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Adverse Reactions (Excluding Non-Drug Related)	Treatment Group DynaCirc CR® (isradipine) (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%–1.0% or less of DynaCirc CR® (isradipine) or immediate-release DynaCirc® (isradipine) treated patients in hypertensive studies, or were noted in postmarketing experience with immediate-release DynaCirc® (isradipine) Capsules. 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® (isradipine) Controlled Release Tablets.

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

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

(See second table at top of previous page)

In open-label, long-term studies of up to two years in duration with immediate-release DynaCirc® (isradipine) Capsules, 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® (isradipine) overdosage, available data suggest that, as with other dihydropyridines, gross overdosage would result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension overdosage 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 over 200 mg/kg and rabbits given about 50 mg/kg of isradipine. Rats tolerated doses of over 2000 mg/kg without effects on survival.

DOSAGE AND ADMINISTRATION

The dosage of DynaCirc CR® (isradipine) Controlled Release Tablets should be individualized. The recommended initial dose of DynaCirc CR® (isradipine) 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 8–10 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 2–4 week intervals up to a maximum dose of 20 mg/day. Adverse experiences are increased in frequency above 10 mg/day.

DynaCirc CR® (isradipine) Controlled Release Tablets should be swallowed whole and should not be bitten or divided.

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

HOW SUPPLIED

DynaCirc CR® (isradipine) 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 65726-235-10)

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 semi-circle.

Bottles of 30 controlled release tablets (NDC 65726-236-10)

Store and Dispense:

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

Rx only

Revised: June, 2007

Distributed by:

Reliant Pharmaceuticals, Inc.

Liberty Corner, NJ 07938

Address Medical Inquiries to:

Reliant Medical Inquiries

c/o PPD

2655 Meridian Parkway

Durham, NC 27713-2203

or Call: 877-311-7515

2352F-02

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2002700

Shown in Product Identification Guide, page 329

LOVAZA™ ℞

(lō-vā-zā)

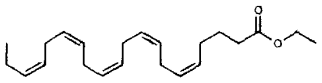
(omega-3-acid ethyl esters)

Capsules

DESCRIPTION

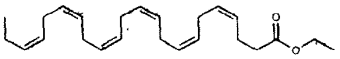
Lovaza, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Lovaza (omega-3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

The structural formula of DHA ethyl ester is



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

Lovaza capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of Lovaza is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies:

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Lovaza) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza was independent of age (<49 years vs ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza in children are not available.

Drug Interactions:

Cytochrome P450-Dependent Monooxygenase Activities:

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

(See table 1 below)

Lovaza 4 g per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

Very High Triglycerides: Monotherapy

The effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16

Continued on next page

Table 1: Response to the Addition of LOVAZA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

Parameter	LOVAZA + Simvastatin N=122			Placebo + Simvastatin N=132			Difference	P-Value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non-HDL-C	137	123	-9.0	141	134	-2.2	-6.8	<0.0001
TG	268	182	-29.5	271	260	-6.3	-23.2	<0.0001
TC	184	172	-4.8	184	178	-1.7	-3.1	<0.05
VLDL-C	52	37	-27.5	52	49	-7.2	-20.3	<0.05
Apo-B	86	80	-4.2	87	85	-1.9	-2.3	<0.05
HDL-C	46	48	+3.4	43	44	-1.2	+4.6	<0.05
LDL-C	91	88	+0.7	88	85	-2.8	+3.5	=0.05

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL), Median % Change = Median Percent Change from Baseline, Difference = LOVAZA Median % Change - Placebo Median % Change

weeks duration The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively Median HDL-C level was 23 0 mg/dL

The changes in the major lipoprotein lipid parameters for the Lovaza and placebo groups are shown in Table 2

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL)

Parameter	LOVAZA N=42		Placebo N=42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6 7	-51 6
Non-HDL-C	271	-13 8	292	-3 6	-10.2
TC	296	-9 7	314	-1 7	-8.0
VLDL-C	175	-41 7	175	-0 9	-40 8
HDL-C	22	+9 1	24	0 0	+9 1
LDL-C	89	+44 5	108	-4 8	+49.3

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline, Difference = Lovaza Median % change - Placebo Median % Change

Lovaza 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals Patients should be monitored to ensure that the LDL-C level does not increase excessively

The effect of Lovaza on the risk of pancreatitis in patients with very high TG levels has not been evaluated

The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been determined.

