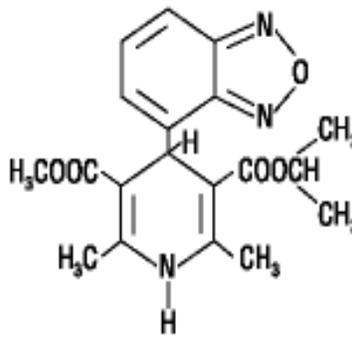


DYNACIRC CR[®]
(isradipine)
Controlled Release Tablets

DESCRIPTION

DYNACIRC CR contains isradipine, a calcium antagonist. It is available for once-daily oral administration as a controlled-release 5-mg and 10-mg tablet. DYNACIRC CR is a registered trademark for isradipine GITS (Gastrointestinal Therapeutic System) tablets.

The structural formula of isradipine is:



Chemically, isradipine is 3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, with a molecular weight of 371.39. The molecular formula is C₁₉H₂₁N₃O₅. Isradipine is a yellow, fine crystalline powder which is odorless or has a faint characteristic odor. Isradipine is practically insoluble in water (<10 mg/L at 37°C), but is soluble in ethanol and freely soluble in acetone, chloroform, and methylene chloride.

Active Ingredient: Isradipine

Inactive Ingredients: Butylated hydroxytoluene, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, propylene glycol, red ferric oxide, silicon dioxide, sodium chloride, titanium dioxide, yellow ferric oxide.

System Components and Performance: Isradipine is delivered from the DYNACIRC CR Controlled Release Tablet as follows: a semipermeable membrane surrounds an osmotically active drug core. The core is composed of 2 layers: an “active” layer containing the drug, and a pharmacologically inert but osmotically active “push” layer. After ingestion, the tablet overcoating is quickly dissipated in the gastrointestinal tract, allowing water to enter the tablet through the semipermeable membrane. The polyethylene oxide polymer swells in the osmotic (“push”) layer and exerts pressure against the “active” drug layer, releasing isradipine as a fine suspension through the laser-drilled tablet orifice which has been positioned on the “active” drug layer side. Drug delivery is essentially constant as long as the osmotic gradient remains constant and, after either 5 mg or 10 mg of isradipine is released, gradually falls to a negligible amount. The controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or

gastrointestinal motility. The delivery of isradipine in DYNACIRC CR depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the GI tract. The biologically inert core of the tablet remains intact and, unless it becomes trapped, is eliminated in the feces.

CLINICAL PHARMACOLOGY

Mechanism of Action: Isradipine is a dihydropyridine calcium channel blocker. It binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and smooth muscle. The effects observed in mechanistic experiments in vitro and studied in intact animals and man are compatible with this mechanism of action and are typical of the class.

Except for diuretic activity, the mechanism of which is not clearly understood, the pharmacodynamic effects of isradipine observed in whole animals can also be explained by calcium channel blocking activity, especially dilating effects in arterioles which reduce systemic resistance and lower blood pressure, with a small increase in resting heart rate. Although like other dihydropyridine calcium channel blockers, isradipine has negative inotropic effects in vitro, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs at doses lower than those which affect contractility. In patients with normal ventricular function, isradipine's afterload-reducing properties lead to some increase in cardiac output.

Effects in patients with impaired ventricular function have not been fully studied.

Clinical Effects: In randomized, placebo-controlled, double-blind, clinical trials, DYNACIRC CR has been shown to have antihypertensive effects proportional to doses between 5 and 20 mg, administered once daily. DYNACIRC CR produced statistically significant reductions in supine and standing blood pressure, compared with placebo, 24 hours postdose. The endpoint results of one parallel-group, dose-ranging trial showed mean responses 24 hours after ingestion of DYNACIRC CR (systolic/diastolic) -5.2/-2.8, -13.4/-9.7, -15.6/-10.2, and -15.5/-11.8 mmHg, for 5-, 10-, 15-, and 20-mg doses, respectively, change from baseline greater than concurrent placebo. The antihypertensive effect of any one dose begins in about 2 hours and reaches a peak at about 8 to 10 hours postdose. At the recommended starting dose (5 mg) the trough response (24 hours after dosing) was about 76% that of the peak. At doses of 10, 15, and 20 mg, the trough blood pressure response was about equal to that at peak effect. In association with the fall in blood pressure, resting heart rate is slightly increased, on average from 1 to 3 beats/minute. The antihypertensive response to DYNACIRC CR has not been detected to be influenced by gender or age.

Hemodynamics: In man, peripheral vasodilation produced by immediate-release DYNACIRC is reflected by decreased systemic vascular resistance and increased cardiac output.

