WHAT IS FIBROCARD

Fibrocard is used alone or together with other medicines to treat heart rhythm problems, severe chest pain (angina), or high blood pressure (hypertension). High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, and kidneys, resulting in a stroke, heart failure, or kidney failure. High blood pressure may also increase the risk of heart attacks. These problems may be less likely to occur if blood pressure is controlled.

Fibrocard is a calcium channel blocker. It works by affecting the movement of calcium into the cells of the heart and blood vessels. As a result, Fibrocard relaxes blood vessels and increases the supply of blood and oxygen to the heart while reducing its workload.

Fibrocard is available only with your doctor's prescription.

FIBROCARD INDICATIONS

Fibrocard hydrochloride tablets USP are indicated for the treatment of the following:

Angina

1.Angina at rest including:

- -Vasospastic (Prinzmetal's variant) angina-Unstable (crescendo, pre-infarction) angina

2.Chronic stable angina (classic effort-associated angina)

Arrhythmias

1.In association with digitalis for the control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation

2.Prophylaxis of repetitive paroxysmal supraventricular tachycardia

Essential hypertension

Fibrocard hydrochloride is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including this drug.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

HOW SHOULD I USE FIBROCARD?

Use Fibrocard as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Take Fibrocard by mouth with or without food.
- Swallow Fibrocard whole. Do not break, crush, or chew before swallowing.
- Check with your doctor before you eat grapefruit or drink grapefruit juice while you use Fibrocard.
- If you cannot swallow the capsule whole, you may open it and sprinkle the contents over a spoonful of applesauce. Mix the medicine with the applesauce and swallow the mixture right away, followed by a glass of water. Do not crush or chew the medicine before swallowing. Do not store the mixture for future use.
- Taking Fibrocard at the same time each day will help you remember to take it.
- If you miss a dose of Fibrocard, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once.

Ask your health care provider any questions you may have about how to use Fibrocard.

Fibrocard is used to treat high blood pressure, control angina (chest pain) and treat certain heart disorders. It is also used for prevention of migraine headache.

FIBROCARD DESCRIPTION

Each tablet contains 240 mg of Fibrocard hydrochloride.

Fibrocard hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). The chemical name of Fibrocard hydrochloride is benzeneacetonitrile,-[3-[{2-(3,4 -dimethoxyphenyl)α ethyl} methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride. It has a molecular weight of 491.07 and the molecular formula is C27H38N204·HCl.

Fibrocard hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Fibrocard hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether.

FIBROCARD DOSAGE

Essential Hypertension

The dose of Fibrocard hydrochloride sustained-release capsules should be individualized by titration. The usual daily dose of sustained-release Fibrocard, Fibrocard hydrochloride sustained-release capsules, in clinical trials has been 240 mg given by mouth once daily in the morning. However, initial doses of 120 mg a day may be warranted in patients who may have an increased response to Fibrocard (e.g., elderly, small people, etc.). Upward titration should be based on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of Fibrocard hydrochloride sustained-release capsules are evident within the first week of therapy.

If adequate response is not obtained with 120 mg of Fibrocard hydrochloride sustained-release capsules, the dose may be titrated upward in the following manner:

(a) 180 mg in the morning.

(b) 240 mg in the morning.

(c) 360 mg in the morning.

(d) 480 mg in the morning.

Fibrocard hydrochloride sustained-release capsules are for once-a-day administration. When switching from immediate-release Fibrocard to Fibrocard hydrochloride sustained-release capsules, the same total daily dose of Fibrocard hydrochloride sustained-release capsules can be used.

As with immediate-release Fibrocard, dosages of Fibrocard hydrochloride sustained-release capsules should be individualized and titration may be needed in some patients.

Sprinkling the Capsule Contents on Food

Fibrocard hydrochloride sustained-release capsules may also be administered by carefully opening the capsule and sprinkling the pellets on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any pellet/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Fibrocard hydrochloride sustained-release capsule is not recommended.

FIBROCARD INTERACTIONS

In vitro metabolic studies indicate that Fibrocard hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Fibrocard has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of Fibrocard hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of Fibrocard hydrochloride, therefore, patients should be monitored for drug interactions.

The table as follows provides a list of potential drug interactions due to pharmacokinetic reasons.

