SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Luminity 150 microlitres/ml gas and solvent for dispersion for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains a maximum of 6.4 x 10^9 perflutren-containing lipid microspheres, with a mean diameter range of 1.1-2.5 micrometres (μm). The approximate amount of perflutren gas in each ml is 150 microlitres (μl).

Excipient(s) with known effect
Each ml contains 2.679 mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gas and solvent for dispersion for injection/infusion

Colourless, uniformly clear to translucent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Luminity is an ultrasound contrast-enhancing agent for use in adult patients in whom non-contrast echocardiography was suboptimal (suboptimal is considered to indicate that at least two of six segments in the 4- or 2-chamber view of the ventricular border were not evaluable) and who have suspected or established coronary artery disease, to provide opacification of cardiac chambers and improvement of left ventricular endocardial border delineation at both rest and stress.

4.2 Posology and method of administration

Luminity should only be administered by trained physicians with technical expertise in performing
and interpreting contrast echocardiograms, and appropriate resuscitation equipment should be
available in case of cardiopulmonary or hypersensitivity reactions (see section 4.4).

Posology

Bolus intravenous injection using non-linear contrast imaging technique at rest and stress:

The recommended dose is multiple injections of 0.1 to 0.4 ml of dispersion, followed by a 3 to 5 ml bolus of sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution for injection to maintain optimal contrast enhancement. The total dose of perflutren should not exceed 1.6 ml.

Bolus intravenous injection using fundamental imaging technique at rest:

The recommended dose is 10 microlitre dispersion/kg by slow bolus intravenous injection, followed by a 10 ml bolus of sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution for injection. If necessary, a second 10 microlitre dispersion/kg dose followed by a second 10 ml bolus of sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution for injection may be administered 5 minutes after the first injection to prolong contrast enhancement.

Intravenous infusion using non-linear contrast imaging technique (rest and stress) or fundamental imaging technique at rest:

The recommended dose via an intravenous infusion is 1.3 ml dispersion added to 50 ml of sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution for injection. The rate of infusion should be initiated at 4 ml/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 ml/minute.

Paediatric population
The safety and efficacy of Luminity in children and adolescents below 18 years have not been established. No data are available.

Patients with hepatic impairment
Luminity has not been specifically studied in patients with hepatic impairment. Use in this patient group should be on the basis of a benefit risk assessment by the physician.

Patients with renal impairment
Luminity has not been specifically studied in patients with renal impairment. Use in this patient group should be on the basis of a benefit risk assessment by the physician.

Elderly patients

Luminity has not been specifically studied in elderly patients. Use in this patient group should be on the basis of a benefit risk assessment by the physician.

Method of administration

Intravenous use.

Before administering Luminity, the medicinal product must be activated by using a mechanical shaking device, the Vialmix, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

This product must only be administered intravenously.

Luminity should not be used with fundamental imaging technique for stress echocardiography since efficacy and safety have not been established.

Patients with unstable cardiopulmonary status
During contrast-enhanced echocardiography, serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes of Luminity administration in patients including those with severe cardiac and pulmonary diseases (see section 4.8). Extreme caution should be used when considering the administration of Luminity to patients with unstable cardiopulmonary status, for example: unstable angina, acute myocardial infarction, severe ventricular arrhythmias, severe heart failure (NYHA IV) or respiratory failure. Luminity should only be administered to such patients after careful risk/benefit assessment.

Contrast-enhanced echocardiography should only be considered in such patients if the results are likely to produce a change in individual patient management.

Patients with unstable cardiopulmonary status should be monitored during and for at least 30 minutes following Luminity administration. For such patients monitoring should include vital sign measurements, electrocardiography, and, if clinically appropriate, cutaneous oxygen saturation. Resuscitation equipment and trained personnel must always be readily available.

