

1. NAME OF THE MEDICINAL PRODUCT

LENVIMA® 4 mg

LENVIMA® 10 mg

hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LENVIMA® 4 mg: Each hard capsule contains 4 mg of lenvatinib (as mesilate).

LENVIMA® 10 mg: Each hard capsule contains 10 mg of lenvatinib (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

LENVIMA® 4 mg:

A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with “C” on the cap, and “LENV 4 mg” on the body.

LENVIMA® 10 mg:

A yellow body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with “C” on the cap, and “LENV 10 mg” on the body.

4. CLINICAL PARTICULARS

Prescriber guide

This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

Patient safety information Card

This product is marketed with patient safety information card (patient card). Please explain to the patient the implications of this treatment including the need for compliance. Please also explain the signs of important adverse events and instruct the patient when to seek medical care.

4.1 Therapeutic indications

LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

4.2 Posology and method of administration

LENVIMA treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.

Posology

The recommended daily dose of lenvatinib is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (see dose adjustment section below).

If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose adjustment

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib until resolution or improvement of the reaction, after which treatment should be resumed at a reduced dose as suggested in Table 1. Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormality judged to be non-life-threatening, in which case they should be managed as severe reaction (e.g., Grade 3).

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Optimal medical management for nausea, vomiting, and diarrhoea should be initiated prior to any interruption or dose reduction of lenvatinib. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or failure (see section 4.4, Renal failure and impairment).

Table 1 Dose modifications from recommended daily dose

Dose level	Daily dose	Number of capsules
Recommended daily dose	24 mg orally once daily	Two 10 mg capsules plus one 4 mg capsule
First dose reduction	20 mg orally once daily	Two 10 mg capsules
Second dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Third dose reduction	10 mg orally once daily ^a	One 10 mg capsule

^a: Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.

Special populations

Patients of age ≥ 75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib (see section 4.8, Other special populations). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended

24 mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see section 4.4).

Patients with hepatic impairment

No adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

Patients with renal impairment

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥ 75 years.

Paediatric population

Lenvatinib must not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3). The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.

Race

No adjustment of starting dose is required on the basis of race (see section 5.2). Limited data are available on use in patients from ethnic origins other than Caucasian or Asian.

Method of administration

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2). The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hypertension

Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Blood pressure should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. The early detection and effective management

of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. Blood pressure should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. The choice of antihypertensive treatment should be individualized to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. For patients with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred. When necessary, manage hypertension as recommended in Table 2.

Table 2 Recommended management of hypertension

Blood Pressure (BP) level	Recommended action
Systolic BP \geq 140 mmHg up to <160 mmHg or diastolic BP \geq 90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP \geq 160 mmHg or diastolic BP \geq 100 mmHg despite optimal antihypertensive therapy	<ol style="list-style-type: none"> 1. Withhold lenvatinib 2. When systolic BP \leq150 mmHg, diastolic BP \leq95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment (see section 4.6). It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Urine protein should be monitored regularly. If urine dipstick proteinuria \geq 2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). LENVIMA should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment

Renal impairment and renal failure have been reported in patients treated with lenvatinib (see section 4.8). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Cardiac failure

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (see section 4.8). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS)

Posterior reversible encephalopathy syndrome (PRES, also known as RPLS), has been reported in patients treated with lenvatinib (<1%; see section 4.8). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (see section 4.4, Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Hepatotoxicity

Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8, Description of selected adverse reactions) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Haemorrhage

Serious cases of haemorrhage have been reported in patients treated with lenvatinib (see section 4.8 Description of selected adverse reactions). Cases of fatal intracranial haemorrhage have been reported in some patients with brain metastases. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see section 4.8). Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. LENVIMA should be discontinued following an arterial thrombotic event.

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with lenvatinib (see section 4.8). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see section 4.8). Electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation, therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment.

