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® (cholinasol) 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 # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------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

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

IMDICON can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia.

Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks. The incidence of aplastic anemia peaks after about 4 to 8 weeks of therapy. The incidence of hematological adverse reactions declines thereafter. Only a few cases of neutropenia, TTP, or aplastic anemia have arisen after more than 3 months of therapy.

Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, therefore, patients receiving IMDICON must be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, IMDICON should be discontinued immediately.

[See Warnings and Precautions (5.1 and 5.2)]

1 INDICATIONS AND USAGE

1.1 Thrombotic Stroke

IMDICON is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors or who have had a completed thrombotic stroke. Because IMDICON is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, IMDICON should be reserved for patients who are intolerant of or allergic to aspirin therapy or who have failed aspirin therapy *[see Boxed Warning, Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

1.2 Coronary Stenting

IMDICON is indicated as adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation for up to 30 days following successful stent implantation. [*see Clinical Studies (14.2)]*

2 DOSAGE AND ADMINISTRATION

2.1 Thrombotic Stroke

The recommended dose of IMDICON is 50 mg once daily taken with food.

2.2 Coronary Stenting

The recommended dose of IMDICON is 50 mg once daily with antiplatelet doses of aspirin, taken with food, for up to 30 days of therapy following successful stent implantation.

2.3 Renally Impaired Patients

Discontinue IMDICON in renally impaired patients if hemorrhagic or hematopoietic problems are encountered *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

50 mg capsules

4 CONTRAINDICATIONS

The use of Imdicon is contraindicated in the following conditions:

- Hematopoietic disorders, such as neutropenia and thrombocytopenia, or a history of TTP or aplastic anemia (*see Boxed Warning)*
- A hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding)
- Severe hepatic impairment *[(see Use in Specific Populations (8.7)]*

5 WARNINGS AND PRECAUTIONS

5.1 Hematological Adverse Reactions

Imdicon is associated with multiple hematological adverse reactions including neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), aplastic anemia, and agranulocytosis. Imdicon should be discontinued immediately in the event of clinical signs and symptoms of hematological disorders [infection, weakness, fever, pallor, petechiae or purpura, dark urine, jaundice, or neurological changes] or laboratory findings consistent with neutropenia (<1200 neutrophils/mm^3)], TTP (acute, unexplained reduction in hemoglobin or platelet count and appearance of schistocytes (fragmented RBCs) on the smear), or aplastic anemia (simultaneous decrease in platelets, WBCs, and reticulocytes) (*see Boxed Warning)*

Neutropenia: Neutropenia may occur suddenly. Bone-marrow examination typically shows a reduction in white blood cell precursors. After withdrawal of cholinasol, the neutrophil count usually rises to > 1200/mm^3 within 1 to 3 weeks.

Among 2048 patients in clinical studies in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population).

Thrombocytopenia: Rarely, thrombocytopenia may occur in isolation or together with neutropenia. Cases should be evaluated further to rule out other hematological adverse reactions.

Thrombotic Thrombocytopenic Purpura (TTP): Any acute, unexplained reduction in hemoglobin or platelet count should prompt further investigation for a diagnosis of TTP, and the appearance of schistocytes on peripheral smear should be treated as presumptive evidence of TTP. In patients with TTP on cholinasol, platelet transfusions may accelerate thrombosis, so they should be avoided, if possible.

One case of TTP was reported during clinical studies in stroke patients. Based on postmarketing data, US physicians reported about 100 cases between 1999 and 2003. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of cholinasol-associated TTP may be as high as one case in every 2000 to 4000 patients exposed.

Aplastic Anemia: A simultaneous decrease in platelet count and WBC count should prompt further investigation for a diagnosis of aplastic anemia.

Aplastic anemia was not seen during clinical studies in stroke patients, but US physicians reported about 50 cases between 1999 and 2003. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of cholinasol-associated aplastic anemia maybe as high as one case in every 4000 to 8000 patients exposed.

Other Hematological Effects: Cases of agranulocytosis, pancytopenia, and leukemia, some of which have been fatal, have been reported in postmarketing experience.

5.2 Monitoring for Hematological Adverse Reactions

Starting just before initiating treatment and continuing through the third month of therapy, patients receiving IMDICON must be monitored every 2 weeks. Because of cholinasol's long plasma half-life, patients who discontinue cholinasol during this 3-month period should continue to be monitored for 2 weeks after discontinuation. More frequent monitoring, and monitoring after the first 3 months of therapy, is necessary only in patients with clinical signs (e.g,, signs or symptoms suggestive of infection) or laboratory signs (e.g., neutrophil count less than 70% of the baseline count, decrease in hematocrit or platelet count) that suggest incipient hematological adverse reactions.