Patients with adult respiratory distress syndrome, endocarditis, prosthetic heart valves, systemic inflammation, sepsis, hyperactive coagulation and/or recurrent thromboembolism

Luminity should be used only after careful consideration and such use should be monitored closely during administration in patients with adult respiratory distress syndrome, endocarditis, a heart with prosthetic valves, acute states of systemic inflammation or sepsis, known states of hyperactive coagulation and/or recurrent thromboembolism.

Hypersensitivity reactions
Serious immediate hypersensitivity reactions (eg: anaphylaxis, anaphylactic shock and anaphylactoid reactions, hypotension and angioedema) have been reported following the administration of Luminity, including in patients with prior allergic reaction(s) to polyethylene glycol (see Section 6.1). Patients should be closely monitored and administration should be under the direction of a physician experienced in the management of hypersensitivity reactions including severe allergic reactions, which might require resuscitation. Emergency equipment and personnel trained in its use must be readily available.

Pulmonary disease
Caution should be exercised in patients with clinically significant pulmonary disease, including diffuse interstitial pulmonary fibrosis and severe chronic obstructive pulmonary disease, as no studies have been performed in these patients.

Sickle Cell Disease
In postmarketing use, patients with sickle cell disease reported episodes of severe acute pain (vaso-occlusive pain) shortly following perflutren-containing microsphere administration. Luminity should be used with caution in patients with sickle cell disease following a benefit risk assessment by the physician.

Patients with Cardiac Shunts
The safety of Luminity in patients with right-to-left, bi-directional or transient right-to-left cardiac shunts has not been studied. In these patients, phospholipid encapsulated microspheres can bypass the lung and directly enter the arterial circulation. Caution must be exercised when considering the administration of Luminity to these patients.

Patients on mechanical ventilation
The safety of microspheres in patients on mechanical ventilation has not been established. Caution should be exercised when considering the administration of Luminity to these patients.

Administration and mechanical activation procedure
Luminity should not be administered by methods not specified in section 4.2 (e.g. intra-arterial injection).

If Luminity is administered directly to the patient without undergoing the mechanical activation procedure using the Vialmix (see section 6.6), the product will not produce its intended effect.

Sodium Content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed and no other forms of interaction have been identified.

4.6 Fertility, Pregnancy and lactation

Pregnancy
For perflutren, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding
It is not known whether Luminity is excreted in human breast milk. Therefore, caution should be exercised when Luminity is administered to breast-feeding women.

Fertility
Animal studies do not indicate direct or indirect harmful effects on fertility.

4.7 Effects on ability to drive and use machines

As Luminity has no pharmacologic effect, and on the basis of its pharmacokinetic and pharmacodynamic profiles, no or negligible influence is expected with the use of this product on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
The reported adverse reactions following the use of Luminity in pivotal and supportive trials (total of 2,526 patients) occur within minutes after administration and usually resolve without therapeutic intervention within 15 minutes. The most frequently reported adverse reactions are: headache (2.0%), flushing (1.0%) and back pain (0.9%).

Tabulated list of adverse reactions
Adverse reactions were reported with the following frequencies (Very common ≥ 1/10; Common ≥ 1/100 to < 1/10; Uncommon ≥ 1/1,000 to < 1/100; Rare ≥ 1/10,000 to < 1/1,000; Very rare < 1/10,000), not known (cannot be estimated from