Impairment of thyroid stimulating hormone suppression

Lenvatinib impairs exogenous thyroid suppression (see section 4.8, Description of selected adverse reactions). Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Special populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged ≥ 75 years. Lenvatinib should be used with caution in such patients, given the reduced tolerability of lenvatinib in Asian and elderly patients (see section 4.8, Other special populations).

There are no data on the use of lenvatinib immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was of 4 weeks.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on lenvatinib

Chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances.

Effect of lenvatinib on other medicinal products

No data is available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or Pgp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/Pgp substrates. This should be considered if co-administering oral CYP3A4/Pgp substrates for which retained efficacy is very important. CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozone, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib.

Oral contraceptives

It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits (see section 5.3).

Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the fetus.

Breast-feeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk (see section 5.3). A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see section 4.3).

Fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

Lenvatinib has a minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions (occurring in $\geq 30\%$ of patients) are hypertension (68.6%), diarrhoea (62.8%), decreased appetite (51.5%), weight decreased (49.1%), fatigue (45.8%), nausea (44.5%), proteinuria 36.9%), stomatitis (35.8%), vomiting (34.5%), dysphonia (34.1%), headache (34.1%), and palmar-plantar erythrodysesthesia syndrome (PPE) (32.7%). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see section 4.8, Description of selected adverse reactions). The majority of Grade 3 to 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time.

The most important serious adverse reactions are renal failure and impairment (2.4%), cardiac failure (0.7%), intracranial tumor haemorrhage (0.7%), PRES / RPLS (0.2%), hepatic failure (0.2%), and arterial thromboembolisms (cerebrovascular accident (1.1%), transient ischaemic attack (0.7%), and myocardial infarction (0.9%).

In 452 patients with RAI-refractory DTC, dose reduction and discontinuation were the actions taken for an adverse reaction in 63.1% and 19.5% of patients, respectively. Adverse reactions that most commonly led to dose reductions (in $\geq 5\%$ of patients) were hypertension, proteinuria, diarrhoea, fatigue, PPE, weight decreased, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism.

Tabulated list of adverse reactions

Table 3 shows the incidence rates of adverse reactions observed in clinical trials.

Frequencies are defined as:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)

Within each frequency category, undesirable effects are presented in order of decreasing seriousness.

Table 3 Adverse reactions reported in patients in clinical trials

System Organ Class (MedDRA terminology*)	Very Common	Common	Uncommon
Infections and infestation	Urinary tract infection		Perineal abscess
Blood and lymphatic disorders	Thrombocytopenia ^a	Lymphopenia ^a	Splenic infarction
Endocrine disorders		Hypothyroidism Blood thyroid stimulating hormone increased [‡]	

System Organ Class (MedDRA terminology [*])	Very Common	Common	Uncommon
Metabolism and nutrition disorders	Hypocalcaemia [‡] Hypokalaemia Weight decreased Decreased appetite	Dehydration Hypomagnesaemia ^b Hypercholesterolaemia ^b	
Psychiatric disorders	Insomnia		
Nervous system disorders	Dizziness Headache Dysgeusia	Cerebrovascular accident	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack
Cardiac disorders		Myocardial infarction ^{c,†} Cardiac failure Electrocardiogram QT prolonged Ejection fraction decreased	
Vascular disorders	Haemorrhage ^{d, †, ‡} Hypertension ^{e, ‡} Hypotension		
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism [†]	
Gastrointestinal disorders	Diarrhoea Gastrointestinal and abdominal pains ^f Vomiting Nausea Oral inflammation ^g Oral pain ^h Constipation Dyspepsia Dry mouth	Anal fistula Flatulence	

System Organ Class (MedDRA terminology*)	Very Common	Common	Uncommon
Hepatobiliary disorders		Aspartate aminotransferase increased [‡] Hypoalbuminaemia [‡] Alanine aminotransferase increased [‡] Blood alkaline phosphatase increased Hepatic function abnormal Gamma-glutamyltransferase increased ^k Blood bilirubin increased [‡]	Hepatocellular damage/hepatitis ⁱ
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome Rash Alopecia	Hyperkeratosis	
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain		
Renal and urinary disorders	Proteinuria [‡]	Renal failure cases ^{j, †} Renal impairment Blood creatinine increased Blood urea increased	
General disorders and administration site conditions	Fatigue Asthenia Oedema peripheral	Malaise	

*: Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.