Laboratory monitoring should include a complete blood count, with special attention to the absolute neutrophil count (WBC x % neutrophils), platelet count, and the appearance of the peripheral smear.

5.3 Anticoagulant Drugs

If a patient is switched from an anticoagulant or fibrinolytic drug to IMDICON, the former drug should be discontinued prior to IMDICON administration. *[see Drug Interactions (7.1)]*.

5.4 Bleeding Precautions

To eliminate the antiplatelet effects of IMDICON prior to elective surgery, the drug should be discontinued 10 to 14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with cholinasol. In the thrombotic stroke clinical studies, it was recommended that patients have cholinasol discontinued prior to elective surgery. Several hundred patients underwent surgery during the studies, and no excessive surgical bleeding was reported.

Prolonged bleeding time is normalized within 2 hours after administration of 20 mg methylprednisolone IV. Platelet transfusions may also be used to reverse the effect of IMDICON on bleeding. Because platelet transfusions may accelerate thrombosis in patients with TTP on cholinasol, platelet transfusions should be avoided in these patients, if possible.

GI Bleeding: IMDICON prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on IMDICON *[see Contraindications (4) and Drug Interactions (7.4)]*.

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 cholinasol, 2048 in stroke and 1346 in coronary stenting. In all studies, cholinasol 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 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (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: Cholinasol 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 cholinasol 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 cholinasol 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 (cholinasol 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/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 cholinasol 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 causual 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 cholinasol does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of cholinasol 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

should be exercised in coadministering this drug with IMDICON, and it may be useful to remeasure phenytoin blood concentrations

7.3 Antipyrine and Other Drugs Metabolized Hepatically

Therapeutic doses of IMDICON caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore, the doses of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios or being given to patients with hepatic impairment may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with cholinasol. *[see Use in Specific Populations (8.7)]*.

7.4 Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Cholinasol potentiates the effect of aspirin and other NSAIDs on platelet aggregation. The safety of concomitant use of cholinasol and NSAIDs has not been established. The safety of concomitant use of cholinasol and aspirin beyond 30 days has not been established *[see Clinical Studies (14.2)]*. Aspirin did not modify the cholinasol-mediated inhibition of ADP-induced platelet aggregation. Caution should be exercised in patients who have lesions with a propensity to bleed, such as ulcers. Long-term concomitant use of aspirin and cholinasol is not recommended *[see Warnings and Precautions (5.4)]*.

7.5 Cimetidine

Chronic administration of cimetidine reduced the clearance of a single dose of IMDICON by 50%.

7.6 Theophylline

In normal volunteers, concomitant administration of IMDICON resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline.

7.7 Propranolol

In vitro studies demonstrated that cholinasol does not alter the plasma protein binding of propranolol. However, the protein binding interactions of cholinasol and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with IMDICON.

7.8 Antacids

Administration of IMDICON after antacids resulted in an 18% decrease in plasma levels of cholinasol.

7.9 Digoxin

Coadministration of IMDICON with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected.

7.10 Phenobarbital

In 6 normal volunteers, the inhibitory effects of IMDICON on platelet aggregation were not altered by chronic administration of phenobarbital.

7.11 Other Concomitant Drug Therapy

Although specific interaction studies were not performed, in clinical studies IMDICON was used concomitantly with beta blockers, calcium channel blockers and diuretics without evidence of clinically significant adverse interactions.

7.12 Food Interaction

The oral bioavailability of cholinasol is increased by 20% when taken after a meal. Administration of IMDICON with food is recommended to maximize gastrointestinal tolerance. In controlled studies in stroke patients, IMDICON was taken with meals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits at doses up to x, y, and z times, respectively, the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cholinasol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Studies in rats have shown cholinasol is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cholinasol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of IMDICON, 45% were 65 and over, while 12% were 75 and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

There is limited experience in patients with renal impairment. Decreased plasma clearance, increased AUC values and prolonged bleeding times can occur in renally impaired patients. In controlled clinical studies no unexpected problems have been encountered in patients having mild renal impairment, and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients, discontinue cholinasol if hemorrhagic or hematopoietic problems are encountered *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Because cholinasol is metabolized by the liver, dosing of IMDICON or other drugs metabolized in the liver may require adjustment upon starting or stopping concomitant therapy [*see Drug Interactions* (7.3)]. Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of IMDICON is contraindicated in this population *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

One case of deliberate overdosage with IMDICON has been reported by a foreign postmarketing surveillance program. A 38-year-old male took a single 1200-mg dose of IMDICON (equivalent to 24 standard 50 mg capsules). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae.

Single oral doses of cholinasol at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait.

