PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
NITASOL 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg ezetimibe.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablets.
White to off-white, capsule-shaped, flat bevel-edged, uncoated tablets debossed with 'EZE' on one side and plain on the other side.

4 CLINICAL PARTICULARS
Therapeutic indications
Primary hypercholesterolaemia
NITASOL, 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)
NITASOL, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

Posology and method of administration
Posology
The patient should be on an appropriate lipid-lowering diet and weight loss program where indicated and should continue on this diet during treatment with NITASOL.
The recommended dose of NITASOL is 10 mg once daily, used alone, with a statin or with fenofibrate.
NITASOL can be administered at any time of the day, with or without food.
Use in the elderly
No dosage adjustment is required for elderly patients (see section 5.2).
Use in paediatric patients
Children ≥ 10 years: No dosage adjustment is required (see section 5.2).
Children < 10 years: No clinical data on safety and efficacy are available; therefore, treatment with NITASOL is contraindicated.
Use in hepatic impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with NITASOL is contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) hepatic impairment due to unknown effects. (See section 4.3).
Concomitant use with bile acid sequestrants
Dosing of NITASOL should occur at least 2 hours before or 4 hours after administration of a bile acid sequestrant.

Method of administration
For oral use.

Contraindications
- Hypersensitivity to ezetimibe or to any of the excipients of NITASOL (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment (Child Pugh score ≥ 7).
- Children under the age of 10 years.
- NITASOL co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

Special warnings and precautions for use
When NITASOL is to be administered with a statin, please refer to the professional information for that particular medicine.

Liver enzymes
In controlled co-administration trials in patients receiving NITASOL with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal (ULN)) have been observed. When NITASOL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin (see section 4.8).

Skeletal muscle
In post-marketing experience with NITASOL, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with NITASOL. However, rhabdomyolysis has been reported with NITASOL monotherapy and with the addition of NITASOL to other medicines known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, NITASOL, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with NITASOL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

Hepatic impairment
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, NITASOL is contraindicated (see section 4.3 and 5.2).

Paediatric population
The safety and efficacy of NITASOL 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 NITASOL co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see sections 4.2).
The long-term efficacy of therapy with NITASOL in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates
The safety and efficacy of NITASOL administered with fibrates have not been established. The co-administration of NITASOL with fibrates other than fenofibrate has not been studied.

Fenofibrate
If cholelithiasis is suspected in a patient receiving NITASOL and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8). Alternative lipid-lowering therapy should be considered.

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

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

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

Interaction with other medicines and other forms of interaction
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 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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.

Cholestyramine
Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding NITASOL to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates
In patients receiving fenofibrate and NITASOL, medical practitioner 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 NITASOL and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).
Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations (approximately 1,5- and 1,7-fold respectively).
Co-administration of NITASOL 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 (see section 5.3). A lithogenic risk associated with the therapeutic use of NITASOL cannot be ruled out.

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

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 NITASOL 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, receiving ezetimibe alone, from another study. In a different study, a renal transplant patient with severe renal impairment (creatinine clearance of 13,2mL/mim/1,73m2) who was receiving ciclosporin and multiple other medicines demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. 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. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating NITASOL in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving NITASOL and ciclosporin (see section 4.4).

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 INR in patients who had NITASOL added to warfarin or fluindione. If NITASOL is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation
NITASOL is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy
No clinical data are available on the use of NITASOL during pregnancy.