[†]: Includes cases with a fatal outcome.

[‡]: See section 4.8 Description of selected adverse reactions for further characterisation.

The following terms have been combined:

- a: Thrombocytopenia includes thrombocytopenia and platelet count decreased.
Lymphopenia includes lymphopenia and lymphocyte count decreased.
- b: Hypomagnesaemia includes hypomagnesaemia and blood magnesium decreased.
Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.
- c: Myocardial infarction includes myocardial infarction and acute myocardial infarction.
- d: Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage,

- aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, melaena, metrorrhagia, nail bed bleeding, pleural haemorrhage, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.
- e: Hypertension includes: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased.
 - f: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
 - g: Oral inflammation includes: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
 - h: Oral pain includes: oral pain, glossodynia, and oropharyngeal pain.
 - i: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
 - j: Renal failure cases includes: acute prerenal failure, renal failure, renal failure acute, and renal tubular necrosis.

Description of selected adverse reactions

Hypertension (see section 4.4)

In the pivotal Phase 3 SELECT trial (see section 5.1), hypertension (including hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) was reported in 72.8% of lenvatinib-treated patients and 16.0% of patients in the placebo-treated group. The median time to onset in lenvatinib-treated patients was 16 days. Reactions of Grade 3 or higher (including 1 reaction of Grade 4) occurred in 44.4% of lenvatinib-treated patients compared with 3.8% of placebo-treated patients. The majority of cases recovered or resolved following dose interruption or reduction, which occurred in 13.0% and 13.4% of patients, respectively. In 1.1% of patients, hypertension led to permanent treatment discontinuation.

Proteinuria (see section 4.4)

In the pivotal Phase 3 SELECT trial (see section 5.1), proteinuria was reported in 33.7% of lenvatinib-treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7% of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction, which occurred in 16.9% and 10.7% of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8% of patients.

Hepatotoxicity (see section 4.4)

In the pivotal Phase 3 SELECT trial (see section 5.1), the most commonly reported liver-related adverse reactions were hypoalbuminaemia (9.6% lenvatinib vs. 1.5% placebo) and elevations of liver enzyme levels, including increases in alanine aminotransferase (7.7% lenvatinib vs. 0 placebo), aspartate aminotransferase (6.9% lenvatinib vs. 1.5% placebo), and blood bilirubin (1.9% lenvatinib vs. 0 placebo). The median time to onset of liver reactions in lenvatinib-treated patients was 12.1 weeks. Liver-related reactions of Grade 3 or higher (including 1 Grade 5 case of hepatic failure) occurred in 5.4% of lenvatinib-treated patients compared with 0.8% in placebo-treated patients. Liver-related reactions led to dose interruptions and reductions in 4.6% and 2.7% of patients, respectively, and to permanent discontinuation in 0.4%.

Amongst 1108 patients treated with lenvatinib, there were 3 cases (0.3%) of hepatic failure, all with a fatal outcome. One occurred in a patient with no liver metastases. There was also a case of acute hepatitis in a patient without liver metastases.

Haemorrhage (see section 4.4)

In the pivotal Phase 3 SELECT trial (see section 5.1), haemorrhage was reported in 34.9% of lenvatinib-treated patients versus 18.3% of placebo-treated patients. Reactions that occurred at an incidence of $\geq 0.75\%$ above placebo were: epistaxis (11.9%), haematuria (6.5%), contusion (4.6%), gingival bleeding (2.3%), haematochezia (2.3%), rectal haemorrhage (1.5%), haematoma (1.1%), haemorrhoidal haemorrhage (1.1%), laryngeal haemorrhage (1.1%), petechiae (1.1%), and intracranial tumour haemorrhage (0.8%). When adjusted to account for the 4-fold greater duration of exposure in the lenvatinib versus the placebo arm, the following reactions occurred less frequently on lenvatinib than placebo: haemoptysis (0.05 episodes/subject-year on lenvatinib vs. 0.21 episodes/subject-year on placebo) and pulmonary haemorrhage (0.02 episodes/subject-year on lenvatinib vs. 0.09 episodes/subject-year on placebo).