the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders	Not known: Sickle cell anaemia vaso-occlusive crisis
Immune system disorders	Not known: Allergic type reactions, anaphylaxis, anaphylactic shock and anaphylactoid type reactions, hypotension, angioedema, lip swelling, bronchospasm, rhinitis, upper airway swelling, throat tightness, facial swelling, eye swelling
Nervous system disorders	Common: Headache Uncommon: Dizziness, dysgeusia Rare: Paraesthesia Not known: seizures, facial hypoaesthesia, loss of consciousness
Eye disorders	Not known: Abnormal vision
Cardiac disorders	Rare: Bradycardia, Tachycardia, Palpitations Not known: Cardiac arrest, Kounis Syndrome, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia, premature ventricular contractions), asystole, atrial fibrillation, cardiac ischaemia, supraventricular tachycardia, supraventricular arrhythmia
Vascular disorders	Common: Flushing Uncommon: Hypotension Rare: Syncope, hypertension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Uncommon: Dyspnoea, Throat Irritation Rare: Respiratory Distress, Cough, Dry Throat Not known: Respiratory arrest, decreased oxygenation, hypoxia**,**
Gastrointestinal disorders	Uncommon: Abdominal Pain, diarrhoea, nausea, vomiting, Rare: Dyspepsia Not known: Tongue disorder
Skin and subcutaneous tissue disorders	Uncommon: Pruritus, increased sweating Rare: Rash, urticaria, erythema, erythematous rash
Musculoskeletal and connective tissue disorders	Uncommon: Back pain Rare: Arthralgia, flank pain, neck pain, muscle cramp Not known: Muscle spasm, musculoskeletal pain, musculoskeletal discomfort, myalgia, hypertonia
General disorders and	Uncommon: Chest Pain, fatigue, feeling hot,

administration site conditions	injection site pain Rare: Pyrexia, rigors
Investigations	Rare: Abnormal electrocardiogram

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The clinical consequences of overdose with Luminity are not known. Single doses of up to 100 microlitres dispersion/kg and multiple doses up to 150 microlitres dispersion/kg were tolerated well in Phase I clinical trials. Treatment of an overdose should be directed towards the support of all vital functions and prompt institution of symptomatic therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ultrasound contrast media, microspheres of phospholipids, ATC Code: V08DA04

The product consists of lipid encapsulated perflutren microspheres. Microspheres in the 1 to < 10 µm diameter size range contribute to the contrast effect by generating strongly enhanced echoes.

The ultrasound echoes from blood and biological soft tissues such as fat and muscles are generated at interfaces due to small differences in the ultrasonic properties of the tissues. The ultrasonic properties of the product are very different from those of soft tissue and will generate strong echoes.

As Luminity consists of microspheres that are stable and small enough for transpulmonary passage, enhanced echo signals in the left heart and systemic circulation are obtained.

A strict dose/response relationship cannot be defined, although higher doses have been shown to produce a contrast effect of longer duration.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Luminity were evaluated in normal healthy subjects and subjects with chronic obstructive pulmonary disease (COPD) following intravenous administration of a 50 µl/kg dose of the product.

The perflutren component of Luminity was rapidly cleared from the systemic circulation via the lungs. The percentage of the perflutren dose excreted in expired air was approximately 50% of the administered dose due to the small quantities of perflutren given and the inability to quantify low levels of perflutren by gas chromatography. In most subjects after 4-5 minutes, perflutren was undetectable in blood and expired air. Perflutren concentrations in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects and 1.9 minutes in COPD subjects. The systemic clearance of perflutren was similar in healthy and COPD subjects. Total lung clearance (CL_{lung}) of perflutren was shown to be no different in healthy subjects compared to COPD subjects. CL_{lung} was found to be significantly reduced (51%) in females compared to males (all subjects). These results suggest that overall perflutren systemic elimination is rapid and is not significantly reduced in COPD patients compared to healthy subjects. Doppler ultrasound measurements were performed with Luminity in conjunction with the pharmacokinetic evaluation of perflutren. Doppler signal intensity corresponded well with measured and extrapolated perflutren concentrations in blood. The time to maximum Doppler signal intensity t_{max} was shown to be similar to the perflutren blood t_{max} (1.13 versus 1.77 minutes). The observed 99% drop in Doppler signal intensity within 10 minutes ($t_{1/2}$ approximately 2 minutes) was in agreement with the decline in measurable blood levels of perflutren.

Fundamental and non-linear imaging techniques (second harmonic, multipulse phase and/or amplitude modulation) using both continuous and triggered acquisition were utilised in clinical studies with Luminity.