Breastfeeding
NITASOL should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human 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.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

Undesirable effects

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	viral infections, pharyngitis, sinusitis
Metabolism and nutrition disorders	Less frequent	decreased appetite
Vascular disorders	Less frequent	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	cough
Gastrointestinal disorders	Frequent	abdominal pain, diarrhoea, flatulence
	Less frequent	dyspepsia, gastroesophageal reflux disease, nausea
Musculoskeletal and connective tissue disorders	Frequent	arthralgia, back pain
	Less frequent	muscle spasms, neck pain
General disorders and administration site conditions	Frequent	headache, fatigue
	Less frequent	chest pain, pain
Investigations	Less frequent	increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), increased blood creatine phosphokinase, increased gamma-glutamyl transferase, abnormal liver function test

NITASOL when administered with a statin

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	pharyngitis, sinusitis, upper respiratory tract infection
Nervous system disorders	Frequent	headache, dizziness
	Less frequent	paraesthesia
Gastrointestinal disorders	Frequent	abdominal pain, constipation, diarrhoea, flatulence, nausea
	Less frequent	dry mouth, gastritis
Skin and subcutaneous tissue disorders	Less frequent	pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Frequent	myalgia, arthralgia, back pain
	Less frequent	muscular weakness, pain in extremity
General disorders and administration site conditions	Frequent	chest pain, fatigue
	Less frequent	asthenia, peripheral oedema
Investigations	Frequent	increased ALT and/or AST

NITASOL when administered with fenofibrate

MedDRA system organ class	Frequency	Adverse reactions
Gastrointestinal disorders	Frequent	abdominal pain

Post-marketing data

MedDRA system organ class	Frequency	Adverse reactions
Blood and the lymphatic system disorders	Frequency unknown	thrombocytopenia
Immune system disorders	Frequency unknown	hypersensitivity reactions (anaphylaxis, rash, urticaria, angioedema)
Psychiatric disorders	Frequency unknown	depression
Respiratory, thoracic and mediastinal disorders	Frequency unknown	dyspnoea
Gastrointestinal disorders	Frequency unknown	pancreatitis
Hepatobiliary disorders	Frequency unknown	hepatitis, cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	Frequency unknown	erythema multiforme
Musculoskeletal and connective tissue disorders	Frequency unknown	myopathy/rhabdomyolysis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of NITASOL is important. It allows continued monitoring of the benefit/risk balance of NITASOL. Health care 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/

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

5 PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Category and class: A 7.5 Serum-cholesterol reducers.
Pharmacotherapeutic group: Other lipid modifying agents.
ATC code: C10A X09.

Mechanism of action
Ezetimibe inhibit the intestinal absorption of cholesterol and related plant sterols.
A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D.

Paediatric population
The safety and efficacy of ezetimibe 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 ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.
The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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. Ezetimibe 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.

Biotransformation
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 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.

Elimination
Following oral administration of 14C-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.

Special populations
Paediatric population
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
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1,7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, NITASOL is contraindicated in these patients (see section 4.4).

Renal impairment
After a single 10-mg dose of ezetimibe in patients with severe renal disease (mean CrCl ≤ 30 mL/min/1,73 m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects. This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medicines, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

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 NITASOL. Therefore, no dosage adjustment is necessary on the basis of gender.

Preclinical safety data
No further information of relevance available.

6 PHARMACEUTICAL PARTICULARS
List of excipients
Colloidal silicon dioxide
Croscarmellose sodium
Hydrogenated castor oil
Hypromellose
Lactose monohydrate
Microcrystalline cellulose
Sodium lauryl sulphate
Sodium stearyl fumerate

Incompatibilities
Not applicable.

Shelf life
3 years

Special precautions for storage
Store at or below 30 °C.
Keep the blisters in the outer carton until required for use.
Keep away from heat.
KEEP OUT OF REACH OF CHILDREN.

Nature and contents of container
Blister of plain Aluminium Foil 140 X 0.025 mm and PVC/PVDC 144 mm, 0.25 mm / PVDC 60 gsm, transparent film (ACG). 10 tablets per blister.
Pack size: 30 tablets.

Special precautions for disposal <and other handling>
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
TRINITY PHARMA (PTY) LTD
106 16th Road,
Midrand,
1686
South Africa

8 REGISTRATION NUMBER(S)
50/7.5/0844

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09 November 2021

10 DATE OF REVISION OF THE TEXT
09 November 2021

TRINITY PHARMA

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PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S4

1 NAAM VAN DIE MEDISYNE
NITASOL 10 mg tablette

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke tablet bevat 10 mg esetimieb.
Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1

3 FARMASEUTIESE VORM
Tablette.
Wit tot naaswit, kapsulevormige, plat skuins-rand, onbedekte tablette gebosseleer met 'EZE' aan die een kant en plein aan die ander kant.