The median time to first onset in lenvatinib-treated patients was 10.1 weeks. No differences between lenvatinib- and placebo-treated patients were observed in the incidences of serious reactions (3.4% vs. 3.8%), reactions leading to premature discontinuation (1.1% vs. 1.5%), or reactions leading to dose interruption (3.4% vs. 3.8%) or reduction (0.4% vs. 0).

Amongst 1108 patients treated with lenvatinib, 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.5%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial tumour haemorrhage, haemoptysis and tumour haemorrhage.

Hypocalcaemia (see section 4.4, QT interval prolongation)

In the pivotal Phase 3 SELECT trial (see section 5.1), hypocalcaemia was reported in 12.6% of lenvatinib-treated patients vs. no cases in the placebo arm. The median time to first onset in lenvatinib-treated patients was 11.1 weeks. Reactions of Grade 3 or 4 severity occurred in 5.0% of lenvatinib-treated vs 0 placebo-treated patients. Most reactions resolved following supportive treatment, without dose interruption or reduction, which occurred in 1.5% and 1.1% of patients, respectively; 1 patient with Grade 4 hypocalcaemia discontinued treatment permanently.

Blood thyroid stimulating hormone increased (see section 4.4 Impairment of thyroid stimulating hormone suppression)

In the pivotal Phase 3 SELECT trial (see section 5.1), 88% of all patients had a baseline TSH level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients as compared with 14% of placebo-treated patients.

Paediatric population

Clinical data are not available in this population (see section 4.2).

Other special populations

Elderly

Patients of age ≥ 75 years were more likely to experience Grade 3 to 4 hypertension, proteinuria, decreased appetite, and dehydration.

Gender

Females had a higher incidence of hypertension (including Grade 3 or 4 hypertension), proteinuria, and PPE, while males had a higher incidence of decreased ejection fraction and gastrointestinal perforation and fistula formation.

Ethnic origin

Asian patients had a higher incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased.

Baseline hypertension

Patients with baseline hypertension had a higher incidence of Grade 3 to 4 hypertension, proteinuria, diarrhoea, and dehydration, and experienced more serious cases of dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting).

Hepatic impairment

Patients with baseline hepatic impairment had a higher incidence of hypertension and PPE, and a higher incidence of Grade 3 or 4 hypertension, asthenia, fatigue, and hypocalcaemia compared with patients with normal hepatic function.

Renal impairment

Patients with baseline renal impairment had a higher incidence of Grade 3 to 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, blood thyroid stimulating hormone increased, pneumonia compared with subjects with normal renal function. These patients also had a higher incidence of renal reactions and a trend towards a higher incidence of liver reactions.

Patients with body weight <60 kg

Patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of grade 3-4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of grade 3-4 decreased appetite.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il> and by email to Neopharm's Patient Safety Unit at: DrugSafety@NeophamGroup.com.

4.9 Overdose

The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. There have also been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

Symptoms and Management

There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and appropriate supportive care given as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE29

Lenvatinib is a multikinase inhibitor which has shown mainly antiangiogenic properties in vitro and in vivo, and direct inhibition of tumour growth was also observed in in vitro models.

Mechanism of action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFR α , KIT, and RET.

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus.

The mechanism of action for hypothyroidism is not fully elucidated.