Hemodynamic studies conducted in patients with normal left ventricular function produced, following intravenous isradipine administration, increases in cardiac index, stroke volume index, coronary sinus blood flow, heart rate, and peak positive left ventricular dP/dt. Systemic, coronary, and pulmonary vascular resistance was decreased. These studies were conducted with

doses of isradipine which produced clinically significant decreases in blood pressure. The clinical consequences of these hemodynamic effects, if any, have not been evaluated.

Effects on heart rate are variable, dependent upon rate of administration and presence of underlying cardiac condition. While increases in both peak positive dP/dt and LV ejection fraction are seen when intravenous isradipine is given, it is impossible to conclude that these represent a positive inotropic effect due to simultaneous changes in preload and afterload. In patients with coronary artery disease undergoing atrial pacing during cardiac catheterization, intravenous isradipine diminished abnormalities of systolic performance. In patients with moderate left ventricular dysfunction, oral and intravenous isradipine in doses which reduce blood pressure by 12% to 30%, resulted in improvement in cardiac index without increase in heart rate, and with no change or reduction in pulmonary capillary wedge pressure. Combination of isradipine and propranolol did not significantly affect left ventricular dP/dt max. The clinical consequences of these effects have not been evaluated.

Electrophysiologic Effects: In general, no detrimental effects on the cardiac conduction system were seen with the use of immediate-release DYNACIRC. Electrophysiologic studies were conducted on patients with normal sinus and atrioventricular node function. Intravenous isradipine in doses which reduce systolic blood pressure did not affect PR, QRS, AH*, or HV* intervals.

No changes were seen in Wenckebach cycle length, atrial, and ventricular refractory periods. Slight prolongation of QT_c interval of 3% was seen in one study. Effects on sinus node recovery time (CSNRT) were mild or not seen.

In patients with sick sinus syndrome, at doses which significantly reduced blood pressure, intravenous isradipine resulted in no depressant effect on sinus and atrioventricular node function.

*AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time

*HV = conduction time through His bundle and the bundle branch-Purkinje system.

Pharmacokinetics and Metabolism: With the immediate-release formulation DYNACIRC, 90% to 95% of the orally administered dose is absorbed. Because of the biotransformation of isradipine during its first-pass through the portal circulation, the bioavailability of DYNACIRC CR ranges from 15% to 24%. Isradipine is 95% bound to plasma proteins.

Peak concentrations of approximately 1 ng/mL/mg dosed occur about 1.5 hours after administration of immediate-release DYNACIRC. The elimination of isradipine is biphasic with an early half-life of 1½ to 2 hours, and a terminal half-life of about 8 hours, resulting in trough concentrations of about 0.1 ng/mL/mg dosed of immediate-release DYNACIRC.

In single-dose studies of DYNACIRC CR, after a 2 to 3 hour lag time, concentrations of isradipine plateau between 7 and 18 hours post-dosing (reaching a C_{max} of 3 to 4 ng/mL with an AUC of 62 to 73 ng•h/mL for a 10-mg dose) and then a concentration >50% of the peak exists for 17 to 20 hours.

There is no evidence of dose dumping either in the presence or absence of food. Food has been shown to decrease the extent of bioavailability of DYNACIRC CR by up to 25%.

The pharmacokinetics of DYNACIRC CR are linear over the dose range of 5 to 20 mg, in that the plasma drug concentrations are proportional to the dose administered.

Isradipine is completely metabolized prior to excretion, and no unchanged drug is detected in the urine. The major routes of isradipine metabolism are ring oxidation of the dihydropyridine moiety to give the corresponding pyridine, and ester cleavage, with or without concomitant oxidation of the dihydropyridine moiety, giving the corresponding carboxylic acids. The cytochrome P450 3A4 system is implicated in the formation of these metabolites, which are hemodynamically inactive. Approximately 60% to 65% of an administered dose is excreted in the urine and 25% to 30% in the feces. With immediate-release DYNACIRC, mild renal impairment (creatinine clearance 30 to 80 mL/min) increases the AUC of isradipine by 45%. Progressive deterioration reverses this trend, and patients with severe renal failure (creatinine clearance <10 mL/min) who have been on hemodialysis show a 20% to 50% lower AUC than healthy volunteers. In elderly patients administered immediate-release DYNACIRC, C_{max} and AUC are increased by 13% and 40%, respectively; in patients with hepatic impairment, C_{max} and AUC are increased by 32% and 52%, respectively (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Hypertension: DYNACIRC CR is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DYNACIRC CR is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None

PRECAUTIONS

General: Blood Pressure: Because DYNACIRC CR decreases peripheral resistance, like other calcium blockers, DYNACIRC CR may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DYNACIRC CR, particularly at the initial recommended doses (see DOSAGE AND ADMINISTRATION).

