ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lumeblue 25 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 25 mg of methylthioninium chloride.

Excipient with known effect

Each prolonged-release tablet contains 3 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Off white to light blue, round, biconvex, enteric coated tablets, with approximate dimensions of 9.5 mm x 5.3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lumeblue is indicated as a diagnostic agent enhancing visualisation of colorectal lesions in adult patients undergoing screening or surveillance colonoscopy (see section 5.1).

4.2 Posology and method of administration

Posology

Adults including the elderly (≥ 65 years)

The recommended total dose is 200 mg methylthioninium chloride, corresponding to eight 25 mg tablets.

The total dose of the medicinal product must be taken orally during or after the intake of low-volume (e.g. 2 L) or high-volume (e.g. 4 L) polyethylene glycol (PEG) based bowel cleansing preparation and should be completed the evening prior to the colonoscopy to ensure there is enough time for the tablets to reach the colon and locally release the methylthioninium chloride prior to the colonoscopy.

Special populations

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Renal impairment

No dose adjustment is required in patients with mild renal impairment. The medicinal product should be used with caution in patients with moderate to severe renal impairment as there are no data in this patient group and methylthioninium chloride is predominantly renally eliminated (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. There is no experience in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of the medicinal product in children aged less than 18 years have not been established. No data are available.

Method of administration

For oral use.

Tablets should be swallowed whole, without crushing, breaking or chewing. The tablets are coated with a gastro-resistant film that facilitates the delivery of the dye into the colon. Breaking the gastro-resistant film by crushing or chewing the tablets may cause early release of the dye in the upper part of the gastrointestinal tract, with a possible loss of the treatment effectiveness.

The patient should take the medicinal product with the low-volume (e.g. 2 L) or high-volume (e.g. 4 L) PEG based bowel cleansing regimen chosen by the healthcare provider according to the dosing schedule below:

- The first dose of 3 tablets should be taken after drinking at least 1 L of the bowel cleansing preparation;
- The second dose of 3 tablets should be taken 1 hour after the first dose;
- The last dose of 2 tablets should be taken 1 hour after the second dose.

Tablets should be taken orally with the bowel cleansing preparation chosen by the healthcare provider or with equivalent water volumes and the proposed dosing schedule is compatible with either full dose or split dose bowel preparations.

4.3 Contraindications

- Hypersensitivity to the active substance, peanut or soya, or to any of the excipients listed in section 6.1;
- Patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency;
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Serotonin syndrome

Serotonin syndrome has been reported with the use of methylthioninium chloride when administered intravenously in combination with serotonergic medicinal products. It is not known if there is a risk of serotonin syndrome when methylthioninium chloride is administered orally in preparation for colonoscopy. Patients treated with methylthioninium chloride in combination with serotonergic medicinal products should be monitored for the emergence of serotonin syndrome. If symptoms of serotonin syndrome occur, use of the medicinal product should be discontinued, and supportive treatment initiated (see section 4.5).

Photosensitivity

Methylthioninium chloride may cause a cutaneous photosensitivity reaction when exposed to strong light sources, such as phototherapy, those found in operating theatres or locally from illuminating devices such as pulse oximeters.

Patients should be advised to take protective measures against exposure to light, because

photosensitivity may occur after administration of methylthioninium chloride.

General colouration

Methylthioninium chloride imparts a blue-green colour to urine, faeces and a blue colour to skin which may hinder a diagnosis of cyanosis.

Interference with *in vivo* monitoring devices

Inaccurate pulse oximeter readings

The presence of methylthioninium chloride in the blood may result in an underestimation of the oxygen saturation reading by pulse oximetry. If a measure of oxygen saturation is required after administration of the medicinal product, it is advisable to check oxygen saturation by CO-oximetry when available.

Bispectral index monitor

A fall in the bispectral index (BIS) has been reported following administration of methylthioninium chloride class products. If Lumeblue is administered during surgery, alternative methods for assessing the depth of anaesthesia should be employed.

Excipient warning

This medicinal product contains soya lecithin. If a patient is allergic to peanut or soya, this medicinal product must not be used (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

The following medicinal product interactions have been reported for medicinal products containing methylthioninium chloride.

