Product Name: INEGY Tablets	Approved Professional Information
Date approved 28 May 2024	

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

INEGY® 10/10 Tablet
INEGY® 10/20 Tablet
INEGY® 10/40 Tablet
INEGY® 10/80 Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each INEGY 10/10 Tablet contains ezetimibe 10 mg and simvastatin 10 mg.
Each INEGY 10/20 Tablet contains ezetimibe 10 mg and simvastatin 20 mg.
Each INEGY 10/40 Tablet contains ezetimibe 10 mg and simvastatin 40 mg.
Each INEGY 10/80 Tablet contains ezetimibe 10 mg and simvastatin 80 mg.

INEGY contains sugar (lactose monohydrate):
Each 10/10 mg Tablet contains 58,2 mg of lactose monohydrate.
Each 10/20 mg Tablet contains 126,5 mg of lactose monohydrate.
Each 10/40 mg Tablet contains 262,9 mg of lactose monohydrate.
Each 10/80 mg Tablet contains 535,8 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

INEGY 10/10: white to off-white, capsule shaped, biconvex compressed tablets debossed with 311 on one side and plain on the other side.

INEGY 10/20: white to off-white, capsule shaped, biconvex compressed tablets debossed with 312 on one side and plain on the other side.

Product Name: INEGY Tablets	Approved Professional Information
Date approved 28 May 2024	

INEGY 10/40: white to off-white, capsule shaped, biconvex compressed tablets debossed with 313 on one side and plain on the other side.

INEGY 10/80: white to off-white, capsule shaped, biconvex compressed tablets debossed with 315 on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Reduction in the risk of Cardiovascular Events

INEGY is indicated to reduce the risk of cardiovascular events in patients with coronary artery heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Benefits have been shown for this group of patients when their LDL-C was above 1,2 mmol/L.

No statistically significant benefit was demonstrated for risk reduction of stroke, hospitalisation for unstable angina pectoris and for coronary artery revascularisation procedures.

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.

4.2 Posology and method of administration

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.

In patients with primary hyperlipidaemia or mixed hyperlipidaemia, 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 (> 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. The 10/80 mg dose of INEGY is only recommended in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses (see Section 4.4).

Patients with Coronary Heart Disease and ACS Event History

The starting dose is 10/40 mg once a day in the evening. The 10/80 mg dose is only recommended in patients who have not achieved a suitable reduction in LDL-C.

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.

In patients taking lomitapide concomitantly with INEGY, the dose of INEGY should not exceed 10/40 mg/day (see Sections 4.4 Myopathy/Rhabdomyolysis and 4.5).

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 amiodarone, verapamil or diltiazem, or products containing elbasvir or grazoprevir concomitantly with INEGY, the dose of INEGY should not exceed 10/20 mg/day (see Sections 4.4 and 4.5).

In patients taking amlodipine concomitantly with INEGY, the dose of INEGY should not exceed 10/40 mg/day (see Sections 4.4 and 4.5).

Special populations

Use in the Elderly

No dosage adjustment is required for elderly patients. Because advanced age (≥ 65 years) is a predisposing factor for myopathy, INEGY should be prescribed with caution in the elderly.

In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients < 65 years of age.

Use in Paediatric (10 to 17 Years of Age) Patients

The recommended usual starting dose is 10/10 mg once a day in the evening. The recommended dosing range is 10/10 to a maximum of 10/40 mg/day. Doses should be individualised according to the recommended goal of therapy.

Children < 10 years: Treatment with INEGY is not recommended in children under 10 years due to insufficient data on safety and efficacy.

Patients with Renal Impairment/Chronic Kidney Disease

In patients with mild renal insufficiency (estimated GFR ≥ 60 mL/min/1,73 m^2) no dosage adjustment is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate < 60 mL/min/1,73 m^2, the dose of INEGY is 10/20 mg once a day in the evening. In such patients, the use of higher doses should be closely monitored (see section 5.2).

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 contraindicated in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction due to unknown effects (see section 4.4).

Method of Administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients of INEGY (listed in section 6.1)
- Active liver disease or unexplained persistent elevations of serum transaminases, moderate to severe hepatic impairment
- Pregnancy and lactation (see Section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicines containing cobicistat (see Sections 4.4 and 4.5)

- Concomitant administration of gemfibrozil, ciclosporin or danazol (see Sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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 fatalities have occurred.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e. elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with simvastatin metabolism and/or transporter pathways (see Section 4.5). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy/rhabdomyolysis is dose related for simvastatin.

