PRESCRIBING INFORMATION

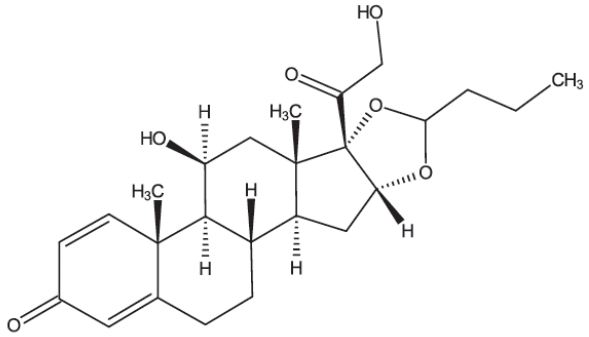
NEFEGAN 4 MG
MODIFIED RELEASE CAPSULE

1. DESCRIPTION

NEFEGAN modified release capsule is a white to off-white coated opaque capsule printed with “CAL10 4MG” in black ink for oral administration. The capsules contain white to off-white beads.

NEFEGAN modified release capsules contain 4 mg budesonide, a synthetic corticosteroid, as the active ingredient. Budesonide is designated chemically as 16α, 17α-[(1RS) Butylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione.

Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in chloroform.

2. INDICATIONS AND USAGE

NEFEGAN is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) $\geqslant$1.5 g/g.

It has not been established whether NEFEGAN slows kidney function decline in patients with IgAN.

3. DOSAGE AND ADMINISTRATION

The recommended duration of therapy is 9 months, with a dosage of 16 mg administered orally once daily *[see Clinical Studies (12.1)]*. When discontinuing therapy, reduce the dosage to 8 mg once daily for the last 2 weeks of therapy *[see Warnings and Precautions (5.1)]*.

The modified release capsules should be swallowed whole in the morning, at least 1 hour before a meal. Do not open, crush or chew.

If a dose is missed, take the prescribed dose at the next scheduled time. Do not double the next dose.

Safety and efficacy of treatment with subsequent courses of NEFEGAN have not been established.

4. CONTRAINDICATIONS

NEFEGAN is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of NEFEGAN. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5. WARNINGS AND PRECAUTIONS

5.1. Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy [see Dosing and Administration (2)] or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) [see Use in Specific Populations (8.5), Clinical Pharmacology (10.3)].

5.2. Risks of Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to

chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3. Other Corticosteroid Effects

NEFEGAN is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.1)]
- Risks of immunosuppression [see Warnings and Precautions (5.2)]
- Other corticosteroid effects [see Warnings and Precautions (5.3)]

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of NEFEGAN has been evaluated in a randomized controlled study in 197 patients.

The most common adverse reactions reported in greater than or equal to 5% of NEFEGAN-treated patients are listed in Table 1.

The majority of adverse reactions were mild or moderate in severity.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of NEFEGAN treated patients, and greater than or equal to 2% higher than Placebo

Adverse Reaction	NEFEGAN 16 mg (N=97) n (%)	Placebo (N=100) n (%)
Patients with any Adverse Reaction	84 (87)	73 (73)
Hypertension	15 (16)	2 (2)
Peripheral edema	14 (14)	4 (4)
Muscle spasms	13 (13)	4 (4)
Acne	11 (11)	2 (2)
Dermatitis	7 (7)	1 (1)

Adverse Reaction	NEFEGAN 16 mg (N=97) n (%)	Placebo (N=100) n (%)
Weight increased	7 (7)	3 (3)
Dyspnea	6 (6)	0 (0)
Face edema	6 (6)	1 (1)
Dyspepsia	5 (5)	2 (2)
Fatigue	5 (5)	2 (2)
Hirsutism	5 (5)	0 (0)

Most adverse reactions that occurred at a greater incidence for NEFEGAN compared to placebo were consistent with hypercortisolism.