The naturally occurring phospholipids in Luminity (see section 6.1) are distributed in the endogenous lipid pools in the body (for example, liver) whereas the synthetic component (MPEG5000) has been shown to be excreted in the urine in preclinical studies. All lipids are metabolised to free fatty acids. The pharmacokinetics and metabolism of MPEG5000 DPPE have not been evaluated in humans.

Pharmacokinetics in special population groups

Elderly
Pharmacokinetics has not been specifically studied in the elderly.

Renal impairment
Pharmacokinetics has not been specifically studied in the renal disease patients.

Hepatic impairment
Pharmacokinetics has not been specifically studied in the hepatic disease patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity, fertility, embryo/foetal development, parturition or post-natal development, and local tolerance.

Abnormal respiration, heart rate changes and decreased activity were observed soon after intravenous injection of Luminity at doses ≥ 0.3 ml/kg in single and repeat-dose toxicity studies in rats and monkeys. Higher doses of the product, typically ≥ 1 ml/kg, resulted in more severe signs including unresponsiveness and occasionally death. These levels are substantially above the recommended maximal clinical dose. Rats treated with Luminity for 1 month exhibited dose-related, reversible perivascular and peribronchiolar eosinophil infiltration, alveolar macrophage accumulation and increased goblet cell size and number in the lungs. These effects were observed at exposure levels in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidyl**c**holine (DPPC)
1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidic **a**cid, monosodium salt (DPPA)
N-(**m**ethoxy**p**oly**e**thylene **g**lycol **5000** carbamoyl)-1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidyl**e**thanolamine, monosodium salt (MPEG5000 DPPE)
Sodium dihydrogen phosphate monohydrate
Disodium hydrogen phosphate heptahydrate
Sodium chloride
Propylene glycol
Glycerol
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

The product should be used within 12 hours of activation. The product can be re-activated up to 48 hours after initial activation and used up to 12 hours after the second activation.
After activation: Do not store above 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C)
For storage conditions after activation of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1.5 ml liquid in clear borosilicate Type I glass vial, closed with a chlorobutyl elastomeric lyophilisation stopper, and sealed with an aluminium crimp seal having a plastic flip-off button.

Pack sizes of 1 or 4 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

It is essential to follow instructions for use and handling of Luminity and to adhere to strict aseptic procedures during preparation. Like all parenteral products, the vials must be inspected visually for particulates and vial integrity. Before administering the product, it must be activated by using the Vialmix, a mechanical shaking device. The Vialmix is not included in the Luminity pack but will be provided to healthcare professionals upon ordering the pack.

Luminity is activated by using the Vialmix which has a programmed shaking time of 45 seconds. The Vialmix will alert the operator if the shaking frequency varies by 5% or more below the target frequency. It also has been programmed to shut down and will provide visual and audio warnings if the shaking frequency exceeds the target frequency by 5%, or falls below the target frequency by 10%.

Activation process and administration

- The vial should be activated using the Vialmix. Immediately after activation, Luminity appears as a milky white dispersion.

Note: if the product is allowed to stand for more than 5 minutes after activation, it should be resuspended with 10 seconds of hand agitation prior to syringe withdrawal from the vial. Luminity should be used within 12 hours following activation. The product can be re-activated up to 48 hours after initial activation and used up to 12 hours after the second activation, whether stored under refrigeration or at room temperature. Do not store the vial above 30°C following activation.

- The vial should be vented with a sterile syringe needle or a sterile non-siliconised mini-spike before withdrawing the dispersion.

- The dispersion should be withdrawn from the vial using a syringe with a 18 to 20 gauge sterile needle or attached to a sterile non-siliconised mini-spike. When using a needle, it should be positioned to withdraw the material from the middle of the liquid in the inverted vial. No air should be injected into the vial. The product should be used immediately after its withdrawal from the vial.

- Luminity may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.

The contents of the vial are intended for single use only.

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

7 MARKETING AUTHORISATION HOLDER

Lantheus MI UK Limited
Festival House,
39 Oxford Street
Newbury, Berkshire, RG14 1JG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 34258/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

18/07/2023