Use in Patients with Congestive Heart Failure: Although acute hemodynamic studies in patients with congestive heart failure have shown that immediate-release DYNACIRC reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses in vitro and possibly in some patients. Caution should be exercised when using DYNACIRC CR in congestive heart failure patients, particularly in combination with a beta-blocker.

Peripheral Edema: Peripheral edema, when it occurs, is usually mild to moderate in severity. It is a localized phenomenon thought to be associated with vasodilation of arterioles and other small blood vessels, and not due to left ventricular dysfunction or generalized fluid retention. Peripheral edema is dose-related with an incidence ranging from approximately 9% at 5 mg, 13% at 10 mg, 16% at 15 mg, and 36% at the highest dose studied (20 mg once-daily). With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this edema from the effects of decreasing left ventricular function. Although the frequency of edema is correlated with dose, no patients treated with DYNACIRC CR discontinued the short-term (6 weeks or less), placebo-controlled hypertension studies as a result of edema. Less than 5% of patients treated with DYNACIRC CR in long-term studies discontinued due to edema.

Other: As with any other non-deformable material, caution should be used when administering DYNACIRC CR in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been reports of obstructive symptoms in patients with known strictures associated with ingestion of other GITS products.

Information for Patients: DYNACIRC CR Controlled Release Tablets should be swallowed whole. Do not chew, divide, or crush tablets. Do not be concerned if you occasionally notice in your stool something resembling a tablet. In DYNACIRC CR, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug for your body to absorb. When this process is completed, the empty tablet shell is eliminated in the stool.

Drug Interactions: Nitroglycerin: Immediate-release DYNACIRC has been safely coadministered with nitroglycerin.

Hydrochlorothiazide: A study in normal healthy volunteers has shown that concomitant administration of immediate-release DYNACIRC and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect.

Propranolol: In a single-dose study in normal volunteers using immediate-release DYNACIRC, co-administration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Significant increases in AUC (27%) and C_{max} (58%) and decreases in T_{max} (23%) of propranolol were noted in this study.

Digoxin: The concomitant administration of immediate-release DYNACIRC and digoxin in a single-dose pharmacokinetic study did not affect renal, non-renal, and total body clearance of digoxin.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. An increased volume of circulating fluids might be required if such an interaction were to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet (approximately 6, 31, and 156 times the maximum recommended daily dose based on a 50 kg man) resulted in dose-

dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. These findings, which were replicated in a subsequent experiment, may have been indirectly related to an effect of isradipine on circulating gonadotropin levels in the rats; a comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for 2 years with 2.5, 15, or 80 mg/kg/day isradipine in the diet (approximately 6, 38, and 200 times the maximum recommended dose based on a 50 kg man) showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenic tests. No effect on fertility was observed in male and female rats treated with up to 60 mg/kg/day isradipine.

Pregnancy: Pregnancy Category C: Isradipine was administered orally to rats and rabbits during organogenesis. Treatment of pregnant rats with doses of 6, 20, or 60 mg/kg/day produced a significant reduction in maternal weight gain during treatment with the highest dose (150 times the maximum recommended human daily dose) but with no lasting effects on the mother or the offspring. Treatment of pregnant rabbits with doses of 1, 3, or 10 mg/kg/day (2.5, 7.5, and 25 times the maximum recommended human daily dose) produced decrements in maternal body weight gain and increased fetal resorption at the 2 higher doses. There was no evidence of embryotoxicity at doses which were not maternotoxic and no evidence of teratogenicity at any dose tested. In a peri/postnatal administration study in rats, reduced maternal body weight gain during late pregnancy at oral doses of 20 and 60 mg/kg/day isradipine was associated with reduced birth weights and decreased peri and postnatal pup survival.

There are no adequate and well controlled studies in pregnant women. The use of DYNACIRC CR during pregnancy should only be considered if the potential benefit outweighs potential risks.

Nursing Mothers: It is not known whether DYNACIRC is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects of DYNACIRC on nursing infants, a decision should be made as to whether to discontinue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness have not been established in children.