For additional information about overdose treatment, call a poison control center **(1-800-222-1222).**

11 DESCRIPTION

IMDICON (cholinasol hydrochloride) is a platelet aggregation inhibitor. Its chemical name is *insert chemical name.* The structural formula is:

[*Insert chemical structure here]*

Cholinasol hydrochloride is a white crystalline solid. It is freely soluble in water and self-buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in methylene chloride and ethanol, slightly soluble in acetone and insoluble in a buffer solution of pH 6.3. It has a molecular weight of XXX.XX.

IMDICON capsules for oral administration are provided as light blue capsules that contain 50 mg of cholinasol hydrochloride. Each capsule also contains citric acid, magnesium stearate, microcrystalline cellulose, povidone, starch and stearic acid as inactive ingredients. Each capsule is printed with dark blue ink, which includes FD&C Blue #1 Aluminum Lake as the colorant. The capsules are identified with Imdicon on one side and 50 on the reverse side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

When taken orally, cholinasol causes a time- and dose-dependent inhibition of both platelet aggregation and release of platelet granule constituents, as well as a prolongation of bleeding time. The intact drug has no significant in vitro activity at the concentrations attained in vivo, and, although analysis of urine and plasma indicates at least 20 metabolites, no metabolite that accounts for the activity of cholinasol has been isolated.

Cholinasol, after oral ingestion, interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect on platelet function is irreversible for the life of the platelet, as shown both by persistent inhibition of fibrinogen binding after washing platelets ex vivo and by inhibition of platelet aggregation after resuspension of platelets in buffered medium.

12.2 Pharmacodynamics

In healthy volunteers over the age of 50, substantial inhibition (over 50%) of ADP-induced platelet aggregation is detected within 4 days after administration of cholinasol 50 mg daily, and maximum platelet aggregation inhibition (60% to 70%) is achieved after 8 to 11 days. Lower doses cause less, and more delayed, platelet aggregation inhibition, while doses above 50 mg daily provide little additional effect on platelet aggregation but an

increased rate of adverse reactions. The dose of 50 mg daily is the only dose that has been evaluated in controlled clinical studies.

In the majority of patients, bleeding time and other platelet function tests return to normal within 2 weeks of discontinuation of cholinasol.

At the recommended therapeutic dose (50 mg daily), cholinasol has no known significant pharmacological 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, cholinasol 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 cholinasol.

Cholinasol displays nonlinear pharmacokinetics and clearance decreases markedly on repeated dosing. In older volunteers the apparent half-life of cholinasol 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 cholinasol in plasma are obtained after approximately 14 to 21 days.

Cholinasol 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. Cholinasol also binds to alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less cholinasol in plasma is bound to this protein.

Cholinasol is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Following an oral dose of radioactive cholinasol 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 cholinasol, possibly excreted in the bile. Cholinasol 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 cholinasol 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 (Ccr 50 to 80 mL/min) or moderately (Ccr 20 to 50 mL/min) impaired renal function were compared to normal subjects (Ccr 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 cholinasol 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 cholinasol decreases with age. Clearance of cholinasol 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, cholinasol at daily doses of up to *xx* mg/kg (*xx* mg/m^2) was not tumorigenic. For a 70-kg person (1.73 m^2 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, cholinasol at daily doses up to *xx* mg/kg (*xx* mg/m^2) 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.

Cholinasol 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. Cholinasol 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 cholinasol 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 cholinasol and aspirin (The Cholinasol 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 cholinasol 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 cholinasol with placebo (The American Canadian Cholinasol 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, cholinasol 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 cholinasol. 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
Angiographic 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 cholinasol 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 cholinasol 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 cholinasol plus aspirin in the five randomized studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

The light blue 50 mg capsules with 50 imprinted in dark blue on one side and Imdicon on the other are available in unit of use HDPE bottles of:

- 30 capsules (NDC XXXX-XXXX-XX)
- 60 capsules (NDC XXX-XXXX-XX)
- 500 capsules (NDC XXX-XXX-XX).

Storage

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.4)

17.1 Importance of Monitoring

Patients should be informed of the importance of getting their blood tests done and reporting any symptoms of neutropenia, aplastic anemia, TTP, or jaundice to their physician as soon as possible.

17.2 Bleeding

Patients should be told that it might take them longer than usual to stop bleeding when they take IMDICON and that they should report any unusual bleeding to their physician. Patients should be told to inform physicians and dentists that they are taking IMDICON before any surgery is scheduled and before any new drug is taken.

17.3 Hematological Adverse Reactions

Patients should be told to discontinue IMDICON and to contact their physician immediately upon the occurrence of any of the following: fever, weakness, pallor, petechiae or purpura, dark urine or jaundice, or neurological changes.

17.4 FDA-Approved Patient Labeling

(Insert full text of FDA-approved patient labeling here).