

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasil) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- Neutropenia/agranulocytosis (5.1)
- Thrombotic thrombocytopenic purpura (5.1)
- Aplastic anemia (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Coronary Stenting (1.2) 2/200X
Dosage and Administration, Coronary Stenting (2.2) 2/200X

INDICATIONS AND USAGE

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

DOSAGE AND ADMINISTRATION

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg (3)

CONTRAINDICATIONS

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

WARNINGS AND PRECAUTIONS

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone #) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch/report.htm

DRUG INTERACTIONS

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

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5.5 Monitoring: Liver function tests

Postmarketing experience includes individuals with elevations in their transaminases and bilirubin to >10X above the upper limits of normal. Based on postmarketing and clinical trial experience, liver function testing, including ALT, AST, and GGT, should be considered whenever liver dysfunction is suspected, particularly during the first 4 months of treatment [see *Adverse Reactions* (6.1)].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

During clinical development, 3394 patients were exposed to cholinisol, 2048 in stroke and 1346 in coronary stenting. In all studies, cholinisol was administered at a dose of 50 mg daily. Duration of exposure ranged from two to five years for the thrombotic stroke studies and at least 30 days for the coronary stenting studies.

Thrombotic Stroke Studies:

Adverse reactions in stroke patients were relatively frequent with over 50% of patients reporting at least one. Most (30% to 40%) involved the gastrointestinal tract. Most adverse reactions are mild, but 21% of patients discontinued therapy because of an adverse reaction, principally diarrhea, rash, nausea, vomiting, GI pain and neutropenia. Most adverse reactions occur early in the course of treatment, but a new onset of adverse reactions can occur after several months.

Adverse reactions observed in at least 1% of patients: The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled clinical studies in stroke patients described above comparing IMDICON, placebo, and aspirin over study periods of up to 5.8 years.

Adverse reactions that occurred in at least 1% of patients treated with IMDICON are shown in the following table:

Percent of Patients With Adverse Reactions in Thrombotic Stroke Controlled Studies			
Event	IMDICON (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Reactions	60.0 (20.9)	53.2 (14.5)	34.3 (6.4)
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	3.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function Test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Hematological: Neutropenia/thrombocytopenia, TTP, aplastic anemia, leukemia; agranulocytosis, pancytopenia, eosinophilia, thrombocytosis and bone marrow depression have been reported [see *Boxed Warning and Warnings and Precautions* (5.1)].

Gastrointestinal: IMDICON therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. These gastrointestinal adverse reactions usually occur within 3 months of initiation of therapy and typically are resolved within 1 to 2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. In some cases of severe or bloody diarrhea, colitis was later diagnosed.

Rash: Cholinisol has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug

rechallenge. There have been rare reports of severe rashes, including Stevens-Johnson syndrome, erythema multiforme and exfoliative dermatitis.

Abnormal Liver Function Tests: IMDICON therapy has been associated with elevations of alkaline phosphatase, bilirubin, and transaminases, which generally occurred within 1 to 4 months of therapy initiation. In controlled clinical studies in stroke patients, the incidence of elevated alkaline phosphatase (greater than two times the upper limit of normal) was 7.6% in cholinisol patients, 6% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than two times upper limit of normal) was 3.1% in cholinisol patients, 4% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical studies (e.g., no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin [see *Warnings and Precautions* (5.5)].

Adverse reactions observed in less than 1% of patients:

Hemorrhagic: IMDICON has been associated with increased bleeding, spontaneous posttraumatic bleeding and perioperative bleeding including, but not limited to, gastrointestinal bleeding. It has also been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, and conjunctival hemorrhage.

Intracerebral bleeding was rare in the stroke clinical studies of IMDICON, with an incidence no greater than that seen with comparator agents (cholinisol 0.5%, aspirin 0.6%, placebo 0.75%). It has also been reported postmarketing.

Coronary Stenting Studies:

The rate of serious bleeding complications and neutropenia in the major coronary stenting study are shown in the table below.

RESAT (Restenosis in Stent Anticoagulation Trial)	IMDICON + Aspirin N=546	Aspirin N=557	Warfarin + Aspirin N=550
Hemorrhagic Complications	30 (5.5%)	10 (1.8%)	34 (6.2%)
Cerebrovascular Accident	0 (0%)	2 (0.4%)	1 (0.2%)
Neutropenia ($\leq 1200/\text{mm}^3$)	3 (0.5%)	0 (0%)	1 (0.2%)

There were no cases of thrombotic thrombocytopenic purpura (TTP) or aplastic anemia reported in 1346 patients who received cholinisol plus aspirin in the five randomized coronary stenting studies.