Geriatric Use: Clinical studies of DYNACIRC CR did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Elderly patients have decreased clearance of DYNACIRC with a higher average AUC and C_{max} (see Pharmacokinetics and Metabolism). The larger extent of bioavailability may be a result of a reduced clearance and/or reduced first-pass metabolism of the drug. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

In a controlled clinical trial with DYNACIRC CR, dose-related edema occurred at an incidence of approximately 9% at 5 mg, 13% at 10 mg, 16% at 15 mg, and 36% at the highest dose studied (20 mg); was mild to moderate in severity; and was not related to age or gender.

The incidences of elicited or volunteered adverse reactions (excluding non-drug related) in the following tables are based on 6-week multicenter, placebo-controlled, double-blind hypertension studies. Less than 1% of patients treated with DYNACIRC CR or placebo discontinued from these studies due to adverse reactions.

The most common adverse experiences ($\geq 1.0\%$) reported with DYNACIRC CR in a dose-response study are shown in the following table. There were no discontinuations of patients treated with DYNACIRC CR in this study due to these common side effects.

Most Frequently Reported Newly-Occurring Adverse Reactions in Dose-Response Study

Adverse Reactions (Excluding Non-Drug Related)	DYNACIRC CR				Placebo Group
	5 mg (N=79)	10 mg (N=79)	15 mg (N=82)	20 mg (N=78)	(N=83)
Headache	13.9%	12.7%	18.3%	10.3%	15.7%
Edema	8.9%	12.7%	15.9%	35.9%	3.6%
Dizziness	5.1%	6.3%	3.7%	6.4%	2.4%
Constipation	3.8%	1.3%	1.2%	2.6%	0.0%
Fatigue	2.5%	7.6%	3.7%	3.8%	2.4%
Flushing	2.5%	3.8%	1.2%	1.3%	1.2%
Abdominal discomfort	1.3%	5.1%	3.7%	5.1%	1.2%
Rash	1.3%	1.3%	0.0%	2.6%	0.0%

The table below shows elicited or volunteered adverse experiences for patients treated with DYNACIRC CR in two 6-week, placebo-controlled, multicenter studies, at doses from 5 to 20 mg, and considered by the investigator to be at least possibly drug related. The results for patients treated with DYNACIRC CR are presented for all doses pooled together (reported by at least 1.0% of active drug-treated patients). The incidence of adverse reactions is listed below:

Adverse Reactions (Excluding Non-Drug Related)	Treatment Group	
	DYNACIRC CR (N=422)	Placebo (N=186)
Edema	15.2%	2.2%
Headache	13.0%	12.4%
Dizziness	4.7%	2.7%
Fatigue	4.3%	2.2%
Abdominal discomfort	2.8%	0.5%
Flushing	1.9%	0.5%
Constipation	1.7%	0.0%
Palpitations	1.2%	0.0%
Nausea	1.2%	1.6%
Abdominal distention	1.2%	0.0%

The following adverse experiences were reported in 0.5% to 1.0% or less of patients treated with DYNACIRC CR or immediate-release DYNACIRC in hypertensive studies, or were noted in postmarketing experience with immediate-release DYNACIRC. More serious events are shown in italics. The relationship of these adverse experiences to isradipine administration is uncertain.

Skin: Pruritus, *urticaria, angioedema*.

Musculoskeletal: Backache/pain, joint pain, neck pain/sore/stiff, legs ache/pain, cramps of legs/feet.

Respiratory: Dyspnea, nasal congestion, cough.

Cardiovascular: Epistaxis, tachycardia, chest pain, shortness of breath, hypotension, *syncope, atrial or ventricular fibrillation, myocardial infarction, heart failure*.

Gastrointestinal: Diarrhea, vomiting, appetite increased or decreased.

Urogenital: pollakiuria, impotence, dysuria, nocturia.

Central Nervous: Drowsiness, insomnia, lethargy, nervousness, libido decrease/frigidity, impotence, depression, *paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke*.

Autonomic: Dry mouth, hyperhidrosis, visual disturbance.

Miscellaneous: Weight gain, throat discomfort, *drug fever, leukopenia, elevated liver function tests*.

No gastrointestinal bleeding has been reported in clinical trials with DYNACIRC CR Controlled Release Tablets.

In a long-term (one-year) open-label, hypertension trial with DYNACIRC CR, the adverse events reported were generally the same as those seen in the short-term placebo-controlled studies. About 6% of patients treated with DYNACIRC CR discontinued the long-term trial due to adverse reactions.

With immediate-release DYNACIRC, most of the adverse experiences were transient, mild, and related to vasodilatory effects. The following table shows the most common adverse events reported in US clinical trials for immediate-release DYNACIRC, volunteered or elicited, and considered by the investigator to be at least possibly drug related.