INDICATIONS AND USAGE

Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels.

Usage Considerations:

In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication

PRECAUTIONS

General:

Initial Therapy: Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy: Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests:

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy

In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy

Drug Interactions.

Anticoagulants: Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants Patients receiving treatment with both Lovaza and anticoagulants should be monitored periodically

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state

Cytochrome P450-Dependent Monooxygenase Activities. Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats The potential of Lovaza to induce P450 activities in humans has not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison) Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurum* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison)

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women It is unknown whether Lovaza can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Lovaza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison)

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison)

In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison)

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison) However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when Lovaza is administered to a woman who is breastfeeding

Pediatric Use:

Safety and effectiveness in pediatric patients under 18 years of age have not been established

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least [illegible] of patients treated with Lovaza 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 3 Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza and 2 6% of patients treated with placebo

Table 3: Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day

BODY SYSTEM Adverse Event	LOVAZA (N = 226) n	%	Placebo* (N = 226) n	%
Subjects with at least 1 adverse event	80	35 4	63	27.9
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4 4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1 3	2	0.9
Digestive				
Dyspepsia	7	3 1	6	2.7
Eructation	11	4 9	5	2.2
Skin				
Rash	4	1 8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version [illegible] Subjects were counted only once for each body system and for each preferred term

* Placebo was corn oil for all studies

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below

BODY AS A WHOLE Enlarged abdomen, asthenia, bad odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death

CARDIOVASCULAR SYSTEM. Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia

DIGESTIVE SYSTEM Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting

HEMATOLOGIC-LYMPHATIC SYSTEM: Lymphadenopathy

INFECTIONS AND INFESTATIONS Viral infection

METABOLIC AND NUTRITIONAL DISORDERS Edema, hyperglycemia, increased ALT, and increased AST

MUSCULOSKELETAL SYSTEM: Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder

NERVOUS SYSTEM Central nervous system neoplasm, depression, dizziness, emotional lability, facial paralysis, hypesthesia, somnia, vasodilatation, and vertigo

RESPIRATORY SYSTEM Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis

SKIN. Alopecia, eczema, pruritus, and sweating.

SPECIAL SENSES. Cataract.

UROGENITAL SYSTEM. Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Lovaza does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza, and should continue this diet during treatment with Lovaza. In clinical studies, Lovaza was administered with meals

The daily dose of Lovaza is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily)

HOW SUPPLIED

Lovaza (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light yellow oil and bearing the designation REL900 in bottles of 60 (NDC 65726-425-15) and 120 (NDC 65726-425-27).

Recommended Storage:

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze Keep out of reach of children.

Rx only

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Distributed by:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
Address Medical Inquiries to:
Reliant Medical Inquiries
c/o PPD
3655 Meridian Parkway
Durham, NC 27713-2203
or Call: 877-311-7515
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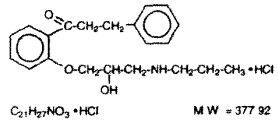
Shown in Product Identification Guide, page 329

RYTHMOL® SR Rx

[ryth-mul]
(propafenone hydrochloride) extended release CAPSULES

DESCRIPTION

RYTHMOL SR (propafenone hydrochloride) is an antiarrhythmic drug supplied in extended-release capsules of 225, 325 and 425 mg for oral administration.
The structural formula of propafenone HCl is given below:



$C_{21}H_{27}NO_3 \cdot HCl$ M W = 377 92

2'-[2-Hydroxy-3-(propylamino) -propoxy]-3-phenylpropiophenone hydrochloride

Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Rythmol SR are capsules filled with cylindrical-shaped 2 × 2 mm microtablets containing propafenone and the following inactive ingredients antifoam, gelatin, hypromellose, red iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and titanium dioxide

CLINICAL PHARMACOLOGY

Mechanism of Action:
Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes The electrophysiological effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged Propafenone reduces spontaneous automaticity and depresses triggered activity Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man In clinical trials with the immediate release formulation, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e the transient outward, the delayed rectifier, and the inward rectifier current) Propafenone has local anesthetic activity approximately equal to procaine. Compared to propafenone, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors).