Clinical efficacy

Radioiodine-refractory differentiated thyroid cancer

The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioiodine-refractory differentiated thyroid cancer with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month window) prior to enrollment. Radioiodine-refractory was defined as one or more measurable lesions either with a lack of iodine uptake or with progression in spite of radioactive-iodine (RAI) therapy, or having a cumulative activity of RAI of >600 mCi or 22 GBq with the last dose at least 6 months prior to study entry. Randomisation was stratified by geographic region (Europe, North America, and Other), prior VEGF/VEGFR-targeted therapy (patients may have received 0 or 1 prior VEGF/VEGFR-targeted therapy), and age (≤ 65 years or >65 years). The main efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Secondary efficacy outcome measures included overall response rate and overall survival. Patients in the placebo arm could opt to receive lenvatinib treatment at the time of confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomised 2:1 to receive lenvatinib 24 mg once daily (n=261) or placebo (n=131). Baseline demographics and disease characteristics were well balanced for both treatment groups. Of the 392 patients randomised, 76.3% were naïve to prior VEGF/VEGFR-targeted therapies, 49.0% were female, 49.7% were European, and the median age was 63 years. Histologically, 66.1% had a confirmed diagnosis of papillary thyroid cancer and 33.9% had follicular thyroid cancer which included Hürthle cell 14.8% and clear cell 3.8%. Metastases were present in 99% of the patients: lungs in 89.3%, lymph nodes in 51.5%, bone in 38.8%, liver in 18.1%, pleura in 16.3%, and brain in 4.1%. The majority of patients had an ECOG performance status of 0;

42.1% had a status of 1; 3.9% had a status above 1. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in lenvatinib-treated patients compared with those receiving placebo ($p<0.0001$) (see figure 1). The positive effect on PFS was seen across the subgroups of age (above or below 65 years), sex, race, histological subtype, geographic region, and those who received 0 or 1 prior VEGF/VEGFR-targeted therapy. Following independent review confirmation of disease progression, 109 (83.2%) patients randomised to placebo had crossed over to open-label lenvatinib at the time of the primary efficacy analysis.

The objective response rate (complete response [CR] plus partial response [PR]) per independent radiological review was significantly ($p<0.0001$) higher in the lenvatinib-treated group (64.8%) than in the placebo-treated group (1.5%). Four (1.5%) subjects treated with lenvatinib attained a CR and 165 subjects (63.2%) had a PR, while no subjects treated with placebo had a CR and 2 (1.5%) subjects had a PR.

The median time to first dose reduction was 2.8 months. The median time to objective response was 2.0 (95% CI: 1.9, 3.5) months; however, of the patients who experienced a complete or partial response to lenvatinib, 70.4% were observed to develop the response on or within 30 days of being on the 24-mg dose.

An overall survival analysis was confounded by the fact that placebo-treated subjects with confirmed disease progression had the option to cross over to open-label lenvatinib. There was no statistically significant difference in overall survival between the treatment groups at the time of the primary efficacy analysis (HR=0.73; 95%CI: 0.50, 1.07, $p=0.1032$). The median OS had not been reached for either the lenvatinib group or the placebo crossover group.

Table 4 Efficacy results

	Lenvatinib N=261	Placebo N=131
Progression-Free Survival (PFS)^a		
Number of progressions or deaths (%)	107 (41.0)	113 (86.3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (99% CI) ^{b,c}	0.21 (0.14, 0.31)	
P-value ^b	<0.0001	
Patients who had received 0 prior VEGF/VEGFR-targeted therapy (%)		
Number of progressions or deaths	195 (74.7)	104 (79.4)
Median PFS in months (95% CI)	76	88
Hazard ratio (95% CI) ^{b,c}	18.7 (16.4, NE)	3.6 (2.1, 5.3)
Patients who had received 1 prior VEGF/VEGFR-targeted therapy (%)		
Number of progressions or deaths	66 (25.3)	27 (20.6)
Median PFS in months (95% CI)	31	25
Hazard ratio (95% CI) ^{b,c}	15.1 (8.8, NE)	3.6 (1.9, 3.7)
Objective Response Rate^a		
Number of objective responders (%)	169 (64.8)	2 (1.5)
(95% CI)	(59.0, 70.5)	(0.0, 3.6)
P-value ^b	<0.0001	
Number of complete responses	4	0
Number of partial responses	165	2