Serotonergic medicinal products

Serious central nervous system (CNS) reactions have been recorded when methylthioninium chloride was administered via intravenous use to patients taking certain psychiatric medicinal products (see section 4.4). Reported cases occurred in patients taking specific serotonergic psychiatric medicinal products, namely a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), monoaminooxidase inhibitors or clomipramine. It is not known if there is a risk of serotonin syndrome when methylthioninium chloride is administered orally in preparation for colonoscopy.

In clinical studies maximal systemic exposure to methylthioninium chloride (maximum plasma concentration [C_{max}]) was lower for orally administered methylthioninium chloride than for intravenous administered methylthioninium chloride, suggesting a lower risk of systemic effects such as serotonin syndrome occurring with oral methylthioninium chloride than for intravenous administered methylthioninium chloride.

Agents metabolised by cytochrome P450 enzymes

There is limited clinical information regarding the concomitant use of methylthioninium chloride with medicinal products that are metabolised by CYP isoenzymes. *In vitro* studies indicated that methylthioninium chloride inhibits a range of CYP isozymes *in vitro*, including 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. These interactions could have a clinical relevance with narrow therapeutic index medicinal products that are metabolised by one of these enzymes (e.g., warfarin, phenytoin, alfentanil, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, and tacrolimus).

This medicinal product may be coadministered with anaesthetics / analgesics and/or sedative / anxiolytic medicinal products, often used during colonoscopy which are cleared through hepatic CYPs reactions such as: midazolam, propofol, diazepam, diphenhydramine, promethazine, meperidine, and fentanyl. The clinical consequences of changes in plasma concentrations of co-administered medicinal products which are substrates of these metabolic enzymes and transporters are not known but cannot be excluded.

Methylthioninium chloride induces CYP isozymes 1A2 and 2B6 in human hepatocytes culture, whereas it does not induce 3A4 at nominal concentrations up to 40 µM. However, these interactions are not expected to have any clinical relevance for the product single dose application.

Transporter interactions

There is limited clinical information regarding the concomitant use of methylthioninium chloride with medicinal products that are inhibitors of P-gp and OAT3. Based on in *vitro* studies, methylthioninium chloride was found to be a possible substrate of the membrane transport proteins P-gp, OCT2, MATE1 and MATE2-K and OAT3 and medicinal products which are inhibitors of these transporters have the potential to decrease excretion efficiency of methylthioninium chloride. Methylthioninium chloride is known to be a potent inhibitor of the transporters OCT2, MATE1 and MATE2-K. The clinical consequences of the inhibition are not known. The administration of methylthioninium chloride has the potential to transiently increase the exposure of medicinal products primarily cleared by renal transport involving the OCT2/MATE pathway, including cimetidine, metformin and acyclovir. However, the clinical impact of these *in vitro* interactions is expected to be minimal due to the short period of administration of the medicinal product (approximately 3 hours).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of methylthioninium chloride in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the evidence that methylthioninium chloride may pass the placenta, and the option to conduct a colonoscopy without supportive use of a visualisation agent, Lumeblue is contraindicated during pregnancy (see section 4.3). Women of childbearing potential must use effective contraception.

Breast-feeding

There is insufficient information on the excretion of methythioninium chloride / metabolites in human milk. Studies in animals have shown that there is the potential for excretion of methylthioninium chloride / metabolites during breast-feeding (see section 5.3). A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued prior to and after treatment with Lumeblue (see section 4.3).

Before administering the medicinal product to a woman who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the woman has ceased breast feeding or whether it is necessary to administer methylthioninium chloride as a visualisation agent for her colonoscopy, bearing in mind the theoretical secretion of active substance and/or metabolite in human milk. If administration is considered necessary, breast-feeding should be interrupted and the expressed feeds discarded. It is usual to advise that breast feeding can be restarted 8 days after the administration of methylthioninium chloride, based upon the methylthioninium chloride half life of 15 ± 5 hours.

Fertility

There is no information on the impact of methylthioninium chloride on human fertility. Animal and *in*

vitro studies with methylthioninium chloride have shown reproductive toxicity. *In vitro*, methylthioninium chloride has been shown to reduce motility of human sperm in a dose dependent manner. It has also been shown to inhibit the growth of cultured two-cell mouse embryos (see section 5.3).

