SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

INEGY ™ 10/10 Tablet

INEGY ™ 10/20 Tablet

INEGY ™ 10/40 Tablet

INEGY ™ 10/80 Tablet

COMPOSITION

Each INEGY 10/10 tablet contains 10 mg ezetimibe and 10 mg simvastatin.

Each INEGY 10/20 tablet contains 10 mg ezetimibe and 20 mg simvastatin.

Each INEGY 10/40 tablet contains 10 mg ezetimibe and 40 mg simvastatin.

Each INEGY 10/80 tablet contains 10 mg ezetimibe and 80 mg simvastatin.

PHARMACOLOGICAL CLASSIFICATION

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.

Ezetimibe in animals inhibited the absorption of [^{14}C] -cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

Simvastatin

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxy acid form which inhibits HMG-CoA reductase (3 hydroxy - 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also decreases during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

PHARMACOKINETICS

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

Absorption

INEGY

INEGY is bioequivalent to co-administered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.

Simvastatin

The availability of the beta-hydroxy acid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the beta-hydroxy acid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are bound 99,7 % and 88 to 92 % to human plasma proteins, respectively.

Simvastatin

Both simvastatin and the beta-hydroxy acid are bound to human plasma proteins (95 %).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1,3 to 2,4 hours post-dose.

Metabolism

Ezetimibe

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all animal species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Simvastatin

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding beta-hydroxy acid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

In man, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependant on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.

Elimination

Ezetimibe

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered

radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Simvastatin

Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the beta-hydroxy acid metabolite, an average of only 0,3 % of the IV dose was excreted in urine as inhibitors.

Characteristics in Patients (Special Populations)

Geriatric Patients

Ezetimibe

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (65 years or older) than in the young (18 to 45 years).

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45 % compared with 18 patients between 18 to 30 years of age.

Renal Insufficiency

Ezetimibe

After a single 10 mg dose of ezetimibe as monotherapy in patients with severe renal disease (n equal to 8; mean creatinine clearance (CrCl) less than or equal to 30 ml/min), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects (n equal to 9).

An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporin) had a 12-fold greater exposure to total ezetimibe.

Simvastatin

In a study of patients with severe renal insufficiency (creatinine clearance less than 30 ml/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately 2-fold higher than those in healthy volunteers.

INDICATIONS

Primary Hypercholesterolaemia

INEGY is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) and to moderately increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

INEGY is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

CONTRA-INDICATIONS

- hypersensitivity to the active substances or to any of the excipients
- active liver disease or unexplained persistent elevations of serum transaminases, moderate to severe hepatic impairment
- pregnancy and lactation (see **PREGNANCY AND LACTATION**)
- children, as safety and efficacy have not been demonstrated.

WARNINGS

The dose of INEGY should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporin, danazol or greater than or equal to 1 g/day of niacin. The combined use of INEGY with these agents should be avoided (see INTERACTIONS and SPECIAL PRECAUTIONS).

The dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of INEGY at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided.

Use of INEGY concomitantly with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors or nefazodone) should be avoided (see SPECIAL PRECAUTIONS). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

All patients starting therapy with INEGY, or whose dose of INEGY is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. INEGY therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms and/or a CK level greater than 10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK

increases resolved. Periodic CK determinations may be considered in patients starting therapy with INEGY or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

INTERACTIONS

INEGY

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

INEGY is bioequivalent to co-administered ezetimibe and simvastatin.

CYP3A4 Interactions

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9 and 3A4, or N-acetyltransferase. Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of INEGY (see **SPECIAL PRECAUTIONS, Myopathy/Rhabdomyolysis**).

Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone, (see WARNINGS and SPECIAL PRECAUTIONS).

Interactions with lipid-lowering medicines that can cause myopathy when given alone (e.g. fibrates and niacin).

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone.