Median time to objective response, ^d months (95% CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Duration of response, ^d months, median (95% CI)	NE (16.8, NE)	NE (NE, NE)
Overall Survival		
Number of deaths (%)	71 (27.2)	47 (35.9)
Median OS in months (95% CI)	NE (22.0, NE)	NE (20.3, NE)
Hazard ratio (95% CI) ^{b, e}	0.73 (0.50, 1.07)	
P-value ^{b, e}	0.1032	

CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time model; VEGF/VEGFR, vascular endothelial growth factor / vascular endothelial growth factor receptor.

a: Independent radiologic review.

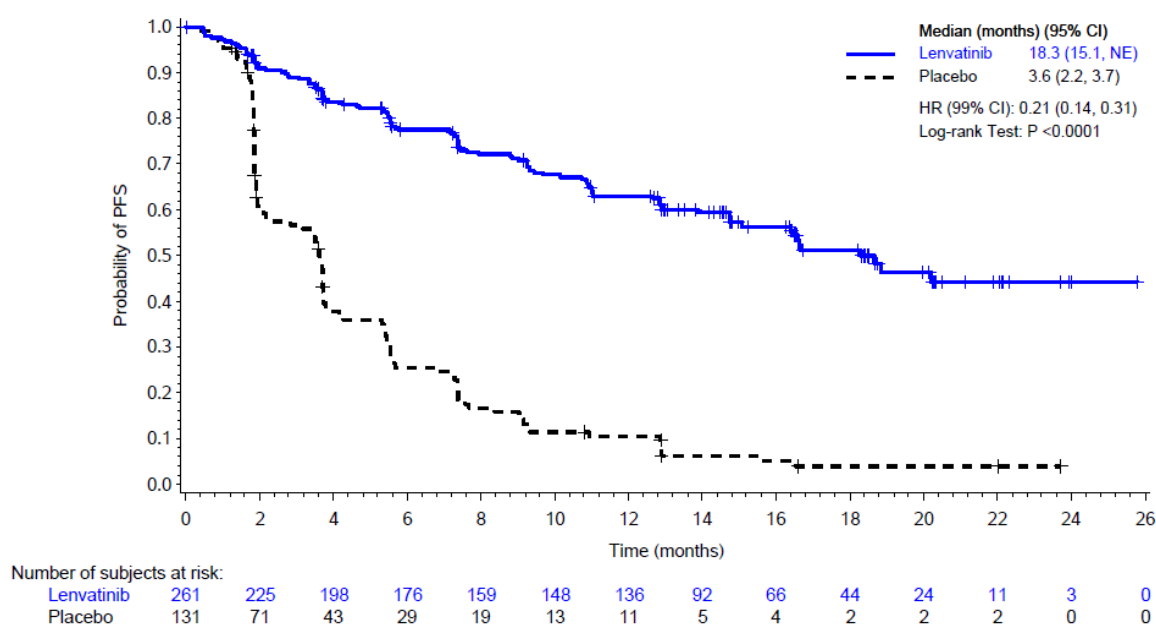
b: Stratified by region (Europe vs. North America vs. Other), age group (≤ 65 year vs > 65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

c: Estimated with Cox proportional hazard model.

d: Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.

e: Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Plot of Progression-Free Survival



CI, confidence interval; NE, not estimable.

QT interval prolongation

A single 32-mg dose of lenvatinib did not prolong the QT/QTc interval based on results from a thorough QT study in healthy volunteers; however, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see sections 4.4 and 4.8).

Paediatric population

No data are available.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lenvatinib have been studied in healthy adult subjects, adult subjects with hepatic impairment, renal impairment, and solid tumors.