4.7 Effects on ability to drive and use machines

Lumeblue has minor influence on the ability to drive and use machines.

Methylthioninium class medicinal products have been found to cause symptoms such as migraine, dizziness, balance disorder, somnolence, confusion and disturbances in vision. Patients who experience undesirable effects with a potential impact on the ability to drive or use machines safely, should refrain from these activities for as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of safety profile

Lumeblue commonly causes chromaturia (32.4%) and discoloured faeces (13.4%), which gradually diminish over the following days. It is associated with transient nausea and vomiting.

Tabulated list of adverse reactions

Adverse reactions are classified according to the following convention: 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), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Data presented below are based upon clinical studies conducted with Lumeblue. All adverse reactions recorded at a frequency greater than placebo are reported. Additionally, adverse drug reactions of known frequency, reported with methylthioninium chloride administered intravenously in the treatment of methaemoglobinaemia are included in the following table.

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Nasopharyngitis	Uncommon
Immune system disorders	Anaphylactic reaction[a]	Not known
Nervous system disorders	Dizziness[b]	Very common
	Dysgeusia[b]	Very common
	Paraesthesia[b]	Very common
	Anxiety[b]	Common
	Headache[b]	Common
	Migraine	Uncommon
	Serotonin syndrome (with concomitant use of serotonergic medicinal products, see sections 4.4 and 4.5)	Not known
Vascular disorders	Hypotension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
	Nasal congestion	Uncommon
	Rhinorrhoea	Uncommon
Gastrointestinal disorders	Faeces discoloured	Very common
	Abdominal pain	Common
	Vomiting[c]	Common
	Nausea[c]	Common
	Haematemesis	Uncommon

System organ class	Adverse reaction	Frequency
	Diarrhoea	Uncommon
	Abdominal discomfort	Uncommon
Skin and subcutaneous tissue disorders	Skin discolouration (blue)[b,c]	Very common
	Sweating[b]	Very common
	Ecchymosis	Uncommon
	Night sweats	Uncommon
	Pruritus	Uncommon
	Rash	Uncommon
	Telangiectasia	Uncommon
	Photosensitivity	Not known
Musculoskeletal and connective tissue disorders	Pain in extremity[b]	Very common
	Flank pain	Uncommon
Renal and urinary disorders	Chromaturia	Very common
	Polyuria	Uncommon
	Dysuria	Uncommon
General disorders and administration site conditions	Chest pain[b]	Common
	Pain	Uncommon
	Chills	Uncommon
Injury, poisoning and procedural complications	Procedural nausea	Uncommon

[a] The inclusion of anaphylactic reactions reported in the table is reflective of sporadic and spontaneous reporting in literature. No event of anaphylactic reaction has been identified during clinical studies of Lumeblue.
[b] These terms are included as they were reported as very common or common in clinical studies with methylthioninium chloride via intravenous administration.
[c] See section below: Description of specific adverse reactions for more detail.

Description of specific adverse reactions

Frequent adverse reactions

In the pooled safety data from the clinical program, the most common related TEAE were chromaturia and discoloured faeces, as described above. In addition, skin discolouration has been reported in clinical studies with methylthioninium chloride administered via intravenous use, and this may interfere with *in vivo* monitoring devices (see section 4.4).

Serotonin syndrome

Serotonin syndrome has been reported with the use of methylthioninium chloride when administered via the intravenous use in combination with serotonergic medicinal products. Patients treated with methylthioninium chloride in combination with serotonergic medicinal products should be monitored for the emergence of serotonin syndrome. If symptoms of serotonin syndrome occur, discontinue treatment, and initiate supportive treatment (see section 4.5).

Nausea and vomiting

Nausea and vomiting are well recognised adverse reactions associated with the use of PEG-based bowel cleansing preparations, however in clinical studies, patients were more likely to experience nausea and vomiting when receiving Lumeblue in combination with a bowel preparation agent, than when receiving the bowel preparation alone.

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 national reporting system listed in Appendix V.

