SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

NOVABE (10 mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe.

Excipient with known effect: NOVABE contains sugar, lactose monohydrate 62 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, uncoated, capsule shaped, bevelled edge tablets debossed with “E Z” on one side and “10” on the other side. The size is 8,1 mm x 4,1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia:

NOVABE administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

NOVABE administered with a statin 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 on an appropriate lipid-lowering diet and weight loss programme where indicated and should continue on this diet during treatment with NOVABE.

The recommended dose of NOVABE is 10 mg once daily, used alone, with a statin, or with fenofibrate.

Elderly patients

No dosage adjustment is required for elderly patients (see section 5.2).

Paediatric patients

Children 10 years of age or older: No dosage adjustment is required (see section 5.2).

Children under 10 years of age: No clinical data on safety and efficacy are available; therefore, treatment with NOVABE is contraindicated.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh A). Treatment with NOVABE is contraindicated in patients with moderate (Child Pugh B) or severe (Child Pugh C) liver dysfunction due to unknown effects (see section 4.3 and 5.2).

Co-administration with bile acid sequestrants

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

Method of administration

For oral use.

NOVABE can be administered any time of the day, with or without food.

4.3 Contraindications

- Hypersensitivity to ezetimibe or to any of the excipients listed in section 6.1.
- Pregnancy, as no clinical data on exposed pregnancies are available.

- Lactation, as it is not known whether ezetimibe is excreted into human breast milk.
- Children below the age of 10 years.
- Moderate (Child Pugh B) to severe hepatic impairment (Child Pugh C).
- NOVABE co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.

4.4 Special warnings and precautions for use

When NOVABE is co-administered with a statin, please refer to the Professional Information for that particular medicine.

Hepatic impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, NOVABE is contraindicated in these patients (see section 4.3).

Liver enzymes

When NOVABE is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin as consecutive transaminase elevations (≥ 3 x ULN) have been observed in co-administration trials (see section 4.8).

Skeletal muscle

Cases of myopathy and rhabdomyolysis have been reported. All patients starting therapy with NOVABE must be advised of the risk of myopathy and be told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

NOVABE and any statin the patient is taking concomitantly, should be stopped immediately if myopathy is suspected or diagnosed. The presence of these symptoms and a creatine phosphokinase (CPK) level > 10 x ULN indicates myopathy.

Rhabdomyolysis has also occurred, most patients who developed rhabdomyolysis were taking a statin concomitantly with NOVABE. Rhabdomyolysis has been reported very rarely in patients taking NOVABE

monotherapy, and also very rarely with the addition of NOVABE to other medicines known to be associated with increased risk of rhabdomyolysis.

Paediatric population

Safety and efficacy of NOVABE in patients 6 to 10 years of age with heterozygous familial or non-familial hypercholesterolaemia have not been studied in treatment periods longer than 12 weeks (see section 4.3).

NOVABE has not been studied in patients younger than 6 years of age (see section 4.3).

Safety and efficacy of NOVABE co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation have not been studied.

The safety and efficacy of NOVABE co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

The safety and efficacy of NOVABE co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see section 4.3).

The long-term efficacy of therapy with NOVABE in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Concomitant use with fibrates

The safety and efficacy of NOVABE administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving NOVABE and fenofibrate, gallbladder investigations are indicated, and this therapy should be discontinued (see section 4.5).

Concomitant use with ciclosporin

Caution should be exercised when initiating NOVABE in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving NOVABE and ciclosporin (see section 4.5).

Anticoagulants

If NOVABE is added to warfarin or another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Excipient

NOVABE contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take NOVABE.

4.5 Interaction with other medicines and other forms of interaction

In preclinical studies, it has been shown that ezetimibe as in NOVABE does not induce cytochrome P450 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe as in NOVABE and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Ezetimibe as in NOVABE had no significant effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration.

Antacids

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

Cholestyramine

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

Fibrates

In patients receiving fenofibrate and NOVABE, medical practitioners should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving NOVABE and fenofibrate, gallbladder investigations are advised, and this therapy should be discontinued (see section 4.8).

Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe as in NOVABE concentrations (approximately 1,5- and 1,7-fold, respectively).

Co-administration of NOVABE with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe increased cholesterol in the gallbladder bile but not in all species. A lithogenic risk associated with the therapeutic use of NOVABE cannot be ruled out.

Statins

No clinically significant pharmacokinetic interactions were seen when NOVABE was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Ciclosporin

Ciclosporin has been reported to increase the plasma concentration of ezetimibe as in NOVABE and patients receiving both medicines should be carefully monitored.

Anticoagulants

Concomitant administration of NOVABE (10 mg once daily) has no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been reports of increased International Normalised Ratio (INR) in patients who were treated concomitantly with NOVABE and warfarin or fluindione. If NOVABE is added to warfarin or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of NOVABE is not recommended in pregnancy, as no clinical data on exposed pregnancies are available (see section 4.3).

Lactation

The use of NOVABE is not recommended during lactation, as it is not known whether NOVABE is excreted into breastmilk (see section 4.3).

Studies on rats have shown that ezetimibe is secreted into breast milk.