7. DRUG INTERACTIONS

7.1. Interaction with CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine [see Clinical Pharmacology (10.3)].

Avoid ingestion of grapefruit juice with NEFEGAN. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide [see Clinical Pharmacology (10.3)].

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism (see Clinical Considerations). In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels (see Data).

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk

of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

Fetal/Neonatal Adverse Reactions

Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly [see Warnings and Precautions (5.1)].

Data

Animal Data

Budesonide was teratogenic and embryo-lethal in rabbits and rats.

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).

Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis).

In a peri-and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures $\geqslant$ 0.012 times the MRHD (on a mg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2. Lactation

Risk Summary

Breastfeeding is not expected to result in significant exposure of the infant to NEFEGAN.

Lactation studies have not been conducted with oral budesonide, including NEFEGAN, and no information is available on the effects of the drug on the breastfed infant or the effects on the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide (see Data). Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEFEGAN and any potential adverse effects on the breastfed infant from NEFEGAN, or from the underlying maternal condition.

Data

One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.

Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg NEFEGAN. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.3. Pediatric Use

The safety and efficacy of NEFEGAN in pediatric patients have not been established.

8.4. Geriatric Use

Clinical studies of NEFEGAN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.5. Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide [see Warnings and Precautions (5.1) and Clinical Pharmacology (10.3)]. Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

9. OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of corticoids are rare.

In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

10. CLINICAL PHARMACOLOGY

10.1. Mechanism of Action

Budesonide is a corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity that undergoes substantial first pass metabolism. Mucosal B-cells present in the ileum, including the Peyer's patches, express glucocorticoid receptors and are responsible for the production of galactose-deficient IgA1 antibodies (Gd-Ag1) causing IgA nephropathy. Through their anti-inflammatory and immunosuppressive effects at the glucocorticoid receptor, corticosteroids can modulate B-cell numbers and activity. It has not been established to what extent NEFEGAN's efficacy is mediated via local effects in the ileum vs systemic effects.

10.2. Pharmacodynamics

Treatment with corticosteroids, including NEFEGAN, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function.

10.3. Pharmacokinetics

Absorption

Following single oral administration of NEFEGAN 16 mg to healthy subjects, the average geometric mean C_{max} (CV%) was 4.4 ng/mL (58.3), and AUC_{0-24} was 24.1 h*ng/mL (49.7). Median T_{lag} (min, max) was 3.1 h (0, 6) while median T_{max} (min, max) was 5.1 h (4.5, 10).

Food Effect

There was no clinically relevant food effect observed on the overall systemic exposure of budesonide when either a moderate or high fat meal was consumed 1 hour after administration of NEFEGAN.

Distribution

Approximately 85 to 90% of budesonide binds to plasma proteins in blood over the concentration range of 0.43 to 99 ng/mL. The volume of distribution at steady state reported in the literature is 3 to 4 L/kg.

Metabolism

Budesonide is metabolized by the liver (and to lesser extent the gut), primarily by oxidative pathways via CYP3A4 to two main metabolites, 16α-hydroxyprednisolone and 6β-hydroxybudesonide, which have less than 1% of the corticosteroid activity of budesonide.

Elimination

Budesonide had a high plasma clearance, 0.9 to 1.8 L/min in healthy adults, which is

close to the estimated liver blood flow, and, accordingly, suggests that budesonide is a high hepatic clearance drug.

Following single oral administration of NEFEGAN 16 mg to healthy subjects, the elimination half-life (t½) for NEFEGAN ranged from 5.0 to 6.8 hours.

Excretion
Budesonide was excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^{3}H]-budesonide, approximately 60% of the recovered radioactivity was found in urine. The major metabolites, including 16α-hydroxyprednisolone and 6β-hydroxybudesonide, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide was detected in urine.

Specific Populations
Age, race, and body weight
The effect of age, race, and body weight on the pharmacokinetics of NEFEGAN has not been established.