4.9 Overdose

Available information from other methylthioninium chloride class medicinal products administered via intravenous, or other non-oral uses in other indications, show that overdose can result in an exacerbation of adverse reactions. Administration of large intravenous doses (cumulative dose ≥ 7 mg/kg) of a methylthioninium chloride caused nausea, vomiting, chest tightness, chest pain, dyspnoea, tachypnoea, tachycardia, apprehension, sweating, tremor, mydriasis, blue green staining of the urine, blue staining of the skin and mucous membranes, abdominal pain, dizziness, paraesthesia, headache, confusion, hypertension, mild methaemoglobinaemia (up to 7%) and electrocardiogram changes (T-wave flattening or inversion). These effects lasted 2 to 12 hours following administration.

In case of overdose, the patient should be observed until signs and symptoms have resolved, including monitoring for cardiopulmonary, haematologic and neurologic toxicities, and instituting supportive measures as necessary.

Paediatric population

Hyperbilirubinaemia has been observed in infants after administration of 20 mg/kg methylthioninium chloride. Death occurred in 2 infants after administration of 20 mg/kg methylthioninium chloride. Both infants had complex medical circumstances and methylthioninium chloride was only partially responsible.

The paediatric patient should be maintained under observation, the methaemoglobin level should be monitored and appropriate supportive measures taken as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic agents, other diagnostic agents, ATC code: V04CX

Mechanism of action

Lumeblue is a delayed and extended-release multi-matrix (MMX) formulation in the form of tablets, each containing 25 mg of methylthioninium chloride as dried substance. The tablets are coated with an enteric coating that is stable at acidic pH (in the stomach) but breaks down at or above pH 7, normally achieved in the terminal ileum. Once the film coating has dissolved, the extended-release MMX formulation provides a slow release of the methylthioninium chloride dye, resulting in its homogeneous and prolonged dispersion on the surface of the colonic mucosa.

Methylthioninium chloride is known to be a “vital dye”, meaning “a dye or stain agent capable of penetrating living cells or tissues and not inducing immediate evident degenerative changes”.

Methylthioninium chloride is taken up across the cell membrane into the cytoplasm of actively absorbing cells such as those found in the small intestine and colon, thereby staining the epithelia of those organs. Vital, absorptive dyes such as methylthioninium chloride, enhance the superficial structure of lesions by exploiting the different degrees of active mucosal stain uptake, highlighting contrast and therefore differences between cell types.

Clinical efficacy and safety

A total of seven clinical studies have been conducted. The efficacy of this medicinal product was evaluated in one pivotal Phase 3 study (CB-17-01/06).

Study CB-17-01/06 was a Phase 3, multicentre, multinational, randomised, double-blind, placebo-

controlled, parallel-group study to evaluate the adenoma or carcinoma detection rate in patients undergoing safety or surveillance colonoscopy high definition white light (HDWL) colonoscopy after colonic mucosal staining and contrast enhancing with methylthioninium chloride tablets (compared to placebo tablets and gold standard HDWL colonoscopy alone). All subjects received 4 litres PEG-based bowel cleansing preparation starting in the late afternoon the day before the colonoscopy. The subjects were prescribed 3, 3, and 2 x 25 mg tablets after the second, third, and fourth litre of bowel preparation, respectively. The subjects drank at least 250 mL of preparation every 15 minutes, so that the intake of study medicinal product and bowel cleansing preparation was completed 4 hours after commencement of the bowel cleansing preparation. The study comprised both a full dose (200 mg) arm and a low dose (100 mg) arm, which was included to assist blinding of the full dose active arm.

Primary endpoint: adenoma detection rate (ADR)

The primary endpoint of Study CB-17-01/06 was the ADR defined as the proportion of subjects with at least one histologically proven adenoma or carcinoma. Histologically proven adenoma was defined as Vienna grade 3 to 4.2, or a traditional serrated adenoma (TSA) or sessile serrated adenoma (SSA). Histologically proven carcinoma was defined as Vienna grade 4.3 to 5.b. The primary analysis population was defined as all randomised subjects who received at least one dose of study treatment and underwent colonoscopy, regardless of the completion status. The primary endpoint was analysed through a logistic regression with treatment, centre, age, gender, reason for colonoscopy, and number of excisions included in the regression model as fixed effects.
Primary endpoint results are provided in table 1 below.