6.2 Postmarketing Experience

The following relatively serious and potentially fatal adverse reactions associated with the use of IMDICON have been identified during post approval use of Imdicon: hemolytic anemia with reticulocytosis, immune thrombocytopenia, intracerebral bleeding, hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis, hepatic failure, peptic ulcer, renal failure, nephrotic syndrome, hyponatremia, vasculitis, sepsis, allergic reactions (including angioedema, allergic pneumonitis, and anaphylaxis), systemic lupus (positive ANA), peripheral neuropathy, serum sickness, arthropathy and myositis.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs

The tolerance and long-term safety of coadministration of IMDICON with heparin, oral anticoagulants or fibrinolytic agents have not been established. In studies for coronary stenting, patients received heparin and IMDICON concomitantly for approximately 12 hours. If a patient is switched from an anticoagulant or fibrinolytic drug to IMDICON, the former drug should be discontinued prior to IMDICON administration [see *Warnings and Precautions* (5.3)].

7.2 Phenytoin

In vitro studies demonstrated that cholinisol does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of cholinisol and its metabolites have not been studied in vivo. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with IMDICON. Caution

of the recommended therapeutic dose (50 mg daily) of cholinol has no significant pharmacologic actions in man other than inhibition of platelet function and prolongation of the bleeding time.

12.3 Pharmacokinetics

After oral administration of a single 50 mg dose, cholinol is rapidly absorbed with peak plasma levels occurring at approximately 2 hours after dosing and is extensively metabolized. Absorption is greater than 80%. Administration after meals results in a 20% increase in the AUC of cholinol.

Cholinol displays nonlinear pharmacokinetics and clearance decreases markedly on repeated dosing. In older volunteers the apparent half-life of cholinol after a single 50 mg dose is about 12.6 hours; with repeat dosing at 50 mg daily, the terminal elimination half-life rises to 4 to 5 days and steady-state levels of cholinol in plasma are obtained after approximately 14 to 21 days.

Cholinol binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. The binding to albumin and lipoproteins is nonsaturable over a wide concentration range. Cholinol also binds to alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less cholinol in plasma is bound to this protein.

Cholinol is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Following an oral dose of radioactive cholinol administered in solution, 60% of the radioactivity is recovered in the urine and 23% in the feces. Approximately 1/3 of the dose excreted in the feces is intact cholinol, possibly excreted in the bile. Cholinol is a minor component in plasma (5%) after a single dose, but at steady-state is the major component (15%). Approximately 40% to 50% of the radioactive metabolites circulating in plasma are covalently bound to plasma protein.

Hepatically Impaired Patients: The effect of decreased hepatic function on the pharmacokinetics of IMDICON was studied in 17 patients with advanced cirrhosis. The average plasma concentration of cholinol in these subjects was slightly higher than that seen in older subjects in a separate trial [see Use in Specific Populations (8.7)].

Renally Impaired Patients: Patients with mildly (Cr 50 to 80 mL/min) or moderately (Cr 20 to 50 mL/min) impaired renal function were compared to normal subjects (Cr 80 to 150 mL/min) in a study of the pharmacokinetic and platelet pharmacodynamic effects of IMDICON (50 mg daily) for 11 days. Concentrations of unchanged IMDICON were measured after a single 50 mg dose and after the final 50 mg dose on Day 11.

AUC values of cholinol increased by 28% and 60% in mild and moderately impaired patients, respectively, and plasma clearance decreased by 37% and 52%, respectively, but there were no statistically significant differences in ADP-induced platelet aggregation. In this small study (26 patients), bleeding times showed significant prolongation only in the moderately impaired. [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

Geriatric patients: Clearance of cholinol decreases with age. Clearance of cholinol is somewhat lower in elderly patients and trough levels are increased. Steady-state trough values in elderly patients (mean age 70 years) are about twice those in younger volunteer populations [see Use in Specific Populations (8.5)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year oral carcinogenicity study in rats, cholinol at daily doses of up to xx mg/kg (xx mg/m²) was not tumorigenic. For a 70-kg person (1.73 m² body surface area) the dose represents xx times the recommended clinical dose on a mg/kg basis and xx times the clinical dose on body surface area basis. In a 78-week oral carcinogenicity study in mice, cholinol at daily doses up to xx mg/kg (xx mg/m²) was not tumorigenic. The dose represents xx times the recommended clinical dose on a mg/kg basis and xx times the clinical dose on a body surface area basis.