Fibrates and Niacin (nicotinic acid) **(greater than or equal to 1 g/day) (see SPECIAL PRECAUTIONS, Myopathy/Rhabdomyolysis).**

Other medicine interactions

Cyclosporin or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin or danazol, particularly with higher doses of INEGY (see **SPECIAL PRECAUTIONS, Myopathy/Rhabdomyolysis**).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of INEGY (see **SPECIAL PRECAUTIONS**).

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental LDL-C reduction due to adding INEGY to cholestyramine may be lessened by this interaction.

Diltiazem: Patients on diltiazem treated concomitantly with INEGY 10/80 have a slightly increased risk of myopathy (see **SPECIAL PRECAUTIONS, Myopathy/Rhabdomyolysis**).

Fusidic Acid: Patients on fusidic acid treated concomitantly with INEGY may have an increased risk of myopathy and rhabdomyolysis (see **SPECIAL PRECAUTIONS**, **Myopathy/Rhabdomyolysis**).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1,5 and 1,7 fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of INEGY administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of INEGY with fibrates is not recommended until use in patients is studied.

Anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1,7 to 1,8 and from 2,6 to 3,4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting INEGY and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of INEGY is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione (see **SPECIAL PRECAUTIONS**).

The effect of INEGY on the prothrombin time has not been studied.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Cyclosporin: In a study of eight post-renal transplant patients with creatinine clearance of greater than 50 ml/min on a stable dose of cyclosporin, a single 10-mg dose of ezetimibe resulted in a 3,4-fold (range 2,3 to 7,9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n equal to 17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 ml/min/1,73 m^2) who was receiving multiple medications, including cyclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of cyclosporin on Day 7 resulted in a mean 15 % increase in cyclosporin, AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of cyclosporin alone (see **SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION

PREGNANCY

INEGY

INEGY is contra-indicated during pregnancy.

No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. The safety of INEGY in pregnant women has not been established.

Maternal treatment with INEGY may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, INEGY should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with INEGY should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see **CONTRA-INDICATIONS**).

Ezetimibe

No clinical data on exposed pregnancies are available for ezetimibe.

LACTATION

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active components of INEGY are excreted into human breast milk; therefore, women who are nursing should not take INEGY.

DOSAGE AND DIRECTIONS FOR USE

The patient should be placed on a standard cholesterol-lowering diet before receiving INEGY and should continue on this diet during treatment with INEGY. The dosage should be individualised according to the

baseline LDL-C level, the recommended goal of therapy, and the patient's response. INEGY should be taken as a single daily dose in the evening, with or without food.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55 %) may be started at 10/40 mg/day. After initiation or titration of INEGY, lipid levels may be analysed after 2 weeks and dosage adjusted, if needed.

Dosage in patients with Homozygous Familial Hypercholesterolaemia

The recommended dosage for patients with Homozygous Familial Hypercholesterolaemia is INEGY 10/40 mg/day or 10/80 mg/day in the evening. INEGY should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Use in the Elderly

No dosage adjustment is required for elderly patients.

Use in Paediatric Patients

Treatment with INEGY is contra-indicated as safety and efficacy have not been demonstrated.

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with INEGY is contra-indicated as safety and efficacy have not been demonstrated in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score greater than 9) liver dysfunction (see **SPECIAL PRECAUTIONS**).

Use in Renal Impairment

No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance less than or equal to 30 ml/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see Characteristics in Patients [Special Populations]).

Co-administration with other medicines

Dosing of INEGY should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant.

In patients taking cyclosporin, danazol or greater than or equal to 1g/day of niacin concomitantly with INEGY, the dose of INEGY should not exceed 10/10 mg/day (see **SPECIAL PRECAUTIONS**, **Myopathy/Rhabdomyolysis** and **INTERACTIONS**).

In patients taking amiodarone or verapamil concomitantly with INEGY, the dose of INEGY should not exceed 10/20 mg/day (see **SPECIAL PRECAUTIONS**, **Myopathy/Rhabdomyolysis** and **INTERACTIONS**).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

INEGY (or co-administration of ezetimibe and simvastatin equivalent to INEGY) has been evaluated for safety in more than 3 800 patients in clinical trials.