4 KLINIESE BESONDERHEDE
Terapeutiese indikasies
Primêre hipercholesterolemie
NITASOL, toegedien met 'n HMG-KoA reduktase inhibeerder (statien) of alleen, word aangedui as aanvullende terapie tot dieet vir die vermindering van verhoogde totale cholesterol (totale-C) en lae-digtheid lipoproteïn cholesterol (LDL-C) by pasiënte met primêre (heterosigotiese familiale en nie-familiale) hipercholesterolemie.

Homosigotiese familiale hipercholesterolemie (HoFH)
NITASOL, toegedien met 'n statien, is aangedui vir die verlaging van die verhoogde totale C- en LDL-C vlakke by pasiënte met HoFH.

Posologie en metode van toediening
Posologie
Die pasiënt moet op 'n toepaslike lipiedverlagende dieet- en gewigsverliesprogram wees, waar aangedui, en moet voortgaan met hierdie dieet tydens behandeling met NITASOL.
Die aanbevole dosis van NITASOL is 10 mg een keer per dag, alleen, met 'n statien of met 'n fenofibraat.
NITASOL kan op enige tyd van die dag toegedien word, met of sonder voedsel.
Gebruik by bejaardes
Geen dosisaanpassings is nodig vir bejaarde pasiënte nie (sien afdeling 5.2).
Gebruik by pediatriese pasiënte
Kinders ≥ 10 jaar: Geen dosisaanpassings is nodig (sien afdeling 5.2).
Kinders < 10 jaar: Geen kliniese data oor die veiligheid en effektiwiteit is beskikbaar nie; dus, is behandeling met NITASOL gekontraïndikeerd.
Gebruik by hepatiese inkorting
Geen dosisaanpassing is nodig by pasiënte met ligte hepatiese ontoereikendheid nie (Child Pugh telling 5 tot 6). Behandeling met NITASOL is gekontraïndikeerd by pasiënte met matige (Child Pugh telling 7 tot 9) of ernstige (Child Pugh-telling > 9) hepatiese inkorting as gevolg van onbekende effekte. (Sien afdeling 4.3).
Gelyktydige gebruik met galsuursekwestrante
Dosering van NITASOL moet plaasvind minstens 2 ure voor of 4 ure na toediening van 'n galsuursekwestrant.

Metode van toediening
Vir orale gebruik.

Kontraïndikasies
- Hipersensitiwiteit vir esetimieb of vir enige van die hulpstowwe van NITASOL (sien afdeling 6.1).
- Swangerskap en laktasie (sien afdeling 4.6).
- Matige tot ernstige hepatiese inkorting (Child Pugh telling ≥ 7).
- Kinders onder die ouderdom van 10 jaar.
- NITASOL gesamentlike toediening met 'n statien is gekontraïndikeerd in pasiënte met aktiewe lewersiekte of onverklaarbare aanhoudende verhogings in serumtransaminase.

Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Wanneer NITASOL saam met 'n statien toegedien moet word, verwys asseblief na die professionele inligting van daardie spesifieke medisyne.

Lewer ensieme
In gekontroleerde gelyktydige-toedieningsproewe by pasiënte wat NITASOL met 'n statien ontvang het, was opeenvolgende transaminaseverhogings (≥ 3 keer die boonste limiet van normaal (BLN)) waargeneem. Wanneer NITASOL saam met 'n statien toegedien word, moet lewerfunksietoetse uitgevoer word met die aanvang van die behandeling en volgens die aanbevelings van die statien (sien afdeling 4.8).

