.M.	4 weeks	1.5 mg/kg: Erythema secondary to cutaneous vasodilation
Rats	5/5 10/10	1 1	5 M/5 F 10 M/10 F	0 5	I.M.	4 weeks	5 mg/kg: Slight irritant effect at injection site

c) Chronic Toxicity

Species/ Strain	Sex M/F	No. of groups	N/group	Dose mg/kg/day	Route	Duration (years)	Toxic Effects
Rats	120/120	4	30 M/30 F	0, 2, 14, 98	oral	2	Green discolouration of the urine at 98 mg/kg. At 2, 14 and 98 mg/kg, deposition of a greenish brown pigment in Kupffer cells of the liver.
Dogs/ Beagle	16/16	4	4 M/4 F	0, 2, 6, 18	oral	2	Tachycardia of 1 week duration. Erythema secondary to cutaneous vasodilatation which was not dose dependent. Emesis and soft stools.
Monkey/ Rhesus	9/9	3	3 M/3 F	0, 2.5, 25	oral	1	At 2.5 mg/kg, heart rate was slowed 15 to 20%. Bradycardia was seen at 25 mg/kg. Green discolouration of the urine at 25 mg/kg.

d) Disposition 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.

Rat: Doses of 30 and 100 mg/kg were administered orally to groups of 20 pregnant rats (Sandoz Closed Strain) on days 7 to16 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 (Swiss Hare Strain) on days 6 to 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 (Sandoz Closed Strain) and 30 female (Carworth Wistar CFE Strain) 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.

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

f) Carcinogenicity Studies

Mouse: Pindolol was administered to 50 male and 50 female mice (Sandoz OFI Strain) 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 (Sandoz OFA Strain) 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 tumor 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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PART III: CONSUMER INFORMATION

PrAPO-PINDOL
(pindolol tablets USP)

This leaflet is part III of a three-part "Product Monograph" published when APO-PINDOL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Apo-Pindol. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-PINDOL lowers high blood pressure (hypertension). APO-PINDOL can be used alone or with other medicines to treat this condition.

APO-PINDOL is also used to treat chest pains (angina) due to ischemic heart disease (disease caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and reduces blood flow to the heart).

What it does:

APO-PINDOL belongs to a class of drugs called "beta-blockers". These drugs block the action of certain chemicals on the heart that increase blood pressure and increase heart rate.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking APO-PINDOL regularly even if you feel fine.

When it should not be used:

Do not take APO-PINDOL if you:

- are allergic to pindolol or any other beta blockers or any of the non-medicinal ingredients of APO-PINDOL listed under "What the nonmedicinal ingredients are"
- have or have had asthma or other lung diseases (such as Chronic obstructive pulmonary disease known as COPD)
- have heart failure
- have high blood pressure that affects the arteries in your lungs and the right side of your heart
- have reduced blood flow to the heart causing heaviness, tightness or pain in your chest
- have a slow heartbeat (less than 45 to 50 beats per minute)
- have had a condition where your heart suddenly could not pump enough blood causing:
  - rapid heartbeat
  - shortness of breath
  - sweating
  - loss of consciousness
- will have surgery where you will need general anesthesia
- have certain types of abnormal heart beat caused when the heart's natural pacemaker doesn't work properly
- have narrowed arteries that reduce the blood flow to your limbs. This can cause paleness or poor circulation in the arms and legs (cold hands and feet)
- have a tumor of the adrenal gland known as pheochromocytoma.

What the medicinal ingredient is:

Pindolol

What the nonmedicinal ingredients are:

Croscarmellose sodium, lactose hydrous (spray dried), magnesium stearate and microcrystalline cellulose.

What dosage forms it comes in:

Tablets; 5, 10 and 15 mg.

WARNING AND PRECAUTIONS

BEFORE you use APO-PINDOL talk to your doctor or pharmacist if you:

- have history of heart failure
- have any of the following:
  - diabetes, and are taking insulin or oral diabetes medicine
  - severe kidney disease
  - liver disease
  - a condition causing overactivity of the thyroid gland
  - psoriasis (a type of skin disease characterized by thickened patches of red/silver skin)
- have had a severe allergic reaction in the past
- are taking medications to treat high blood pressure
- have asthma, chronic bronchitis, and emphysema, or an inflammation in the nose due to allergies
- are undergoing surgery or dental treatment
- are pregnant, or plan to become pregnant
- are breastfeeding (Apo-Pindol may pass into your milk and harm your baby)
- are less than 18 years old
- are currently taking or have recently taken any other prescription or over-the-counter medications.