The following common (greater than or equal to 1/100, less than 1/10) medicine-related adverse experiences were reported in patients taking INEGY.

INEGY

Gastro-intestinal disorders

Common: flatulence

Musculoskeletal and connective tissue disorders

Common: myalgia

Nervous system disorders

Common: headache

Clinical adverse experiences reported in more than or equal to 2 % of patients and at an incidence greater than placebo in three similarly designed, placebo-controlled trials, regardless of causality assessment, are shown in Table 1.

Table 1*

Clinical Adverse Events Occurring in more than or equal to 2 % of Patients Treated with INEGY and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1 234	INEGY** (%) n=1 236
Body as a whole - general disorders				

Headache	6,4	6,0	5,9	6,8
Upper respiratory tract infection	2,6	5,0	5,0	3,9
Musculoskeletal system disorders				
Myalgia	2,9	2,3	2,6	3,5
Pain in limb	1,3	3,0	2,0	2,3

*Includes two placebo-controlled combination studies in which the active ingredients equivalent to INEGY were co-administered and one placebo-controlled study in which INEGY was administered

**All doses

The frequency of less common adverse events was comparable between INEGY and placebo.

LABORATORY VALUES

In controlled clinical co-administration trials, the incidence of clinically important elevations in serum transaminases [alanine transaminase (ALT) and/or aspartate transaminase (AST) greater than or equal to 3 times the upper limit of normal (ULN), consecutive] was 1,7 % for patients treated with INEGY. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see **SPECIAL PRECAUTIONS**).

Clinically important elevations of creatinine kinase (CK) (greater than or equal to 10 times the ULN) were seen in 0,2 % of the patients treated with INEGY.

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other undesirable effects previously reported during clinical studies or post-marketing use (regardless of causality assessment) with one of the individual components may be potential undesirable effects with INEGY.

Very Common (greater than or equal to 1/10), Common (greater than or equal to 1/100, less than 1/10), Uncommon (greater than or equal to 1/1 000, less than 1/100), Rare (greater than or equal to 1/10 000, less than 1/1 000) and Very Rare (less than 1/10 000).

EZETIMIBE

Gastrointestinal disorders

Common: abdominal pain and diarrhoea

Rare: nausea

Very Rare: pancreatitis

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions, including rash and urticaria

Very Rare: anaphylaxis, and angio-oedema and erythema multiforme

General disorders and administration site conditions

Common: fatigue

Blood and lymphatic system disorders

Very Rare: thrombocytopenia

Hepatobiliary disorders

Rare: hepatitis

Very Rare: cholelithiasis, cholecystitis

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia

Very Rare: myopathy/rhabdomyolysis *(*see **SPECIAL PRECAUTIONS**)

Psychiatric Disorders

Very Rare: depression

Nervous system disorders

Rare: dizziness

Very Rare: paraesthesia

Laboratory values

Rare: increased CPK*,* elevations of liver transaminases

SIMVASTATIN

Blood and lymphatic system disorders

Rare: anaemia

Nervous system disorders

Rare: dizziness, paraesthesia, peripheral neuropathy, memory impairment

Gastrointestinal disorders

Rare: constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting and pancreatitis

General disorders and administration site conditions
asthenia

Hepatobiliary disorders
Rare: hepatitis/jaundice
Very rare: hepatic failure

Skin and subcutaneous tissue disorders
Rare: alopecia, pruritus and rash

Psychiatric disorders
Rare: insomnia

Musculoskeletal, connective tissue and bone disorders
Rare: muscle cramps, myopathy and rhabdomyolysis (see **SPECIAL PRECAUTIONS**)

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angio-oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

SPECIAL PRECAUTIONS

Myopathy/Rhabdomyolysis

Simvastatin may cause myopathy manifested as muscle pain, tenderness or weakness with CK above 10 times the ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by use of INEGY with the following:**

Potent inhibitors of CYP3A4

Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of INEGY (see INTERACTIONS).