Skeletspier
In na-bemarkingservaring met NITASOL is gevalle van miopatie en rabdomioliese aangemeld. Meeste pasiënte wat rabdomioliese ontwikkel het, het 'n statien saam met NITASOL geneem. Alhoewel, rabdomioliese was aangemeld met NITASOL monoterapie en met die toevoeging van NITASOL by ander medisyne wat bekend is met verhoogde risiko vir rabdomioliese. Indien miopatie vermoed word, gebaseer op spiersimptome of deur kreatienfosfokinase (KFK) vlak > 10 keer die BLN, moet NITASOL, enige statien, en enige van hierdie ander medisyne wat die pasiënt gelyktydig neem onmiddellik gestaak word. Alle pasiënte wat terapie met NITASOL begin, moet ingelig word van die risiko vir miopatie en hulle moet aangesê word om onverklaarbare spierpyn, teerheid of swakheid onmiddellik aan te meld (sien afdeling 4.8).

Hepatiese inkorting
Vanweë die onbekende effekte van die verhoogde blootstelling aan esetimieb by pasiënte met matige of erge hepatiese inkorting, is NITASOL gekontraïndikeerd (sien afdeling 4.3 en 5.2).

Pediatriese bevolking
Die veiligheid en effektiwiteit van NITASOL gesamentlike toediening met simvastatien dosisse bo 40 mg daagliks, is nie bestudeer by pediatriese pasiënte 10 tot 17 jarige ouderdom nie.
Die veiligheid en effektiwiteit van NITASOL gesamentlike toediening met simvastatien, is nie bestudeer by pediatriese pasiënte < 10 jarige ouderdom nie (sien afdeling 4.2).
Die langtermyneffektiwiteit van terapie met NITASOL in pasiënte onder 17 jarige ouderdom om morbiditeit en mortaliteit in volwassenheid te verminder, is nie bestudeer nie.

Fibrate
Die veiligheid en effektiwiteit van NITASOL toegedien met fibrate, is nie vasgestel nie. Die gesamentlike toediening van NITASOL met fibrate anders as fenofibraat is nie bestudeer nie.

Fenofibraat
As cholelitiase vermoed word by 'n pasiënt wat NITASOL en fenofibraat ontvang, word galblaasondersoeke geïndikeerd en hierdie behandeling moet gestaak word (sien afdelings 4.5 en 4.8). Alternatiewe lipiedverlagende terapie moet oorweeg word.

Siklosporien
Sorg word aanbeveel wanneer NITASOL geïnisieer word in die teenwoordigheid van siklosporien. Siklosporien konsentrasies moet gemonitor word by pasiënte wat NITASOL en siklosporien ontvang (sien afdeling 4.5).

Antikoagulante
Indien NITASOL by warfarien, 'n ander kumarien-antikoagulant of fluindioon gevoeg word, moet die Internasionale Genormaliseerde Verhouding (IGV) toepaslik gemonitor word (sien afdeling 4.5).

Laktose monohidraat
NITASOL bevat laktose monohidraat. Pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, totale laktase-gebrek, of glukose-galaktose wanabsorpsie moet nie NITASOL neem nie.

Interaksie met ander medisyne en ander vorms van interaksie
In pre-kliniese studies, was dit aangetoon dat esetimieb nie sitochroom P450 medisyne metaboliserende ensieme induseer nie. Geen klinies beduidende farmakokinetiese interaksies was waargeneem tussen esetimieb en medisyne wat bekend is dat dit gemetaboliseer word deur sitochrome P450 1A2, 2D6, 2C8, 2C9 en 3A4, of N-asetieltransferase nie.

In kliniese interaksiestudies het esetimieb geen effek op die farmakokinetika van dapsoon, dekstrometorfaan, digoksien, orale voorbehoedmiddels (etiniel estradiol en levonorgestrel), glipisied, tolbutamied of midasolam tydens gelyktydige toediening gehad nie. Simetidien, wat gelyktydig toegedien was met esetimieb, het geen effek op die biobeskikbaarheid van esetimieb gehad nie.

Teensuurmiddels
Gelyktydige toediening van teensuurmiddels het die absorpsietempo van esetimieb verlaag, maar het geen invloed op die biobeskikbaarheid van esetimieb gehad nie. Hierdie verlaagde absorpsietempo word nie as klinies beduidend beskou nie.