Sex
Of the 143 healthy volunteers included in the Phase 1 studies, 29% were female. Pharmacokinetics of budesonide was similar between males and females.

Hepatic Impairment
Subjects with moderate hepatic impairment (Child-Pugh class B) had 3.5 times the budesonide AUC compared with healthy volunteers while subjects with mild hepatic impairment (Child-Pugh class A) had approximately 40% higher budesonide AUC compared with healthy volunteers.

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment
Intact budesonide is not excreted renally. The main metabolites of budesonide, which have negligible corticosteroid activity, are largely (60%) excreted in urine.

Drug Interaction Studies
Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase plasma levels of budesonide.

Thus, clinically relevant drug interactions with potent CYP3A inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, and grapefruit juice, are to be expected. Conversely, induction of CYP3A4 potentially could result in the lowering of budesonide plasma concentrations.

Effects of Other Drugs on Budesonide

Ketoconazole

In an open, non-randomized, cross-over study, 6 healthy subjects were given budesonide 10 mg as a single dose, either alone or concomitantly with the last ketoconazole dose of 3 days treatment with ketoconazole 100 mg twice daily. Co-administration of ketoconazole resulted in 8-fold the AUC of budesonide, compared to budesonide alone.
In an open, randomized, cross-over study 8 healthy subjects were given Entocort EC 3 mg as a single dose, either alone or concomitantly with the last ketoconazole dose of 4 days treatment with ketoconazole 200 mg once daily. Co-administration of ketoconazole resulted in 6.5-fold the AUC of budesonide, compared to budesonide alone.

Grapefruit Juice
In an open, randomized, cross-over study, 8 healthy subjects were given Entocort EC 3 mg, either alone, or concomitantly with 600 mL concentrated grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), on the last of 4 daily administrations. Concomitant administration of grapefruit juice resulted in doubling the bioavailability of budesonide compared to budesonide alone.

Proton Pump Inhibitors
The pharmacokinetics of NEFEGAN have not been evaluated in combination with proton pump inhibitors (PPIs). Since the disintegration of NEFEGAN is pH dependent, the release properties and uptake of budesonide may be altered when NEFEGAN is taken after treatment with PPIs. In a study assessing intragastric and intraduodenal pH in healthy volunteers after repeated dosing with the PPI omeprazole 40 mg once daily, intragastric and intraduodenal pH did not exceed that required for disintegration of NEFEGAN. Beyond the duodenum, PPIs such as omeprazole are unlikely to affect pH.

Oral Contraceptives (CYP3A4 Substrates)
In a parallel study, the pharmacokinetics of budesonide were not significantly different between healthy female subjects who received oral contraceptives containing desogestrel 0.15 mg and ethinyl estradiol 30 µg and healthy female subjects who did not receive oral contraceptives. Budesonide 4.5 mg once daily for one week did not affect the plasma concentrations of ethinyl estradiol, a CYP3A4 substrate. The effect of budesonide 16 mg once daily on the plasma concentrations of desogestrel and ethinyl estradiol was not studied.

11. NONCLINICAL TOXICOLOGY

11.1. Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.03 times the maximum recommended human dose (MRHD) on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.015 times the MRHD on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose

of 50 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.03 times the MRHD of a body surface area basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.06 times the MRHD on a body surface area basis).

Budesonide was not genotoxic in the Ames text, the mouse lymphoma cell forward gene mutation (TK+/-) test, the human lymphocyte chromosome aberration test, the Drosophila melanogaster sex-linked recessive lethal test, the rat hepatocyte UDS test and the mouse micronucleus test.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.05 times the MRHD on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal food consumption and body weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.012 times the MRHD on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.003 times the MRHD on a body surface area basis).