Other Drug Interactions and Additional Drug Interaction Information: HIV Antiviral Agents: Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of Fibrocard may increase. Caution should be used or dose of Fibrocard may be decreased.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant Fibrocard hydrochloride-lithium therapy with either no change or an increase in serum lithium levels. The addition of Fibrocard hydrochloride, however, has also resulted in the lowering of the serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs should be monitored carefully.

Neuromuscular Blockers: Clinical data and animal studies suggest that Fibrocard hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of Fibrocard hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Acetylsalicylic Acid: Increased tendency to bleed.

Ethanol (Alcohol): Elevation of ethanol plasma levels.

HMG Co-A Reductase Inhibitors ("Statins"): Treatment with HMG CoA reductase inhibitors (eg. simvastatin, atorvastatin or lovastatin) in a patient taking Fibrocard should be started at the lowest possible dose and titrated upwards. If Fibrocard treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with Fibrocard.

Antihypertensives, Diuretics, Vasodilators: Potentiation of the hypotensive effect.

FIBROCARD SIDE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Serious adverse reactions are uncommon when Fibrocard therapy is initiated with upward dose titration within the recommended single and total daily dose. See,,,, for discussion of heart failure, hypotension, elevated liver enzymes, AV block and rapid ventricular response. Reversible (upon discontinuation of Fibrocard) non-obstructive, paralytic ileus has been infrequently reported in association with the use of Fibrocard. The following reactions (Table 1) to orally administered Fibrocard hydrochloride extended-release capsules (PM) occurred at rates of 2% or greater or occurred at lower rates but appeared to be drug-related in clinical trials in hypertension.

In previous experience with other formulations of Fibrocard (N = 4,954) the following reactions (Table 2) have occurred at rates greater than 1% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4,954 patients.

In clinical trials related to the control of ventricular response in patients taking digoxin who had atrial fibrillation or atrial flutter, ventricular rate below 50/min

at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

Open Trials / Post-marketing Experience

The following reactions, reported with orally administered Fibrocard in 2% or less of patients, occurred under conditions [open Fibrocard trials, post-marketing experience (reactions added since the initial U.S. approval of Fibrocard hydrochloride extended-release capsules (PM) in 1998 are marked with an asterisk)] where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: angina pectoris, atrioventricular dissociation, ECG abnormal*, chest pain, claudication, hypertension*, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: diarrhea, dry mouth, elevated liver enzymes*, gastrointestinal distress, gingival hyperplasia.
Hemic and Lymphatic: ecchymosis or bruising.

Nervous System: cerebrovascular accident, confusion, equilibrium disorders, extrapyramidal symptoms, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

Respiratory: dyspnea.

Skin: arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson Syndrome, erythema multiforme.

Special Senses: blurred vision, tinnitus.

Urogenital: gynecomastia, galactorrhea/hyperprolactinemia, impotence, increased urination, spotty menstruation.

Other: allergy aggravated, asthenia*.

Treatment of Acute Cardiovascular Adverse Reactions

The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of Fibrocard, apply the appropriate emergency measures immediately; e.g., intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol hydrochloride (all in the usual doses), or calcium gluconate (10%

solution). In patients with hypertrophic cardiomyopathy, use alpha-adrenergic agents (phenylephrine hydrochloride, metaraminol bitartrate, or methoxamine hydrochloride) to maintain blood pressure, and isoproterenol and avoid norepinephrine. If further support is necessary, inotropic agents (dopamine hydrochloride or dobutamine hydrochloride) may be administered. Actual treatment and dosage depends on the severity of the clinical situation and the judgment and experience of the treating physician.

FIBROCARD CONTRAINDICATIONS

Hypersensitivity to Fibrocard hydrochloride or to any of the excipients of Fibrocard.

Acute myocardial infarction with complications (bradycardia, hypotension, left ventricular failure); cardiogenic shock; 2nd- or 3rd-degree AV block (except in patients with a functioning artificial pacemaker); sick sinus syndrome (except in patients with a functioning artificial pacemaker); severe congestive heart failure (unless secondary to a supraventricular tachycardia amenable to Fibrocard hydrochloride therapy); atrial fibrillation/flutter in the presence of an accessory bypass tract (eg, WPW, LGL syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if Fibrocard hydrochloride is administered; severe hypotension.
Patients receiving-adrenergicIV blockingβ drugs (eg, propranolol).
Fibrocard hydrochloride IV and-adrenergicβ blocking drugs IV, should not be administered in close proximity to each other (within a few hrs), since both may have a depressant effect on myocardial contractility and AV conduction.