Cholestiramien
Gelyktydige toediening van cholestiramien het die gemiddelde oppervlakte onder die kurwe (AOK) van die totale esetimieb (esetimieb + esetimieb glukuronied) met ongeveer 55 % verminder. Die inkrementele verlaging van lae-digtheid lipoproteïn cholesterol (LDL-C) as gevolg van die toevoeging van NITASOL by cholestiramien, kan verminder word deur hierdie interaksie (sien afdeling 4.2).

Fibrate
By pasiënte wat fenofibraat en NITASOL ontvang, moet mediese praktisyne bewus wees van die moontlike risiko van cholelitiase en galblaas siekte (sien afdelings 4.4 en 4.8). Indien cholelitiase vermoed word by 'n pasiënt wat NITASOL en fenofibraat ontvang, is galblaasondersoeke geïndikeerd en hierdie terapie moet gestaak word (sien afdeling 4.8).
Gelyktydige toediening van fenofibraat of gemfibrosil het die totale konsentrasies van esetimieb verhoog (ongeveer 1,5- en 1,7 keer onderskeidelik).
Gelyktydige toediening van NITASOL met ander fibrate is nie bestudeer nie.
Fibrate kan die uitskeiding van cholesterol in die gal verhoog, wat tot cholelitiase kan lei. In dierestudies het esetimieb cholesterol verhoog in die galblaas gal, maar nie by alle spesies nie (sien afdeling 5.3). 'n Litogene risiko verbonde aan die terapeutiese gebruik van NITASOL kan nie uitgesluit word nie.

Statiene
Geen klinies beduidende farmakokinetiese interaksies was gesien toe esetimieb saam met atorvastatien, simvastatien, pravastatien, lovastatien, fluvastatien of rosuvastatien toegedien was nie.

Siklosporien
In 'n studie van agt na-renale oorplantingspasiënte met kreatinienopruiming van > 50 ml/min op 'n stabiele dosis van siklosporien, het 'n enkele 10 mg dosis NITASOL 'n 3,4-voudig (gebied van 2,3- tot 7,9-voudig) toename in die gemiddelde AOK tot gevolg gehad vir totale esetimieb in vergelyking met 'n gesonde beheerpopulasie vanuit 'n ander studie, wat esetimieb alleen ontvang het. In 'n ander studie het 'n renale oorplantingspasiënt met ernstige renale inkorting (kreatinienopruiming van 13,2 ml/mim/1,73 m^2) wat siklosporien en verskeie ander medisyne ontvang het, 'n 12-voudige groter blootstelling aan totale esetimieb getoon in vergelyking met gelyktydige kontroles wat esetimieb alleen ontvang het. In 'n twee-periode oorkruis-studie by twaalf gesonde proefpersone, het daaglikse toediening van 20 mg esetimieb vir 8 dae met 'n enkele 100 mg dosis siklosporien op dag 7 gelei tot 'n gemiddelde 15 % toename in die AOK vir siklosporien (gebied van 10 % afname tot 51 % toename) in vergelyking met 'n enkele dosis van 100 mg siklosporien alleen. 'n Beheerde studie oor die effek van gesamentlike toediening van esetimieb op siklosporien blootstelling by renale oorplantingspasiënte is nie uitgevoer nie. Sorg word aanbeveel wanneer NITASOL geïnisieer word in teenwoordigheid van siklosporien. Siklosporien konsentrasies moet gemonitor word by pasiënte wat NITASOL en siklosporien ontvang (sien afdeling 4.4).

Antikoagulante
Gelyke toediening van esetimieb (10 mg een keer per dag) het geen beduidende effek op die biobeskikbaarheid van warfarien en protrombientyd gehad in 'n studie van twaalf gesonde volwasse mans nie. Alhoewel, daar was na-bemarkingsverslae van verhoogde IGV by pasiënte waar NITASOL by warfarien of fluindioon gevoeg was. Indien NITASOL by warfarien, 'n ander kumarien-antikoagulant, of fluindioon gevoeg word, moet die IGV toepaslik gemonitor word (sien afdeling 4.4).