Other medicines

Fibrates, or greater than or equal to 1 g/day of niacin, particularly with higher doses of INEGY (see INTERACTIONS).

Cyclosporin or danazol particularly with higher doses of INEGY (see INTERACTIONS).

Amiodarone or verapamil with higher doses of INEGY (see INTERACTIONS).

In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.

Diltiazem

Patients on diltiazem treated concomitantly with INEGY 10/80 have a slightly increased risk of myopathy. In clinical studies, the risk of myopathy in patients taking simvastatin 40 mg with diltiazem was similar to that in patients taking simvastatin 40 mg without diltiazem (see **INTERACTIONS**).

Fusidic acid

Patients on fusidic acid treated concomitantly with INEGY may have an increased risk of myopathy and rhabdomyolysis (see **INTERACTIONS**).

- **The risk of myopathy/rhabdomyolysis is dose related for simvastatin.** In a clinical trial database in which 41 050 patients were treated with simvastatin, with 24 747, (approximately 60 %) treated for at least 4 years, the incidence of myopathy was approximately 0,02 %, 0,08 % and 0,53 % at 20, 40 and 80 mg/day, respectively. However, in these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Consequently

1. **Use of INEGY concomitantly with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone) should be avoided (see WARNINGS).** If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with INEGY should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates, especially gemfibrozil. The safety and effectiveness of ezetimibe administered with fibrates have not been formally studied. **Therefore, the concomitant use of INEGY and fibrates should be avoided (see INTERACTIONS).**

3. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking INEGY need closer monitoring. Therapy with INEGY should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

4. Patients on fusidic acid and INEGY should be closely monitored. Temporary suspension of INEGY treatment may be considered.

Liver Enzymes

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (greater than or equal to 3 times the ULN) have been observed (see **SIDE EFFECTS**).

It is recommended that liver function tests be performed before treatment with INEGY begins and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80 mg dose, and periodically thereafter (e.g. semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the ULN and are persistent, the drug should be discontinued.

INEGY should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contra-indications to the use of INEGY.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, INEGY is not recommended in these patients.

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of INEGY and fibrates is not recommended (see **INTERACTIONS**).

Cyclosporin

Caution should be exercised when initiating INEGY in the setting of cyclosporin. Cyclosporin concentrations should be monitored in patients receiving INEGY and cyclosporin (see **INTERACTIONS**).

Anticoagulants

If INEGY is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see **INTERACTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

INEGY

No specific treatment of overdosage with INEGY can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1 000 mg/kg) and simvastatin (1 000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe greater than or equal to 1 000 mg/kg simvastatin greater than or equal to 1 000 mg/kg.

EZETIMIBE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

SIMVASTATIN

A few cases of overdosage have been reported; the maximum dose taken was 3,6 g. All patients recovered without sequelae.

IDENTIFICATION

INEGY 10/10 is a white to off-white, capsule shaped, biconvex compressed tablet debossed with 311 on one side and plain on the other side.
INEGY 10/20 is a white to off-white, capsule shaped, biconvex compressed tablet debossed with 312 on one side and plain on the other side.
INEGY 10/40 is a white to off-white, capsule shaped, biconvex compressed tablet debossed with 313 on one side and plain on the other side.
INEGY 10/80 is a white to off-white, capsule shaped, biconvex compressed tablet debossed with 315 on one side and plain on the other side.

PRESENTATION

INEGY 10/10: Aluminium blister with push-through aluminium lidding; pack of 30 tablets.
INEGY 10/20: White opaque PVC/Aclar blister with push-through aluminium lidding; pack of 30 tablets.
INEGY 10/40: White opaque PVC/Aclar blister with push-through aluminium lidding; pack of 30 tablets

INEGY 10/80: White opaque PVC/Aclar blister with push-through aluminium lidding; pack of 30 tablets.

STORAGE INSTRUCTIONS

Store below 30 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

INEGY 10/10: A39/7.5/0031

INEGY 10/20: A39/7.5/0032

INEGY 10/40: A39/7.5/0033

INEGY 10/80: A39/7.5/0034

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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