Ventricular Tachycardia: Administration of Fibrocard hydrochloride IV to patients with wide-complex ventricular tachycardia (QRS >0.12 sec) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper pretherapy diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.

FIBROCARD PREGNANCY

Fibrocard Sanbe Farma is contraindicated during pregnancy and lactation.

Category effects on the fetus by FDA - C.

FIBROCARD OVERDOSE

Overdose with Fibrocard may lead to pronounced hypotension, bradycardia, and conduction system abnormalities (e.g., junctional rhythm with AV

dissociation and high degree AV block, including asystole). Other symptoms secondary to hypoperfusion (e.g., metabolic acidosis, hyperglycemia, hyperkalemia, renal dysfunction, and convulsions) may be evident.

Treat all Fibrocard overdoses as serious and maintain observation for at least 48 hours
[especially ISOPTIN® SR (verapamil hydrochloride)]inuous prefe hospital care. Delayed pharmacodynamic consequences may occur with the sustained release formulation. Fibrocard is known to decrease gastrointestinal transit time.

In overdose, tablets of Fibrocard have occasionally been reported to form concretions within the stomach or intestines. These concretions have not been visible on plain radiographs of the abdomen, and no medical means of gastrointestinal emptying is of proven efficacy in removing them. Endoscopy might reasonably be considered in cases of massive overdose when symptoms are unusually prolonged.

Treatment of overdosage should be supportive. Beta adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with Fibrocard. Continued treatment with large doses of calcium may produce a response. In a few reported cases, overdose with calcium channel blockers that was initially refractory to atropine became more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride. Fibrocard cannot be removed by hemodialysis. Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

FIBROCARD PRECAUTIONS

THE CONTENTS OF THE Fibrocard HYDROCHLORIDE SUSTAINED-RELEASE CAPSULES SHOULD NOT BE CRUSHED OR CHEWED. Fibrocard HYDROCHLORIDE SUSTAINED-RELEASE CAPSULES ARE TO BE SWALLOWED WHOLE OR THE ENTIRE CONTENTS OF THE CAPSULE SPRINKLED ONTO APPLESAUCE.

General

Use in Patients with Impaired Hepatic Function

Since Fibrocard is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release Fibrocard to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects should be carried out.

Use in Patients with Attenuated (Decreased) Neuromuscular Transmission

It has been reported that Fibrocard decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that Fibrocard prolongs recovery from the neuromuscular blocking agent vecuronium and causes a worsening of myasthenia gravis. It may be necessary to decrease the dosage of Fibrocard when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients with Impaired Renal Function

About 70% of an administered dose of Fibrocard is excreted as metabolites in the urine. Until further data are available, Fibrocard should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage.

Information for Patients

When the sprinkle method of administration is prescribed, details of the proper technique should be explained to the patient.

Drug-Drug Interactions

Drug Interactions: Effects of other drugs on Fibrocard pharmacokinetics

In vitro metabolic studies indicate that Fibrocard is metabolized by cytochrome P450, CYP3A4, CYP1A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g., erythromycin, ritonavir) causing elevation of plasma levels of Fibrocard while inducers of CYP3A4 (e.g., rifampin) have caused a lowering of plasma levels of Fibrocard. Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics.

HMG-CoA Reductase Inhibitors

The use of HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with Fibrocard has been associated with reports of myopathy/rhabdomyolysis.

Co-administration of multiple doses of 10 mg of Fibrocard with 80 mg simvastatin resulted in exposure to simvastatin 2.5-fold that following simvastatin alone. Limit the dose of simvastatin in patients on Fibrocard to 10 mg daily. Limit the daily dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as Fibrocard may increase the plasma concentration of these drugs.

Beta Blockers

Concomitant therapy with beta-adrenergic blockers and Fibrocard may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. The combination of sustained-release Fibrocard and beta-adrenergic blocking agents has not been studied. However, there have been reports of excess bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension.

For hypertensive patients, the risk of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral Fibrocard.

A decrease in metoprolol clearance has been reported when Fibrocard and metoprolol were administered together. A similar effect has not been observed when Fibrocard and atenolol are given together.