Pediatriese bevolking
Interaksiestudies is slegs by volwassenes uitgevoer.

Vrugbaarheid, swangerskap en borsvoeding
NITASOL is gekontraïndikeerd tydens swangerskap en laktasie (see afdeling 4.3).

Swangerskap
Geen kliniese data is beskikbaar oor die gebruik van NITASOL tydens swangerskap nie.

Borsvoeding
NITASOL moet nie tydens laktasie gebruik word nie. Studies op rotte het getoon dat esetimieb in borsmelk uitgeskei word. Dit is nie bekend of esetimieb in menslike borsmelk uitgeskei word nie.

Vrugbaarheid
Geen kliniese proefdata is beskikbaar oor die effekte van esetimieb op menslike vrugbaarheid nie.
Esetimieb het geen effek op die vrugbaarheid van man of vrou gehad nie.

Uitwerking op die vermoë om te bestuur en masjiene te gebruik
Geen studies op die invloed van bestuursvermoë en die gebruik van masjiene is uitgevoer nie. Alhoewel, by die bestuur van voertuie of hantering van masjiene moet daar in ag geneem word dat duiseligheid aangemeld was.

Newe-effekte

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Infeksies en infestasies	Gereeld	virale infeksies, faringitis, sinusitis
Metabolisme- en voedingsversteurings	Minder gereeld	verminderde eetlus
Vaskulêre versteurings	Minder gereeld	warm gloede, hipertensie
Respiratories-, torakale- en mediastinale versteurings	Gereeld	hoes
Gastro-intestinale versteurings	Gereeld	abdominale pyn, diarree, winderigheid
	Minder gereeld:	dispepsie, gastroesofageale refluks siekte, naarheid
Muskuloskeletale bindweefselversteurings	Gereeld	artralgie, rugpyn
	Minder gereeld	spierspasmas, nekpyn
Algemene siektes en toedieningsarea toestande	Gereeld	hoofpyn, moegheid
	Minder gereeld	borspyn, pyn
Ondersoeke	Minder gereeld	verhoogde alanien aminotransferase (ALT) en/of aspartaat aminotransferase (AST), verhoogde bloed kreatienfosfokinase, verhoogde gamma glutamieltransferase, abnormale lewerfunksietoetse

NITASOL wanneer saam met statiene toegedien word

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Infeksies en infestasies	Gereeld	faringitis, sinusitis, boonste lugweginfeksie
Senusisteemversteurings	Gereeld	hoofpyn, duiseligheid
	Minder gereeld:	parestesie
Gastro-intestinale versteurings	Gereeld	abdominale pyn, konstipasie, diarree, winderigheid, naarheid
	Minder gereeld:	droë mond, gastritis
Vel- en Onderhuidse weefselversteurings	Minder gereeld:	pruritus, uitslag, urtikarie
Muskuloskeletale bindweefselversteurings	Gereeld	mialgie, artralgie, rugpyn
	Minder gereeld:	spierswakheid, pyn in ledemate
Algemene siektes en toedieningsarea toestande	Gereeld	borspyn, moegheid
	Minder gereeld:	astenie, perifere edeem
Ondersoeke	Gereeld:	verhoogde ALT en/of AST

NITASOL wanneer saam met fenofibraat toegedien word

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Gastro-intestinale versteurings	Gereeld	abdominale pyn

Na-bemarkingsdata

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Bloed- en Limfatiese Sisteem-versteurings	Frekwensie onbekend	trombositopenie
Senusisteemversteurings	Frekwensie onbekend	hipersensitiwiteitsreaksies (anafilakse, uitslag, urtikarie, angioedeem)
Psigiatriese versteurings	Frekwensie onbekend	depressie
Respiratories-, torakale- en mediastinale versteurings	Frekwensie onbekend	dispnee
Gastro-intestinale versteurings	Frekwensie onbekend	pankreatitis
Hepato-biliêre versteurings	Frekwensie onbekend	hepatitis, cholelitiase, cholesistitis
Vel- en Onderhuidse weefselversteurings	Frekwensie onbekend	eriteem multiforme
Muskuloskeletale bindweefselversteurings	Frekwensie onbekend	miopatie/rabdomioliese