Table 1: Efficacy results from study CB-17-01/06 - primary endpoint: ADR

Adenoma detection rate (ADR)	**Methylthioninium chloride tablets vs. placebo**		
Absolute value	56.29% vs. 47.81%		
Magnitude of effect	8.48%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
OR without logistic regression	1.41	[1.09, 1.81]	0.0099
OR with logistic regression	1.46	[1.09, 1.96]	0.0106
OR with logistic regression excluding excisions as regression covariate	1.51	[1.15, 1.97]	0.0027

Secondary endpoint: false positive rate (FPR)

The FPR was introduced to control for possible false positive study results, in that a high FPR would indicate a higher sampling rate in the methylthioninium chloride tablets group without a concomitant increase in 'hit rate' for detecting patients with positive lesions (adenomas or carcinomas). In this occurrence, a positive difference between methylthioninium chloride tablets and placebo (i.e., increase in the FPR) was hypothesised and a maximum threshold (non-inferiority margin) was set at 15%.

Table 2 and table 3 below present the FPR at both a subject and excision level. Methylthioninium chloride tablets was statistically not inferior to placebo in FPR at both the subject and excision level. FPR at the subject level was numerically lower (-6.44%) in the treatment group than in the placebo group. At the excision level, the FPR of methylthioninium chloride tablets was numerically slightly greater (+2.63%) than placebo, however this was not considered clinically significant. These data demonstrate the effectiveness of methylthioninium chloride tablets at visualising lesions that were subsequently determined to be adenoma and carcinoma.

Table 2: Efficacy results from the study CB-17-01/06 - secondary endpoint: FPR (subject level)

False positive rate (FPR) (subject level)	**Methylthioninium chloride tablets / placebo**		
Absolute value	23.31% vs. 29.75%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
Magnitude of effect = difference in FPR (≥ 15% threshold for rejecting null hypothesis)	-6.44	[-13.07, 0.19]	< 0.0001

Table 3: Efficacy results from the study CB-17-01/06 - secondary endpoint: FPR (excision level)

False positive rate (FPR) (excision level)	**Methylthioninium chloride tablets / placebo**		
Absolute value	49.79% vs. 47.16%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
Magnitude of effect = difference in FPR (≥ 15% threshold for rejecting null hypothesis)	2.63	[-1.55, 6.81]	< 0.0001

The tables below present further prespecified and post-hoc clinically meaningful endpoints from the pivotal Phase III study (CB17-01/06):

Table 4: Efficacy results from the study CB-17-01/06 - secondary endpoint: proportion of subjects with at least one adenoma

Proportion of subjects with at least one adenoma	**Methylthioninium chloride tablets / placebo**		
Absolute value	55.88% vs. 47.18%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
Magnitude of effect = difference in proportion	8.69	[2.41, 14.98]	0.0082
OR without logistic regression	1.42	[1.10, 1.83]	0.0082

Table 5: Efficacy results from the study CB-17-01/06 - exploratory endpoint: proportion of subjects with at least one non-polypoid lesion

Proportion of subjects with at least one non-polypoid lesion	**Methylthioninium chloride tablets / placebo**		
Absolute value	43.92% vs. 35.07%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
Magnitude of effect = difference in proportion	8.84%	[2.70, 14.99]	0.0056
OR without logistic regression	1.45	[1.12, 1.88]	0.0056
OR with logistic regression	1.66	[1.21, 2.26]	0.0015

Table 6: Post hoc analysis: proportion of subjects with at least one non-polypoid adenoma or carcinoma

Proportion of subjects with at least one non-polypoid adenoma or carcinoma	**Methylthioninium chloride tablets / placebo**		
Absolute value	25.77% vs. 19.21%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval limits	p-value
Magnitude of effect = difference in proportion	6.57%	[1.31, 11.82]	0.0167
OR without logistic regression	1.46	[1.08, 1.98]	0.0167

5.2 Pharmacokinetic properties

Clinical studies show that methylthioninium chloride is well absorbed by the oral use, and rapidly taken up by the tissues. The majority of the dose is excreted in the urine, usually in the form of leucomethylthioninium chloride.