In a clinical trial database in which 41 413 patients were treated with simvastatin, 24 747 (approximately 60 %) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0,03 %, 0,08 % and 0,61 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored, and some interacting medicines were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6,7 years), the incidence of myopathy was approximately 1,0 % compared with 0,02 % for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0,1 %.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Therefore, the 10/80 mg dose of INEGY should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses. In patients taking INEGY 10/80 mg for whom an interacting agent is needed, a lower dose of INEGY or an alternative statin-ezetimibe regimen with less potential for interactions should be used (see Sections 4.2 and 4.3).

Patients who develop rhabdomyolysis on therapy with simvastatin may have complicated medical histories, including renal insufficiency which may be as a consequence of long-standing diabetes mellitus. Such patients taking INEGY merit closer monitoring.

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. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved (See Section 4.8). Periodic CK determinations may be considered in patients starting therapy with INEGY or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Therapy with INEGY should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n=7367) compared with 0.24% for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing INEGY to Asian patients and the lowest dose necessary should be employed.

Medicine Interactions

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

Contraindicated Medicines

- **Potent inhibitors of CYP3A4:** Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or medicines containing cobicistat), is contraindicated.
- If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with INEGY should be suspended during the course of treatment (see Sections 4.3, 4.5 and 5.2).
- **Gemfibrozil, ciclosporin or danazol:** Concomitant use of these medicines with INEGY is contraindicated. See Sections 4.3, 4.5 and 5.2.

Other Medicines

- **Fusidic acid**: Patients on fusidic acid treated concomitantly with INEGY (simvastatin component) may have an increased risk of myopathy/rhabdomyolysis (see section 4.5). Co-administration with fusidic acid is not recommended. In patients where the use of

systemic fusidic acid is considered essential, INEGY should be discontinued throughout the duration of fusidic acid treatment.

- **Amiodarone:** In a clinical trial, myopathy was reported in 6 % of patients receiving simvastatin 80 mg and amiodarone. **The dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone** (see section 4.5).
- **Calcium channel blockers:**
  Verapamil or diltiazem: Patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem** (see Section 4.5).

  Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had an increased risk of myopathy (see Section 4.5).

  The dose of INEGY should not exceed 10/40 mg daily in patients receiving concomitant medication with amlodipine.
- **Lomitapide: The dose of INEGY should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide** (see Section 4.5).
- **Moderate inhibitors of CYP3A4:** Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with INEGY, particularly higher INEGY doses, may have an increased risk of myopathy. When co-administering INEGY with a moderate inhibitor of CYP3A4, a dose adjustment of INEGY may be necessary.
- **Inhibitors of Breast Cancer Resistant Protein (BCRP):** Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of INEGY may be necessary. Coadministration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of INEGY should not exceed 10/20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see Section 4.5).
- **Other Fibrates:** There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates, especially gemfibrozil. The safety and effectiveness of INEGY administered with fibrates, except fenofibrate, have not been studied. Therefore, the concomitant use of INEGY and fibrates, except fenofibrate, should be avoided. Concomitant use of gemfibrozil is contraindicated (see Section 4.3).
- **Niacin (1 g or more per day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid modifying doses (≥ 1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release niacin/laropiprant 2 g/40 mg. While the only Asian population assessed in this clinical trial was Chinese, co-administration of INEGY with lipid-modifying doses of niacin (≥ 1 g/day) in Asian patients is not recommended (see Section 4.5).

- **Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either medicine can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending INEGY temporarily in patients taking daptomycin (see Section 4.5).
- **Anticoagulants:** If INEGY is added to warfarin, the International Normalised Ratio (INR) should be appropriately monitored (see Section 4.5).

Myasthenia Gravis / Ocular Myasthenia

Statins as contained in INEGY have been reported to induce new onset or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). INEGY should be discontinued in the case these conditions occur. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

Liver Enzymes

In controlled trials in patients receiving INEGY, consecutive transaminase elevations (≥ 3 times the ULN) have been observed (see Section 4.8).

Hepatic function tests should 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, INEGY should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see Section 4.4).

There have been post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with INEGY, promptly interrupt therapy. If an alternate aetiology is not found, treatment with INEGY should not be restarted.

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 contraindications 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.

Lactose

INEGY contains sugar (lactose monohydrate).

