1 cm Barcode

hovid-Ezetimibe Tablet 10 mg

VIFLOxx-PC3
(MALAYSIA)

DESCRIPTION
Oblong, white to off-white uncoated tablet, shallow convex, "H" and "10" embossed on the each side separated with a score line on the same face.

COMPOSITION
Each tablet contains: Ezetimibe 10 mg

ACTIONS AND PHARMACOLOGY
hovid-Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. hovid-Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). 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.

PHARMACOKINETICS
Absorption
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe glucuronide). Mean maximum plasma concentrations (Cmax) 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. hovid-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 drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination
Ezetmibe is excreted primarily in the faeces via bile and undergoes enterohepatic recycling; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide. The elimination half-life for both ezetimibe and the glucuronide is about 22 hours.

SPECIAL POPULATIONS
Paediatric patients
The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults.

Geriatric patients
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). Therefore, no dosage adjustment is necessary in the elderly.

Hepatic insufficiency
No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, hovid-Ezetimibe is not recommended in these patients.

INDICATION
Primary Hypercholesterolaemia
hovid-Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.

Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Homozygous Familial Hypercholesterolaemia (HoFH)
hovid-Ezetimibe co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (phytosterolaemia)
hovid-Ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

CONTRAINDICATIONS
- Hypersensitivity to ezetimibe or to any of the excipients
- When hovid-Ezetimibe is co-administered with a statin, please refer to the package insert for that particular medicinal product.
- Therapy with hovid-Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.
- Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

WARNING AND PRECAUTIONS
- When Ezetimibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin
- Cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with hovid-Ezetimibe. However, rhabdomyolysis has been reported very rarely with hovid-Ezetimibe monotherapy and very rarely with the addition of hovid-Ezetimibe to other agents 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 upper limit of normal (ULN), hovid-Ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued.
- All patients starting therapy with Ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness
- Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Ezetimibe is not recommended
- The safety and efficacy of hovid-Ezetimibe administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving hovid-Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued
- Caution should be exercised when initiating hovid-Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving hovid-Ezetimibe and ciclosporin
- If Ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PREGNANCY AND LACTATION
hovid-Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.
Pregnancy
hovid-Ezetimibe should be given to pregnant women only if clearly necessary.

Lactation
hovid-Ezetimibe should not be used during lactation.

XXX

1 cm
Barcode

DRUG INTERACTIONS

- **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) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding hovid-Ezetimibe to cholestyramine may be lessened by this interaction.
- **Fibrates:** In patients receiving fenofibrate and hovid-Ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease.
- If cholelithiasis is suspected in a patient receiving hovid-Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.
- Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively).
- Co-administration of hovid-Ezetimibe with other fibrates has not been studied.
- Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. A lithogenic risk associated with the therapeutic use of hovid-Ezetimibe 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:** Caution should be exercised when initiating hovid-Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving hovid-Ezetimibe and ciclosporin.
- **Anticoagulants:** If hovid-Ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, International Normalised Ratio (INR) should be appropriately monitored.

MAIN SIDE/ADVERSE EFFECTS

<u>hovid-Ezetimibe MONOTHERAPY</u>

Investigations
Uncommon: ALT and/or AST increased, blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal

Respiratory, Thoracic and Mediastinal Disorders
Uncommon: Cough

Gastrointestinal Disorders
Common: Abdominal pain, diarrhea, flatulence
Uncommon: Dyspepsia, gastro esophageal reflux disease, nausea

Musculoskeletal and Connective Tissue Disorders
Uncommon: Arthralgia, muscle spasms, neck pain

Metabolism and Nutrition Disorders
Uncommon: Decreased appetite

Vascular Disorders
Uncommon: Hot flush, hypertension

General Disorders and Administration Site Condition
Common: Fatigue
Uncommon: Chest pain, pain

<u>ADDITIONAL ADVERSE REACTIONS WITH hovid-Ezetimibe CO-ADMINISTERED WITH A STATIN</u>

Investigations
Common: ALT and/or AST increased

Nervous System Disorders
Common: Headache
Uncommon: Paraesthesia

Gastrointestinal Disorders
Uncommon: Dry mouth, gastritis

Skin and Subcutaneous Tissue Disorders
Uncommon: Pruritus, rash, urticaria

Musculoskeletal and Connective Tissue Disorders
Common: Myalgia
Uncommon: Back pain, muscular weakness, pain in extremity

General Disorders and Administration Site Condition
Uncommon: Asthenia, oedema peripheral

<u>WITH OR WITHOUT A STATIN</u>
Not known: Thrombocytopaenia, dizziness, paraesthesia, dyspnoea, pancreatitis, constipation, erythema multiforme, myalgia, myopathy/rhabdomyolysis, asthenia, hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema, hepatitis, cholelithiasis, cholecystitis, depression

OVERDOSE AND TREATMENT

A few cases of overdosage with hovid-Ezetimibe have been reported: most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

DOSAGE AND ADMINISTRATION

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with hovid-Ezetimibe.

Route of administration is oral. The recommended dose is one Ezetimibe 10 mg tablet daily. hovid-Ezetimibe can be administered at any time of the day, with or without food.

When hovid-Ezetimibe is added to a statin, either the indicated usual initial dose of that particular statin or the already established higher statin dose should be continued. In this setting, the dosage instructions for that particular statin should be consulted.

Co-administration with bile acid sequestrants
Dosing of hovid-Ezetimibe should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

Use in Paediatric Patients
Initiation of treatment must be performed under review of a specialist.

Children and adolescents ≥ 6: The safety and efficacy of hovid - Ezetimibe in children aged 6 to 17 years has not been established.

When hovid - Ezetimibe is administered with a statin, the dosage instructions for the statin in children should be consulted.

Children <6 years: The safety and efficacy of hovid - Ezetimibe in children aged < 6 years has not been established. No data are available.

Use in Hepatic Impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with hovid-Ezetimibe is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction.

Note: The information given here is limited. For further information, consult your doctor or pharmacist

Storage: Store below 30°C

Presentation/Packing: Blisters of 10's, 30's and 100's

Product Registration Holder: HOVID Bhd.
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar),
30010 Ipoh, Malaysia.

Manufactured by: HOVID Bhd.
Lot 56422, 7½ Miles, Jalan Ipoh/Chemor,
31200 Chemor, Malaysia.

Information Date: June 2016

hovid