Absorption

Following the oral administration of methylthioninium chloride tablets at a total dose of 200 mg (8 prolonged-release tablets, 25 mg each) in healthy subjects, peak plasma concentration (C_{max}) was 1.15 ± 0.26 mcg/mL, with a median time to peak concentration (T_{max}) of 16 hours (10 – 24 hours). Absolute bioavailability was calculated to be approximately 100%.

Biotransformation

Methylthioninium chloride inhibits a range of CYP isozymes *in vitro*, including 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, and induces CYP isozymes 1A2 and 2B6, but not 3A4, in human hepatocytes culture. *In vitro*, methylthioninium chloride acts as a substrate and weak inhibitor of P-gp, and as a substrate of OAT-3, OCT2, MATE1 and MATE2-K (see sections 4.4 and 4.5).

Elimination

In a Phase 1 clinical study with 200 mg methylthioninium chloride cumulative excretion of unchanged methylthioninium chloride at 60 hours postdose was approximately 39 ± 16% of the administered dose. The mean terminal half-life ($T_{1/2}$) was determined to be approximately 15 hours.

Special populations

In clinical studies, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy. There are limited data in patients ≥ 75 years of age.

Elderly

Methylthioninium chloride tablets was investigated in subjects undergoing screening or surveillance colonoscopy, with a mean age of 58.4 years (range 21 to 80 years) and 250 subjects at least 65 years of age, thus the subject population was representative of the intended clinical population, however there is limited data in patients ≥ 75 years of age. Overall, the safety profile of this medicinal product was broadly similar regardless of age. It is therefore proposed that neither warnings nor dose adjustments are required in respect of age.

Renal impairment

Retrospective analysis of the safety dataset identifying subjects with some degree of renal impairment concluded that the incidence and pattern of TEAE in subjects receiving methylthioninium chloride tablets was consistent with the observed pooled safety database, and thus no warnings nor dose adjustments are required in respect to mild renal impairment. There are no data in patients with moderate to severe renal impairment, and therefore the medicinal product should be used with caution in patients with moderate to severe renal impairment (see section 4.2).

Hepatic impairment

Retrospective analysis of the safety dataset identifying subjects with some degree of hepatic impairment concluded that the incidence and pattern of TEAE in subjects receiving methylthioninium chloride tablets was consistent with the observed pooled safety database, and thus no warnings nor dose adjustments are required in respect to mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment.

5.3 Preclinical safety data

Repeated dose toxicity

In repeat dose toxicity studies, no observed adverse effect level (NOAEL) was considered to be 600 mg/four days. Therefore, effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Genotoxicity

Methylthioninium chloride has been shown to be mutagenic in gene mutation assays in bacteria and mouse lymphoma cells, but not *in vivo* mouse micronucleus assay when administered intravenously at 62 mg/kg.

Carcinogenicity

Some evidence of carcinogenic activity of methylthioninium chloride in male mice and rats, equivocal evidence of carcinogenic activity in female mice and no evidence of carcinogenic activity in female rats.

Reproductive toxicology

In animal studies, methylthioninium chloride produced adverse developmental outcomes in rats and rabbits when administered orally during organogenesis. As a precautionary measure, the use of methylthioninium chloride during pregnancy is contraindicated (see section 4.3).

Studies reported in literature suggest that exposure to methylthioninium chloride results in the reduction of sperm motility *in vitro* and teratogenic effects on embryo-foetal developmental effects in rats and rabbits. However, there were no consistent effects of methylthioninium chloride administration on reproductive system measures in male or female rats after 3-months oral treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Stearic acid 50 (E570)
Soya lecithin (E322)
Microcrystalline cellulose (E460)
Hypromellose 2208 (E464)
Mannitol (E421)
Talc (E553b)
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Tablet coating

Methacrylic acid - methyl methacrylate copolymer (1:1)
Methacrylic acid - methyl methacrylate copolymer (1:2)
Talc (E553b)
Titanium dioxide (E171)
Triethyl citrate (E1505)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyamide/aluminium/PVC foil blister with aluminium push-through foil.