Patients with rare hereditary problems of galactose intolerance e.g., galactosemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take INEGY.

Paediatric use

INEGY has not been studied in patients younger than 10 years of age or in pre-menarchal girls (see Section 4.2).

4.5 Interaction with other medicines and other forms of interaction

INEGY

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

INEGY is bioequivalent to co-administered ezetimibe and simvastatin.

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Medicines or herbal products that inhibit certain enzymes (e.g., CYP3A4) and/or transporter (e.g., OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used medicines to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

Potent Inhibitors of CYP3A4

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1B2, 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 medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin

component of INEGY. Concomitant use of medicines labelled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and medicines containing cobicistat is contraindicated (see Sections 4.3, 4.4, and 5.2).

Gemfibrozil, Ciclosporin or Danazol (see Sections 4.3 and 4.4)

- **Gemfibrozil:** In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1,7-fold. Co-administration with INEGY is contraindicated. No clinical data are available (see Sections 4.3 and 4.4).
- **Ciclosporin:** In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, 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=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 medicines including ciclosporin, 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 ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone (see Sections 4.3 and 4.4).

Other medicine interactions

Fibrates: Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1,5-fold, however this increase is 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.

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid (see Section 4.4).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of INEGY (see Sections 4.2 and 4.4).

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.

Calcium channel blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see Sections 4.2 and 4.4).

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see Sections 4.2 & 4.3).

Moderate inhibitors of CYP3A4: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with INEGY, particularly higher INEGY doses, may have an increased risk of myopathy (see section 4.4).

Inhibitors of the transport protein OATP1B1: Simvastatin acid is a substrate of the transporter protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transporter protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see sections 4.3 and 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP): Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g.,, elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When co-administering simvastatin with an inhibitor of BCRP, a dose adjustment of INEGY may be necessary (see Sections 4.2 and 4.4).

Niacin: In a study of 15 healthy adults, concomitant INEGY (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22 %) and nicotinuric acid (19 %) administered as NIASPAN extended-release tablets (1 000 mg for 2 days and 2 000 mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9 %), total ezetimibe (26 %), simvastatin (20 %) and simvastatin acid (35 %). Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (see Section 4.4 Myopathy/Rhabdomyolysis).

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and INEGY in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin: Because rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin therapy (e.g.,, treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93 % with concomitant administration of rifampicin.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin (see Section 4.4).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250 mL glass daily) is a 13 % increase in active plasma HMG-CoA reductase inhibitory activity. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during INEGY therapy (see Section 4.4).

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 Normalised Ratio in patients who had ezetimibe added to warfarin Section 4.4).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

INEGY is contraindicated during pregnancy (see Section 4.3).

Reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received.

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 Section 4.3).

Lactation

Ezetimibe is excreted in rat milk. Women who are taking INEGY should not breastfeed their infants.

Fertility

Ezetimibe

Ezetimibe did not affect the fertility of male or female rats.

Simvastatin

At maximally tolerated doses in both the rat and the rabbit, simvastatin had no effects on fertility or reproductive function.

4.7 Effects on ability to drive and use machines

Certain side effects that have been reported with INEGY may affect some patients' ability to drive or operate machinery. Individual responses to INEGY may vary (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

INEGY (or co-administration of ezetimibe and simvastatin equivalent to INEGY) has been evaluated for safety in approximately 12 000 patients in clinical trials.

The following common (≥ 1/100, < 1/10) or uncommon (≥ 1/1 000, < 1/100) medicine-related adverse experiences were reported:

INEGY (ezetimibe plus **simvastatin)**

Organ class	**Adverse reaction**
Psychiatric disorders	

Uncommon	sleep disorder; insomnia
Nervous system disorders	
Uncommon	dizziness; headache; paraesthesia
Gastrointestinal disorders	
Uncommon	abdominal pain; abdominal discomfort; abdominal distension; abdominal pain upper; dyspepsia; flatulence; diarrhoea; nausea; vomiting; dry mouth; gastroesophageal reflux disease
Skin and subcutaneous tissue disorders	
Uncommon	pruritus; rash; urticaria
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; musculoskeletal pain; neck pain; back pain; pain in extremity
General disorders and administration site conditions	
Uncommon	asthenia; fatigue; malaise; chest pain; oedema peripheral
Investigations	
Common	ALT and/or AST increased; blood CK increased
Uncommon	blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalised ratio increased; protein urine present; weight decreased

LABORATORY VALUES

Adverse effects with combination

In controlled clinical co-administration trials, the incidence of clinically important elevations in serum transaminases [alanine transaminase (ALT) and/or aspartate transaminase (AST) ≥ 3 times the upper limit of normal (ULN), consecutive] was 1,7 % for patients treated with INEGY.