Cholinol was not mutagenic in vitro in the Ames test, the rat hepatocyte DNA repair assay, or the Chinese-hamster fibroblast chromosomal aberration test; or in vivo in the mouse spermatozoid morphology test, the Chinese-hamster micronucleus test, or the Chinese-hamster bone-marrow-cell sister-chromatid exchange test. Cholinol was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day.

14 CLINICAL STUDIES

14.1 Thrombotic Stroke

The effect of cholinol on the risk of thrombotic stroke was studied in two multicenter, randomized, double-blind studies.

1. Study in Patients Experiencing Stroke Precursors: In a study comparing cholinol and aspirin (The Cholinol Aspirin Stroke Study or

CASS), 3047 patients (1975 men, 1072 women) who had experienced such stroke precursors as transient ischemic attack (TIA), transient monocular blindness (amaurosis fugax), reversible ischemic neurological deficit or minor stroke, were randomized to cholinol 50 mg daily or aspirin 650 mg daily. The study was designed to follow patients for at least 2 years and up to 5 years.

Over the duration of the study, IMDICON significantly reduced the risk of fatal and nonfatal stroke by 24% (p = .011) from 18.1 to 13.8 per 100 patients followed for 5 years, compared to aspirin. During the first year, when the risk of stroke is greatest, the reduction in risk of stroke (fatal and nonfatal) compared to aspirin was 48%; the reduction was similar in men and women.

2. Study in Patients Who Had a Completed Thrombotic Stroke: In a study comparing cholinol with placebo (The American Canadian Cholinol Study or ACCS) 1064 patients who had experienced a previous atherothrombotic stroke were treated with IMDICON 50 mg daily or placebo for up to 3 years.

IMDICON significantly reduced the overall risk of stroke by 24% (p = .017) from 24.6 to 18.6 per 100 patients followed for 3 years, compared to placebo. During the first year the reduction in risk of fatal and nonfatal stroke over placebo was 33%.

14.2 Coronary Stenting

The ability of IMDICON to reduce the rate of thrombotic events after the placement of coronary artery stents has been studied in five randomized studies, one of substantial size (Restenosis in Stent Anticoagulation Trial or RESAT) described below, and four smaller studies. In these studies, cholinol 50 mg daily with aspirin (dose range from 100 mg daily to 325 mg daily) was compared to aspirin alone or to warfarin plus aspirin. The studies enrolled patients undergoing both planned (elective) and unplanned coronary stent placement. The types of stents used, the use of intravascular ultrasound, and the use of high-pressure stent deployment varied among the studies, although all patients in RESAT received a Palmaz-Schatz stent. The efficacy endpoints of the studies were similar, and included death, myocardial infarction and the need for repeat coronary angioplasty or CABG. All studies followed patients for at least 30 days.

In RESAT, patients were randomized to receive one of three regimens for 30 days: aspirin alone, aspirin plus warfarin, or aspirin plus cholinol. Therapy was initiated following successful coronary stent placement. The composite primary endpoint was the incidence of stent thrombosis, defined as death, Q-Wave MI, or angiographic thrombus within the stented vessel demonstrated at the time of documented ischemia requiring emergent revascularization. The incidence rates for the primary endpoint and its components at 30 days are shown in the table below.

RESAT	IMDICON + Aspirin N=546	Aspirin N=557	Warfarin + Aspirin N=550	Odds Ratio (95% C.I.)*	p-Value*
Composite Primary Endpoint	3 (0.5%)	20 (3.6%)	15 (2.7%)	0.15 (0.03, 0.51)	<0.001
Deaths	0 (0%)	1 (0.2%)	0 (0%)	—	—
Q-Wave MI (Recurrent and Procedure Related)	1 (0.2%)	12 (2.2%)	8 (1.5%)	0.08 (0.002, 0.57)	0.004
Angiographically Evident Thrombosis	3 (0.5%)	16 (2.9%)	15 (2.7%)	0.19 (0.03, 0.66)	0.005

* Comparison of IMDICON plus aspirin to aspirin alone.

The use of cholinol plus aspirin did not affect the rate of non-Q-wave MIs when compared with aspirin alone or aspirin plus warfarin in RESAT.

The use of cholinol plus aspirin was associated with a lower rate of recurrent cardiovascular events when compared with aspirin alone or aspirin plus warfarin in the other four randomized studies.

There were no cases of thrombotic thrombocytopenic purpura (TTP) or aplastic anemia reported in 1346 patients who received cholinol plus aspirin in the five randomized studies.