Packs contain 8 prolonged-release tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Cosmo Technologies Ltd
Riverside II
Sir John Rogerson's Quay
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1470/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 August 2020
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. **MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

B. **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

C. **OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

D. **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Cosmo S.p.A
Via C. Colombo, 1
20045, Lainate
Milan,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Lumeblue 25 mg prolonged-release tablets
methylthioninium chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 25 mg methylthioninium chloride.

3. LIST OF EXCIPIENTS

Contains soya lecithin. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablets
8 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole. Do not crush or chew the tablets.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cosmo Technologies Ltd
Riverside II
Sir John Rogerson's Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1470/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lumeblue

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Lumeblue 25 mg prolonged-release tablets
methylthioninium chloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cosmo Technologies Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lumeblue 25 mg prolonged-release tablets
methylthioninium chloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lumeblue is and what it is used for

Lumeblue contains methylthioninium chloride (also known as methylene blue). This medicine is a blue dye.

This medicine is used in adults to temporarily stain the colon (large bowel) before colonoscopy, in which a flexible instrument is inserted into the rectum to view inside the bowel. The staining allows the doctor to see the lining of the colon more clearly and improves the detection of abnormalities.

2. What you need to know before you take Lumeblue

Do not take Lumeblue
- if you are allergic to **methylthioninium chloride**, **peanut** or **soya**, or any of the other ingredients of this medicine (listed in section 6);
- if you have been told you have **glucose-6-phosphate dehydrogenase (G6PD) deficiency**;
- if you are **pregnant** or think you **may be pregnant**, or are **breastfeeding** as your doctor may decide that you do not need to take this medicine before your procedure.

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:
- If you are taking certain antidepressant medicine or a medicine for psychiatric illness. Such as:
  - selective serotonin reuptake inhibitor (SSRI) antidepressants such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram and zimeldine;
  - bupropion, venlafaxine, mirtazapine, clomipramine, buspirone;
  - medicines classified as monamine oxidase inhibitors (often used for treating depression).

  Giving methylthioninium chloride injection (into a vein) in patients also taking these medicines has sometimes resulted in a life-threatening complication called serotonin syndrome. It is not known if serotonin syndrome can occur when methylthioninium chloride is given as a tablet. Your doctor will decide what to do if you are taking an antidepressant or another medicine for a psychiatric illness.

This medicine may cause a photosensitivity reaction in the skin (sunburn-like reaction) when exposed

to strong light sources, such as light therapy, lights in operating rooms and pulse oximeters. You should take protective measures against exposure to light.

Your urine and stools may turn a blue-green colour; and skin may possibly turn a blue colour when you are treated with this medicine. This discolouration is expected and will disappear after the treatment has ended.

This medicine could affect the results of monitoring instruments used to measure the oxygen levels in the blood or the depth of anaesthesia.

Children and adolescents

This medicine should not be given to children and adolescents under 18 years of age as it is not known if the medicine is safe and effective in this age group.

Other medicines and Lumeblue

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Other medicines and Lumeblue taken together may affect how they each work or are processed and removed from the body.

In addition to antidepressants and the other medicines for psychiatric illness mentioned under 'Warnings and precautions', you should tell your doctor before you take this medicine if you are also taking or have recently been given:
- Medicines to treat irregular heart beats such as amiodarone, digoxin and quinidine
- Warfarin, to prevent blood clots
- Medicines to treat cancer such as alectinib, everolimus, lapatinib, nilotinib and topotecan
- Medicines to prevent organ transplant rejection such as ciclosporin, sirolimus and tacrolimus
- Medicines to treat HIV infection such as ritonavir and saquinavir
- Medicines to treat migraine such as dihydroergotamine, ergotamine
- Medicines used to treat anxiety or insomnia, such as diazepam
- Sedative medicines such as midazolam and propofol
- Antihistamine medicines to treat allergies such as diphenhydramine or promethazine
- Probenecid to treat gout
- Phenytoin to treat epilepsy
- Pimozide to treat psychosis or schizophrenia
- Medicines to treat severe pain such as alfentanil, fentanyl and pethidine (also known as meperidine)
- Cimetidine to treat stomach ulcers and acid reflux
- Metformin to treat type 2 diabetes
- Aciclovir to treat herpes simplex virus infections (e.g. cold sores, genital warts) and varicella–zoster virus infections (e.g. chicken pox, shingles)

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, do not use this medicine as it is not known whether this medicine can harm your unborn baby.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking this medicine. Your doctor may decide that you do not need to take this medicine if you require a colonoscopy whilst breast-feeding.