Fertility

No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

Tabulated summary of adverse reactions

NOVABE monotherapy:		
System organ class	**Adverse reaction**	**Frequency**
Investigations	ALT and/or AST increased; blood CPK increased; gamma-glutamyl transferase increased; liver function test abnormal	Less frequent
Respiratory, thoracic and mediastinal disorders	Cough	Less frequent

Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence	Frequent
	Dyspepsia, gastroesophageal reflux disease, nausea	Less frequent
Musculoskeletal, connective tissue and bone disorders	Arthralgia, muscle spasms, neck pain	Less frequent
Metabolism and nutrition disorders	Decreased appetite	Less frequent
Vascular disorders	Hot flush, hypertension	Less frequent
General disorders and administration site conditions	Headache, fatigue	Frequent
	Chest pain, pain.	Less frequent

Additional adverse reactions with NOVABE co-administered with a statin:		
System organ class	**Adverse reaction**	**Frequency**
Investigations	ALT and/or AST increased	Frequent
Nervous system disorders	Headache	Frequent
	Paraesthesia	Less frequent
Gastrointestinal disorders	Dry mouth, gastritis	Less frequent
Skin and subcutaneous tissue disorders	Pruritis, rash, urticaria	Less frequent
Musculoskeletal and connective tissue disorders	Myalgia	Frequent
	Back pain, muscular weakness, pain in extremity	Less frequent
General disorders and administration site conditions	Asthenia, peripheral oedema	Less frequent

NOVABE co-administration with fenofibrate:		
Gastrointestinal disorders	Abdominal pain.	Frequent

Post-marketing Experience (with or without a statin):

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Thrombocytopaenia	Frequency unknown
Nervous system disorders	Dizziness, paraesthesia	Frequency unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Frequency unknown
Gastrointestinal disorders	Pancreatitis; constipation	Frequency unknown
Skin and subcutaneous tissue disorders	Erythema multiforme	Frequency unknown
Musculoskeletal and connective tissue disorders	Myalgia, myopathy/rhabdomyolysis (see section 4.4)	Frequency unknown
General disorders and administration site conditions	Asthenia	Frequency unknown
Immune system disorders	Hypersensitivity, including rash, urticaria, anaphylaxis and angioedema	Frequency unknown
Hepato-biliary disorders	Hepatitis, cholelithiasis, cholecystitis	Frequency unknown
Psychiatric disorders	Depression	Frequency unknown

Description of selected adverse reactions

NOVABE co-administered with fenofibrate:

Clinically important elevations (> 3X ULN, consecutive) in serum transaminases have been reported in patients with mixed hyperlipidaemia treated with NOVABE and fenofibrate. The reported incidence rates for cholecystectomy were higher in patients treated with NOVABE and fenofibrate (see sections 4.4 and 4.5).

Paediatric (10 to 17 years of age) patients:

Elevations of ALT and/or AST (≥ 3X ULN, consecutive) and CPK (≥ 10X ULN) have been reported in adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia treated with NOVABE and simvastatin; no cases of myopathy were reported.

Coronary heart disease and ACS event history:

A higher incidence of myopathy has been reported in patients treated with ezetimibe and simvastatin compared to simvastatin monotherapy. Myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN.

The reported incidence of rhabdomyolysis was higher in simvastatin monotherapy compared to ezetimibe and simvastatin combination treatment. Rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 times ULN and < 10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10 000 IU/L without evidence of renal injury.

The reported incidence of consecutive elevations of transaminases (≥ 3 X ULN), gallbladder-related adverse effects, cholecystectomy hospitalisations and diagnosis of cancer (new malignancy) were comparable in ezetimibe and simvastatin combination treatment and simvastatin monotherapy (see section 4.4.).

Chronic kidney disease:

A higher incidence of myopathy/rhabdomyolysis has been reported in patients treated with NOVABE combined with simvastatin. Consecutive elevations of transaminases (> 3X ULN) have been reported (see section 4.4.).

Laboratory values:

Monotherapy studies reported elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) with NOVABE treatment. A higher incidence of elevations in serum transaminases has been reported in co-administration of NOVABE with a statin compared to a statin alone. These reported elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4.).

CPK > 10 X ULN has been reported in patients administered NOVABE alone or with a statin. No excess of myopathy or rhabdomyolysis associated with NOVABE were reported (see section 4.4).

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10A X09

A 7.5 Serum-cholesterol reducers

Mechanism of action:

Ezetimibe is a lipid-lowering compound that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

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; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.

Pharmacodynamic effects:

Preclinical studies performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption reported that ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

5.2 Pharmacokinetic properties

Absorption:

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 NOVABE 10 mg tablets. NOVABE can be administered with or without food.

Distribution:

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

Metabolism:

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) is observed in all animal species evaluated. Ezetimibe and ezetimibe-glucuronide are the major active ingredient-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total active ingredient 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.

Elimination:

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounts for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity is recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there is no detectable levels of radioactivity in the plasma.

Special populations:

Paediatric patients:

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults.

Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

Elderly patients:

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). Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment:

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1,7 fold in patients with mild hepatic insufficiency (Child Pugh A), compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. In a 14 day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh B), the mean AUC for total ezetimibe was increased approximately 4 fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh B or C) hepatic insufficiency, ezetimibe is contraindicated in these patients (see sections 4.3 and 4.4).

Renal impairment:

After a single 10 mg dose of ezetimibe in patients with severe renal disease (mean creatinine clearance (CrCl) < 30 mL/min/l,73 m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects.

An additional patient in this study (post-renal transplant and receiving multiple medicines, including ciclosporin) had a 12 fold greater exposure to total ezetimibe (see section 4.5).

Gender:

Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men, LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Race:

Based on meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between blacks and Caucasians.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline

Croscarmellose sodium

Crospovidone

Hypromellose

Lactose monohydrate

Magnesium stearate

Sodium laurylsulfate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C in the original package.

Do not remove blister from carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

NOVABE tablets are packaged in three-layer cold form laminate film (PVC/Al/OPA) and aluminium foil blister packs or clear PVC/PVdC and aluminium foil blister packs. The blisters are further packed into an outer carton. Each carton contains 30 tablets (3 blisters of 10 tablets each).

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria

0041

8. REGISTRATION NUMBER(S)

55/7.5/0381

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 April 2022

10. DATE OF REVISION OF THE TEXT

06 April 2022