Electrophysiology:
Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged In patients with Wolff-Parkinson-White (WPW) syndrome, RYTHMOL immediate release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see **ADVERSE REACTIONS/Electrocardiograms**).

Hemodynamics:
Studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium Cardiac catheterization studies in patients with moderately impaired ventricular function (mean C I = 2 61 L/min/m^2), utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min+ followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 µg/mL (a dose that produces plasma levels of propafenone greater than does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Table 1: Analysis of tachycardia-free period (days) from Day 1 of randomization

	RYTHMOL SR Dose			
Parameter	225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event†	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	112	291	*	41
Range	0 – 285	0 – 293	0 – 300	0 – 289
p-Value (Log-rank test)	0 014	< 0 0001	< 0 0001	—
Hazard Ratio compared to placebo	0 67	0.43	0 35	—
95% CI for Hazard Ratio	(0.49, 0 93)	(0 31, 0.61)	(0.24, 0 51)	—

* Fewer than 50% of the patients had events. The median time is not calculable
† Terminating events comprised 91% atrial fibrillation, 5% atrial flutter, and 4% PSVT.

Pharmacokinetics and Metabolism:
Absorption/Bioavailability: Maximal plasma levels of propafenone are reached between three to eight hours following the administration of RYTHMOL SR. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute bioavailability of 3 4%, while a 300 mg immediate release tablet had an absolute bioavailability of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate release tablets increased still further
Relative bioavailability assessments have been performed between RYTHMOL SR capsules and RYTHMOL immediate release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase in overall first pass metabolism (see **Metabolism**) As a result of the increased first pass effect, higher daily doses of propafenone were required from the SR formulation relative to the immediate release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20–25% higher after SR capsule administration than after immediate-release tablet administration.
Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose BID), the difference between the fed and fasted state was not significant.
Distribution: Following intravenous administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a two compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about five minutes. The volume of the central compartment was about 88 liters (1 1 L/kg) and the total volume of about 252 liters.
In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5 – 2 µg/mL Protein binding decreases to about 88% in patients with severe hepatic dysfunction.
Metabolism: There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2–10 hours These patients metabolize propafenone into two active metabolites 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10–32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.
As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day At low doses the differences are greater, with slow metabolizers attaining concentrations about three to four times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics are linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after four to five days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The large inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see **DOSAGE AND ADMINISTRATION**).
The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in vitro*. In man after administration of RYTHMOL SR, the 5-hydroxypropafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.

Inter-Subject Variability:
With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.
The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see **PRECAUTIONS**). Decreased liver function also increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the RYTHMOL SR capsule formulation. Absolute bioavailability of RYTHMOL immediate release tablets has been demonstrated to be inversely related to indocyanine green clearance, reaching 60–70% at clearances of 7 mL/min and below.

Stereochemistry:
RYTHMOL is a racemic mixture. The R- and S-enantiomers of propafenone display stereoselective disposition characteristics *in vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent ß-antagonist than the R-enantiomer. Following administration of RYTHMOL immediate release tablets or RYTHMOL SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7 The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg RYTHMOL SR are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time

Clinical Trials:
RYTHMOL SR has been evaluated in patients with a history of electrocardiographically documented recurrent episodes of symptomatic atrial fibrillation in two randomized, double-blind, placebo controlled trials
RAFT: In one US multicenter study (Rythmol SR Atrial Fibrillation Trial, RAFT), three doses of RYTHMOL SR (225 mg BID, 325 mg BID and 425 mg BID) and placebo were compared in 523 patients with symptomatic, episodic atrial fibrillation The patient population in this trial was 59% male with a mean age of 63 years, 91% White and 6% Black The patients had a median history of atrial fibrillation of 13 months, and documented symptomatic atrial fi-

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