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat NITASOL goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van NITASOL toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reactions Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/

Oordosering
In kliniese studies was die toediening van esetimieb, 50 mg/dag by 15 gesonde proefpersone vir tot 14 dae, of 40 mg/dag by 18 pasiënte met primêre hipercholesterolemie vir tot 56 dae, oor die algemeen goed verdra.
In die geval van 'n oordosis, moet simptomatiese en ondersteunende maatreëls getref word.

5 FARMAKOLOGIESE EIENSKAPPE
Farmakodinamiese eienskappe
Kategorie en klas: A 7.5 Serum-cholesterol reduseerders.
Farmakoterapeutiese groep: Ander lipied modifiserende agente.
ATC kode: C10A X09.
Meganisme van werking
Esetimieb inhibeer die intestinale absorpsie van cholesterol en verwante plantsterole.
'n Reeks pre-kliniese studies was uitgevoer om die selektiwiteit van esetimieb vir die inhibering van cholesterolabsorpsie te bepaal. Esetimieb het die absorpsie van [^{14}C]-cholesterol geïnhibeer met geen effek op die absorpsie van trigliseriede, vetsure, galsure, progesteroon, etiniel estradiol of vetoplosbare vitamiene A en D nie.

Pediatriese bevolking
Die veiligheid en effektiwiteit van esetimieb gesamentlike toediening met dosisse simvastatien van bo 40 mg per dag, was nie bestudeer by pediatriese pasiënte van 10 tot 17 jarige ouderdom nie. Die veiligheid en effektiwiteit van esetimieb gesamentlike toediening met simvastatien, was nie by pediatriese pasiënte < 10 jarige ouderdom bestudeer nie.
Die langtermyneffektiwiteit van terapie met esetimieb by pasiënte onder 17 jarige ouderdom om morbiditeit en mortaliteit te verminder in volwassenheid is nie bestudeer nie.

Farmakokinetiese eienskappe
Absorpsie
Na orale toediening word esetimieb vinnig geabsorbeer en ekstensief gekonjugeer na 'n farmakologies aktiewe fenoliese glukuroniede (esetimieb-glukuroniede). Gemiddelde maksimum plasmakonsentrasies (K_{maks}) kom voor binne 1 tot 2 uur vir esetimieb-glukuroniede en 4 tot 12 uur vir esetimieb. Die absolute biobeskikbaarheid van esetimieb kan nie bepaal word nie, aangesien die verbinding feitlik onoplosbaar is in waterige media geskik vir inspuiting.
Gelyktydige toediening van voedsel (hoë vet of geen-vet maaltye) het geen effek op die orale biobeskikbaarheid van esetimieb gehad nie. Esetimieb kan toegedien word met of sonder voedsel.

Verspreiding
Esetimieb en esetimieb-glukuronied is onderskeidelik 99,7 % en 88 tot 92 % aan menslike plasmaproteïene gebind.

Biotransformasie
Esetimieb word hoofsaaklik in die dunderm en lewer gemetaboliseer deur glukuroniedkonjugasie ('n fase II-reaksie) met daaropvolgende biliêre uitskeiding. Minimale oksidatiewe metabolisme ('n fase I-reaksie) was waargeneem by alle spesies wat geëvalueer was. Esetimieb en esetimieb-glukuronied is die hoof medisyne-afgeleide verbindings wat in plasma opgespoor word, en vorm onderskeidelik ongeveer 10 tot 20 % en 80 tot 90 % van die totale medisyne in plasma. Beide esetimieb en esetimieb-glukuronied word stadig uit die plasma geëlimineer met bewyse van beduidende enterohepatiese herwinning.
Die halfleeftyd vir esetimieb en esetimieb-glukuronied is ongeveer 22 uur.