If any of these apply to you, **tell your doctor before taking Apo-Pindol**. The doctor will take these things into account before and during your treatment with

APO-PINDOL . Your doctor may need to monitor you more closely while you are using this medicine.

Driving and using machines:
Before you perform tasks which may require special attention, wait until you know how you respond to Apo-Pindol. Dizziness, and/or fatigue can especially occur after the first dose and when the dose is increased.

Slow heart beat
You may experience a slow heart beat while taking Apo-Pindol, If this happens, contact your doctor. Your dose may need to be reduced.

Laboratory Tests
Your doctor may perform tests at regular intervals if you are taking APO-PINDOL for a long time.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including prescription and over-the counter medicines.

The following medicines may interact with APO-PINDOL:

- medicines used to treat the irregular rhythm of the heart such as digoxin and digitalis
- medicines found in some cold remedies and nose drops (e.g. noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, xanthine derivative
- medicines used to treat high blood pressure, including clonidine and calcium channel blockers (e.g. oral verapamil, diltizem). Your doctor should carefully monitor you if you are taking these in combination with Apo-Pindol.
- insulin or oral antidiabetic medicines
- nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling (such as ibuprofen, naproxen, celecoxib)
- ergot alkaloids, a class of medicines used in the prevention and treatment of migraine headaches
- cimetidine, used to relieve heartburn and gastrointestinal ulcers
- medicines used to treat depression, seizures, schizophrenia, or psychotic disorders (e.g., tricyclic antidepressants, barbiturates, phenothiazines, monoamine oxidase inhibitors)
- fingolimod, a medicine used to treat multiple sclerosis
- medicines used for anaesthesia such as cyclopropane, trichloroethylene.

PROPER USE OF THIS MEDICATION

Your doctor will determine your dose based on your individual medical needs and will tell you when and how to take APO-PINDOL. Take APO-PINDOL exactly as prescribed. It is recommended to take your dose at about the same time every day.
APO-PINDOL should be taken with food.

Do not stop taking APO-PINDOL or change your dose without first talking to your doctor. Serious side effects, such as chest pain or heart attack can occur if you abruptly stop taking this medication.

Usual adult dose:

To treat high blood pressure:
The usual starting dose is 5 mg twice a day. In some cases, your doctor may prescribe a higher dose, up to a maximum of 45 mg each day.

To treat chest pain due to heart disease:
The usual starting dose is 5 mg, three times a day. In some cases, your doctor may prescribe a higher dose if needed, up to a maximum recommended dose of 40 mg each day.

Overdose:

If you think you have taken too much Apo-Pindol, contact your doctor, nurse pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, skip the missed dose and carry on with the next one at the usual time. Do not double the dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients taking APO-PINDOL may experience side effects. Keep track of your side effects and consult the table below for appropriate action.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Common	Nausea	√		
Uncommon	Dry eyes		√	
Unknown	Allergic			✓

frequency:	**Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			
	Slow heart beat			✓
	Heart rhythm disturbance			✓
	Heart failure			✓
	Chest Pain: sudden and oppressive			✓
	Coldness, burning, tingling or numbness in arms or legs		✓	
	Difficulty breathing with wheezing or coughing		✓	
	Hallucination: see or hear things that are not there		✓	
	Low blood pressure	✓		
	Shortness of breath	✓		
	Tiredness	✓		
	Dizziness	✓		
	Headache	✓		
	Trembling	✓		
	Nausea	✓		
	Vomiting	✓		
	Abdominal pain	✓		
	Diarrhea	✓		
	Muscle cramp	✓		
	Sleep	✓		
	Depression	✓		
	Skin reaction	✓		
	Excessive sweating	✓		
	Aggravation of psoriasis (thick patches of red/silver skin)	✓		

This is not a complete list of side effects. For any unexpected effects while taking Apo-Pindol, contact your doctor or pharmacist.

HOW TO STORE IT

- Do not use after the expiry date shown on the box.
- Store in the original package, protect from light.
- Store at room temperature 15°C to 30°C. Protect from moisture.
- Keep out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-PINDOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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