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

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin as in INEGY.

Adverse effects with individual components

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 with one of the individual components may be potential undesirable effects with INEGY.

Ezetimibe

Adverse reactions from clinical trials

Metabolism and nutrition disorders

Less frequent: decreased appetite

Vascular disorders

Less frequent: hot flush; hypertension

Respiratory, thoracic and mediastinal disorders

Less frequent: cough

Gastrointestinal disorders

Less frequent: gastritis

General disorders and administration site conditions

Less frequent: pain

Investigations

Less frequent: liver function test abnormal

Post-marketing

Blood and lymphatic system disorders

Thrombocytopenia

Psychiatric Disorders

Depression

Gastrointestinal disorders

Constipation; pancreatitis

Hepatobiliary disorders

Hepatitis/jaundice, cholelithiasis, cholecystitis

Skin and subcutaneous tissue disorders

Hypersensitivity reactions, including rash, urticaria, anaphylaxis angioedema, erythema multiforme

Musculoskeletal, connective tissue and bone disorders

Myopathy/rhabdomyolysis (see Section 4.4 *Myopathy/Rhabdomyolysis*).

Simvastatin

Adverse reactions from clinical trials

Gastrointestinal disorders

Less frequent: constipation

Post-marketing

Blood and lymphatic system disorders

Anaemia

Nervous system disorders

Peripheral neuropathy, frequency unknown: myasthenia gravis

Eye disorders

Frequency unknown: ocular myasthenia

Respiratory, thoracic and mediastinal disorders

Cough, interstitial lung disease

Hepatobiliary disorders

Hepatitis/jaundice, fatal and non-fatal hepatic failure

Skin and subcutaneous tissue disorders

Alopecia, lichen planus

Musculoskeletal, connective tissue and bone disorders

Muscle cramps

There have been reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents (see Section 4.4 *Myopathy/Rhabdomyolysis*).

Reproductive system and breast disorders

Erectile dysfunction

There have been reports of an apparent hypersensitivity syndrome with simvastatin which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

There have been post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects due to the statin component may be exacerbated and exaggerated (see Section 4.8).

INEGY (ezetimibe plus simvastatin)

No specific treatment of overdosage with INEGY can be recommended.

In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolaemia for 26 weeks was generally well tolerated.

Cases of overdosage have been reported; some have been associated with adverse experiences.

Simvastatin

Cases of overdosage have been reported; the maximum dose taken was 3,6 g.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological Classification**:** A.7.5 Serum-cholesterol reducers

ATC Classification: C10BA02

5.1 Pharmacodynamic properties

Mechanism of Action

Ezetimibe

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

Ezetimibe localises 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, ethinylestradiol 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 protein (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.

5.2 Pharmacokinetic properties

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 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 < 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 simvastatin 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.

Biotransformation

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 medicine-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine 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 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 dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of simvastatin equivalents in the bile. Consequently, availability of active simvastatin 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 simvastatin equivalents excreted in bile as well as unabsorbed simvastatin. 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.

Special Populations

Geriatric population

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.

Paediatric population

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population < 10 years of age are not available.

Renal impairment

Ezetimibe

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

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

Simvastatin

In a study of patients with severe renal insufficiency (creatinine clearance < 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

INEGY contains the following inactive ingredients: butylated hydroxyanisole, citric acid monohydrate, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and propyl gallate.

6.2 Incompatibilities

Product Name: INEGY Tablets	Approved Professional Information
Date approved 28 May 2024	

N/A

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

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.

Not all pack strengths may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor, 22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8 REGISTRATION NUMBER(S)

Product Name: INEGY Tablets	Approved Professional Information
Date approved 28 May 2024	

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

9 DATE OF FIRST AUTHORISATION

11 August 2006

10 DATE OF REVISION OF THE TEXT

28 May 2024

WPPI-MK0653A-T-10/2012; WPPI-MK0653A-T-092013; WPC-MK0653AT- 102013; WPC-MK0653A-T-102015; WPPI-MK0653A-T-082021; RCN 100002964