Adverse Experience	DYNACIRC				Placebo	Active Controls*
	All Doses	2.5 mg twice-daily	5 mg twice-daily [†]	10 mg twice-daily ^{††}	(N=297) %	(N=414) %
Headache	13.7	12.6	10.7	22.0	14.1	9.4
Dizziness	7.3	8.0	5.3	3.4	4.4	8.2
Edema	7.2	3.5	8.7	8.5	3.0	2.9
Palpitations	4.0	1.0	4.7	5.1	1.4	1.5
Fatigue	3.9	2.5	2.0	8.5	0.3	6.3
Flushing	2.6	3.0	2.0	5.1	0.0	1.2
Chest pain	2.4	2.5	2.7	1.7	2.4	2.9
Nausea	1.8	1.0	2.7	5.1	1.7	3.1
Dyspnea	1.8	0.5	2.7	3.4	1.0	2.2
Abdominal discomfort	1.7	0.0	3.3	1.7	1.7	3.9
Tachycardia	1.5	1.0	1.3	3.4	0.3	0.5
Rash	1.5	1.5	2.0	1.7	0.3	0.7
Pollakiuria	1.5	2.0	1.3	3.4	0.0	<1.0
Weakness	1.2	0.0	0.7	0.0	0.0	1.2
Vomiting	1.1	1.0	1.3	0.0	0.3	0.2
Diarrhea	1.1	0.0	2.7	3.4	2.0	1.9

* Propranolol, prazosin, hydrochlorothiazide, enalapril, and captopril.

† Initial dose of 2.5 mg twice-daily followed by maintenance dose of 5.0 mg twice-daily.

†† Initial dose of 2.5 mg twice-daily followed by sequential titration to 5.0 mg twice-daily, 7.5 mg twice-daily, and maintenance dose of 10.0 mg twice-daily.

In open-label, long-term studies of up to 2 years in duration with immediate-release DYNACIRC, the adverse experiences reported were generally the same as those reported in the short-term controlled trials. The overall frequencies of these adverse events were slightly higher in the long-term than in the controlled studies, but in the controlled studies most adverse reactions were mild and transient.

OVERDOSAGE

Although there is no well documented experience with DYNACIRC overdose, available data suggest that, as with other dihydropyridines, gross overdose would result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension overdose calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of lower extremities and attention to circulating fluid volume and urine output. A vasoconstrictor (such as epinephrine, norepinephrine, or levarterenol) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Since isradipine is highly protein bound, dialysis is not likely to be of benefit.

Significant lethality was observed in mice given oral doses of more than 200 mg/kg and rabbits given about 50 mg/kg of isradipine. Rats tolerated doses of more than 2,000 mg/kg without effects on survival.

DOSAGE AND ADMINISTRATION

The dosage of DYNACIRC CR Controlled Release Tablets should be individualized. The recommended initial dose of DYNACIRC CR is 5 mg once-daily as monotherapy or in combination with a thiazide diuretic. An antihypertensive response usually occurs within 2 hours, with the peak antihypertensive response occurring 8 to 10 hours post-dose; blood pressure reduction is maintained for at least 24 hours following drug administration. If necessary, the dose may be adjusted in increments of 5 mg at 2 to 4 week intervals up to a maximum dose of 20 mg/day. Adverse experiences are increased in frequency above 10 mg/day.

DYNACIRC CR Controlled Release Tablets should be swallowed whole and should not be bitten or divided.

The bioavailability (increased AUC) of immediate-release DYNACIRC is increased in elderly patients (older than 65 years of age), patients with hepatic functional impairment, and patients with mild renal impairment. Ordinarily, a starting dose of DYNACIRC CR 5 mg once-daily should be used in these patients.

HOW SUPPLIED

DYNACIRC CR Controlled Release Tablets

5 mg: A light pink, round, standard, biconvex and film coated tablet. Printing is in red with “DynaCirc CR” in a semicircle with “5” centered below the semicircle.

Bottles of 30 controlled-release tablets (NDC 0173-0784-01)

10 mg: A beige, round, standard biconvex and film coated tablet. Printing is in red with “DynaCirc CR” in a semicircle with “10” centered below the semicircle.

Bottles of 30 controlled-release tablets (NDC 0173-0785-01)

Store and Dispense: Below 86°F (30°C) in a tight container, protected from moisture and humidity.

Jointly manufactured for:



GlaxoSmithKline

Research Triangle Park, NC 27709

By: **Novartis Consumer Health, Inc.**

Lincoln, NE 68517 and

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Cincinnati, OH 45237

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