Clonidine

Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with Fibrocard. Monitor heart rate in patients receiving concomitant Fibrocard and clonidine.

Digitalis

Consider reducing digoxin dose when Fibrocard and digoxin are to be given together. Monitor digoxin level periodically during therapy. Chronic Fibrocard treatment can increase serum digoxin levels by 50% to 75% during the first

week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of Fibrocard on digoxin pharmacokinetics is magnified. Fibrocard may reduce total body clearance and extrarenal clearance of digoxin by 27% and 29%, respectively. If digoxin toxicity is suspected, suspend or discontinue digoxin therapy.

In previous clinical trials with other Fibrocard formulations related to the control of ventricular response in patients taking digoxin who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

Antihypertensive Agents

Fibrocard administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with Fibrocard may result in reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of Fibrocard and prazosin.

Antiarrhythmic Agents

Disopyramide: Until data on possible interactions between Fibrocard and disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after Fibrocard administration.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and Fibrocard may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and Fibrocard may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of Fibrocard and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of Fibrocard and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiological effects of quinidine and Fibrocard on AV conduction were studied in 8 patients. Fibrocard significantly counteracted the effects of

quinidine on AV conduction. There has been a report of increased quinidine levels during Fibrocard therapy.

Nitrates: Fibrocard has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Alcohol: Fibrocard has been found to significantly inhibit ethanol elimination resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol.

Other

Aspirin: In a few reported cases, coadministration of Fibrocard with aspirin has led to increased bleeding times greater than observed with aspirin alone.

Cimetidine: The interaction between cimetidine and chronically administered Fibrocard has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of Fibrocard was either reduced or unchanged.

Grapefruit Juice: Grapefruit juice may significantly increase concentrations of Fibrocard. Grapefruit juice given to nine healthy volunteers increased S- and R-Fibrocard AUC0-12 by 36% and 28%, respectively. Steady state Cmax and Cmin of S-verapamil increased by 57% and 16.7%, respectively with grapefruit juice compared to control. Similarly, Cmax and Cmin of R-verapamil increased by 40% and 13%, respectively. Grapefruit juice did not affect half-life, nor was there a significant change in AUC0-12 ratio R/S compared to control. Grapefruit juice did not cause a significant difference in the PK of norverapamil. This increase in Fibrocard plasma concentration is not expected to have any clinical consequences.

Lithium: Pharmacokinetic and pharmacodynamic interactions between oral Fibrocard and lithium have been reported. The former may result in a lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Fibrocard therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral Fibrocard bioavailability.

Phenobarbital: Phenobarbital therapy may increase Fibrocard clearance.

Cyclosporine: Fibrocard therapy may increase serum levels of cyclosporine.

Inhalation Anesthetics: Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as Fibrocard, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that Fibrocard may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of Fibrocard and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

An 18-month toxicity study in rats, at a low multiple (6 fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of Fibrocard administered in the diet of rats for two years at doses of 10, 35 and 120 mg/kg per day or approximately 1x, 3.5x and 12x, respectively, the maximum recommended human daily dose (480 mg per day or 9.6 mg/kg/day).

Fibrocard was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Pregnancy

Pregnancy Category C. Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the maximum recommended human daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Fibrocard crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Labor and Delivery

It is not known whether the use of Fibrocard during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of Fibrocard HCl in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing Mothers

Fibrocard is excreted in human milk. Because of the potential for adverse reactions in nursing infants from Fibrocard, nursing should be discontinued while Fibrocard is administered.

Pediatric Use

Safety and efficacy of Fibrocard in children below the age of 18 years have not been established.

Geriatric Use

Clinical studies of Fibrocard did not include sufficient numbers of subjects aged 65 and over 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. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Aging may affect the pharmacokinetics of Fibrocard. Elimination half-life may be prolonged in the elderly.
Fibrocard is highly metabolized by the liver, and about 70% of the administered dose is excreted as metabolites in the urine. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered. In general, lower initial doses of Fibrocard hydrochloride sustained-release capsules may be warranted in the elderly.

Animal Pharmacology and/or Animal Toxicology

In chronic animal toxicology studies Fibrocard caused lenticular and/or suture line changes at 30 mg/kg/day or greater and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not the rat. Development of cataracts due to Fibrocard has not been reported in man.