12. CLINICAL STUDIES

12.1. Treatment of IgAN

The effect of NEFEGAN on proteinuria was assessed in a randomized, double-blind, multicenter study (Nef-301, NCT: 03643965) in patients with biopsy-proven IgAN, eGFR ≥35 mL/min/1.73 m^2, and proteinuria (defined as either ≥1 g/day or UPCR ≥0.8 g/g) who were on a stable dose of maximally-tolerated RAS inhibitor therapy. Patients with other glomerulopathies, nephrotic syndrome, or those who had been treated with systemic immunosuppressive medications were excluded. Patients were randomized 1:1 to either NEFEGAN 16 mg once daily or placebo and treated for nine months followed by a 2-week taper of either NEFEGAN 8 mg once daily or placebo.

Of the 199 patients who completed the Month 9 visit, 68% were male, 86% were Caucasian, 12% were Asian, and 16% were from the US. The median age was 44 years (range 23 to 73 years). At baseline, the mean eGFR was approximately 58 mL/min/1.73 m^2, with 62% of patients having an eGFR <60 mL/min/1.73 m^2. The mean baseline UPCR was 1.6 g/g and 25% of patients had proteinuria >3.5 g/24 hours. Approximately 73% of patients had a history of hypertension and 5% had a history of type 2 diabetes mellitus. At baseline, 98% were treated with an ACE inhibitor or ARB and <1% of patients were on an SGLT2 inhibitor.

The primary endpoint was the percentage reduction in UPCR at 9 months compared to baseline. The results are shown in Table 2.

Table 2: Analysis of the primary efficacy endpoint at 9 months in Phase 3 Study Nef-301

Primary Endpoint: UPCR g/g[a]	**NEFEGAN 16 mg (N=97)**	**Placebo (N=102)**
Percentage reduction from baseline (Adjusted for baseline)[b]	34%	5%
NEFEGAN 16 mg versus Placebo : Percentage reduction (95% CI)[C]; 2- sided p-value	31% (16% to 42%); p=0.0001	

[a] *All patients with a UPCR reading regardless of use of prohibited medication at 9 months.*

[b] *Adjusted geometric least squares mean ratio of UPCR relative to baseline were based on a longitudinal repeated measures model.*

[c] *The estimate of the ratio of geometric mean ratio of UPCR relative to baseline comparing NEFEGAN 16 mg with placebo was reported as percentage reduction along with the respective 95% confidence interval from the longitudinal repeated measures model and p-values.*
CI: confidence interval; UPCR: urine protein creatinine ratio.

The treatment effect for the UPCR endpoint at 9 months were consistent across key subgroups, including key demographic (such as age, sex, race) and baseline disease (such as baseline proteinuria) characteristics.

13. SHELF LIFE

36 months

14. SPECIAL PRECAUTIONS FOR STORAGE

Store at below 30°C. Keep container tightly closed. Protect from moisture.

Keep out of the reach of children.

15. HOW SUPPLIED

NEFEGAN modified release capsules 4 mg, are white to off-white opaque-coated capsules marked with “CAL10 4 MG” in black ink on the body of the capsule. The capsules contain white to off-white beads.

Supplied on white high density polyethylene (HDPE) bottle with a white polypropylene (PP) child-resistant closure with an induction seal.

Pack size: 1 bottle containing 120 NEFEGAN modified release capsules 4 mg.

15.1. List of excipients

Capsule content

- Sugar spheres (sucrose and corn starch)
- Hypromellose
- Polyethylene glycol /Macrogol 400
- Citric acid monohydrate
- Ethylcellulose
- Medium chain triglycerides
- Oleic acid

Capsule Shell
- Hypromellose
- Titanium Dioxide

Capsule Coating
- Hypromellose
- Polyethylene glycol /Macrogol 400
- Methacrylic acid - methyl methacrylate co-polymers
- Talc
- Dibutyl sebacate

Printing ink
- Shellac
- Propylene glycol
- Black iron oxide (E172)

16. PRODUCT REGISTRANT

Everest Medicines (Singapore) Pte. Ltd.
30 Cecil Street, #19-08
Prudential Tower
Singapore 049712

17. DATE OF REVISION OF THE TEXT

March 2024