Eliminasie
Na orale toediening van 14C-esetimieb (20 mg) aan menslike proefpersone, was die totale esetimieb ongeveer 93 % van die totale radioaktiwiteit in plasma. Ongeveer 78 % en 11 % van die toegediende radioaktiwiteit is onderskeidelik in die feses en urine herwin oor 'n 10-dae versamelingstydperk. Na 48 uur was daar geen waarneembare vlakke van radioaktiwiteit in die plasma nie.

Spesiale pasiëntgroepe
Pediatriese bevolking
Die absorpsie en metabolisme van esetimieb is soortgelyk tussen kinders van 10 jarige ouderdom of ouer en volwassenes. Op grond van totale esetimieb, is daar geen farmakokinetiese verskille tussen adolessente en volwassenes nie.
Farmakokinetiese data in die pediatriese populasie jonger as 10 jarige ouderdom is nie beskikbaar nie.

Bejaardes
Plasmakonsentrasies vir totale esetimieb is ongeveer 2-voudig hoër by bejaardes (≥ 65 jaar) as by jong mense (18 tot 45 jaar). LDL-C vermindering en die veiligheidsprofiel is vergelykbaar tussen bejaardes en jong persone wat met esetimieb behandel word. Dus, geen dosisaanpassing is nodig by bejaardes nie.

Hepatiese inkorting
Na 'n enkele 10-mg dosis esetimieb, is die gemiddelde AOK vir totale esetimieb ongeveer 1,7-voudig verhoog by pasiënte met ligte hepatiese inkorting (Child Pugh telling 5 of 6), vergeleke met gesonde persone. In 'n 14-dae, meervoudige dosisstudie (10 mg daagliks) by pasiënte met matige hepatiese inkorting (Child Pugh telling 7 tot 9), is die gemiddelde AOK vir totale esetimieb ongeveer 4-voudig verhoog op Dag 1 en Dag 14 in vergelyking met gesonde proefpersone. Geen dosisaanpassing is nodig vir pasiënte met ligte hepatiese inkorting nie. Vanweë die onbekende effekte van die verhoogde blootstelling aan esetimieb by pasiënte met matige of ernstige (Child Pugh telling > 9) hepatiese inkorting, is NITASOL gekontraïndikeerd by hierdie pasiënte (sien afdeling 4.4).

Renale inkorting
Na 'n enkele 10 mg dosis esetimieb by pasiënte met ernstige renale siekte (gemiddelde CrCl ≤ 30 ml/min/1,73 m^2), is die gemiddelde AOK vir totale esetimieb ongeveer 1,5-voudig verhoog, vergeleke met gesonde proefpersone. Hierdie resultaat word nie as klinies beduidend beskou nie. Geen dosisaanpassing is nodig vir renale ingekorte pasiënte nie.
'n Bykomende pasiënt in hierdie studie (na-renale oorplanting en die ontvangs van veelvuldige medisyne, insluitend siklosporien) het 'n 12-voudige groter blootstelling aan totale esetimieb gehad.

Geslag
Plasmakonsentrasies vir totale esetimieb is effens hoër (ongeveer 20 %) by vroue as by mans. LDL-C vermindering en veiligheidsprofiel is vergelykbaar tussen mans en vroue wat behandel word met NITASOL. Dus, geen dosisaanpassing is nodig op grond van geslag nie.

Pre-kliniese veiligheids data
Geen verdere inligting van belang is beskikbaar nie.

6 PHARMACEUTICAL PARTICULARS
Lys van hulpstowwe
Gehidrogeneerde kasterolie
Hipromellose
Kolloïdale silikon dioksied
Laktose monohidraat
Mikrokristallien sellulose
Natriumkroskarmellose
Natriumlaurielsulfaat
Natriumstearielfumeraat

Onverenigbaarheid
Nie van toepassing

Rakleeftyd
3 jaar

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Hou weg van hitte.
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9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
09 November 2021

10 DATUM VAN HERSIENING VAN DIE TEKS
09 November 2021