Absorption

Lenvatinib is rapidly absorbed after oral administration with t_{\max} typically observed from 1 to 4 hours postdose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests that it is in the order of 85%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Distribution

In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 µg/mL, mesilate). This binding was mainly to albumin with minor binding to α 1-acid glycoprotein and γ -globulin.

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL, mesyilate).

Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP.

In patients, the median apparent volume of distribution (V_z/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (V_z/F_{ss}) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation

In vitro, cytochrome P450 3A4 was demonstrated as the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo*, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see section 4.5).

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0-\infty)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials.

In vitro transporter studies

For the following transporters, clinically relevant inhibition was excluded based on a cutoff of $IC_{50} > 50 \times C_{\max, \text{unbound}}$.

Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed.

Lenvatinib showed minimal or no inhibitory effect on OATP1B3. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

Elimination

Plasma concentrations decline bi-exponentially following C_{\max} . The mean terminal exponential half-life of lenvatinib is approximately 28 hours.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4% of the dose).

Linearity/non-linearity

Dose proportionality and accumulation

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (C_{\max} and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily.

Lenvatinib displays minimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg).

Special populations

Hepatic impairment

The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5-mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10-mg dose. The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Lenvatinib exposure, based on dose-adjusted AUC_{0-t} and $AUC_{0-\infty}$ data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment,

respectively. It is unknown whether there is a change in the plasma protein binding in hepatically impaired subjects. See section 4.2 for dosing recommendation.

Renal impairment

The pharmacokinetics of lenvatinib following a single 24-mg dose were evaluated in 6 subjects each with mild, moderate, and severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied.

Lenvatinib exposure, based on AUC_{0-inf} data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It is unknown whether there is a change in the plasma protein binding in renally impaired subjects. See section 4.2 for dosing recommendation.

Age, sex, weight, race

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no significant effects on clearance (see section 4.2).

Paediatric Population

Paediatric patients have not been studied.

5.3 Preclinical safety data

In the repeated-dose toxicity studies (up to 39 weeks), lenvatinib caused toxicologic changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib including glomerulopathy, testicular hypocellularity, ovarian follicular atresia, gastrointestinal changes, bone changes, changes to the adrenals (rats and dogs), and arterial (arterial fibrinoid necrosis, medial degeneration, or haemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Elevated transaminase levels associated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity

Lenvatinib was not genotoxic.

Carcinogenicity studies have not been conducted with lenvatinib.

Reproductive and developmental toxicity

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period.

Administration of lenvatinib during organogenesis resulted in embryoletality and teratogenicity in rats (foetal external and skeletal anomalies) at exposures below the clinical exposure (based on AUC) at the maximum tolerated human dose, and rabbits (foetal external, visceral or skeletal anomalies) based on body surface area; mg/m² at the maximum tolerated human dose. These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent. Lenvatinib and its metabolites are excreted in rat milk.

Juvenile animal toxicity studies

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age. Therefore mortality may be attributed to complications related to primary duodenal lesions with possible contribution from additional toxicities in immature target organs.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats at 10 mg/kg compared with adult rats administered the same dose level. Growth retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Calcium carbonate

Mannitol

Microcrystalline cellulose (PH-101, PH-102)

Hydroxypropylcellulose

Low-substituted hydroxypropylcellulose

Talc

Capsule shell

Hypromellose

Titanium dioxide

Yellow iron oxide (E172)

Red iron oxide (E172)

Printing ink

Shellac

Black iron oxide (E172)

Potassium hydroxide

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blisters containing 10 capsules. Each carton contains 30 capsules

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

7. MANUFACTURER

Eisai Manufacturing Ltd., Hertfordshire, UK.

8. REGISTRATION HOLDER

Neopharm Scientific Ltd,
6 Hashiloach St. P.O.Box 7063, Petach Tikva 49170.
Email: DrugSafety@NeopharmGroup.com
Fax: 03-9264227



9. REGISTRATION NUMBERS

LENVIMA[®] 4 mg: 155-36-34514
LENVIMA[®] 10 mg: 155-37-34530

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