Driving and using machines

It is unlikely that taking Lumeblue will affect your ability to drive or use machines. However if you

experience any side effects that could impair your ability to drive or use machines safely, such as migraine, feeling dizzy, or disturbance to your vision, then you should not drive or use machines until you feel better.

Lumeblue contains soya lecithin

If you are allergic to **peanut** or **soya**, do not take this medicine.

3. How to take Lumeblue

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The medicine is supplied as tablets. These must be swallowed whole because they have a special coating to make sure that they pass through your stomach and only break up in your intestines to release the methylthioninium chloride that stains the colon blue. You must not crush or chew them.

You will be given a pack containing 8 tablets (a total of 200 mg methylthioninium chloride). These must all be taken over a period of 2 hours, the night before your colonoscopy. Your doctor will explain how you should take the tablets, which are normally taken together with a bowel cleansing preparation (a medicine to clear out your colon).

Take the tablets as instructed by your doctor.

Typical instructions are:

1. After drinking at least 1 litre of the bowel cleansing preparation (or water) take the first dose of 3 tablets.

2. Wait 1 hour then take the second dose of 3 tablets.

3. Wait another hour, then take the final dose of 2 tablets.

If you take more Lumeblue than you should

The box contains one complete dose of Lumeblue. Therefore you cannot take more Lumeblue than you should. However, if you take more tablets than you should, you might get some of the side effects listed in section 4. If you think you have taken more of this medicine than you should, tell your doctor or nurse as soon as possible.

If you notice any of the following symptoms you should tell your doctor straight away:
- Feeling or being sick, or stomach pain
- Abnormally fast beating of the heart, or chest pain
- Tight chest or difficulty breathing (e.g. breathlessness)
- Confusion, dizziness, or headache
- Sweating, tremor, feeling weak, paler skin than usual, or skin turning blue
- An increase in methaemoglobin (an abnormal form of haemoglobin in the blood);
- High blood pressure.

If you forget to take one or more of the doses of Lumeblue

Do not take a double dose to make up for forgotten tablets, take the next dose of tablets according to the bowel cleansing schedule given to you by your doctor, it may be helpful to set an alarm to remind you when to take the medicine.

If you stop taking Lumeblue

At your colonoscopy, tell your doctor that you did not take all the tablets.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects are common, but tell your doctor or nurse if you are worried about any side effect you get:

Very common (may affect more than 1 in 10 people)
- Discoloured urine
- Discoloured faeces
- Dizziness
- Changes in your sense of taste
- Pins and needles sensation, tingling or prickling
- Pain or discomfort in your hands or feet
- Blue discolouration of the skin
- Sweating

Common (may affect up to 1 in 10 people)
- Nausea
- Vomiting
- Stomach or chest pain
- Headache
- Anxiety

Uncommon (may affect up to 1 in 100 people)
- Cold-like symptoms, including blocked or runny nose
- Migraine
- Low blood pressure
- Cough
- Vomiting blood
- Bruising-like discolouration of the skin,
- Night sweats
- Itchy skin
- Rash
- Spidery veins
- Pain in the back or sides
- Abnormally large amounts of urine, or pain or difficulty when passing urine
- General pain
- Chills

Not known (frequency cannot be estimated from the available data)
- Signs of serotonin syndrome, such as muscle spasms, clumsiness, tremors, confusion or other mental changes
- Signs of an anaphylactic reaction, such as itchy rash, throat or tongue swelling, shortness of breath.
- Sensitivity to light

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lumeblue

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lumeblue contains

- The active substance is methylthioninium chloride. Each prolonged-release tablet contains 25 mg methylthioninium chloride.
- The other ingredients are:
  Tablet core: stearic acid 50 (E570), soya lecithin (E322) – see section 2 under 'Lumeblue contains soya lecithin', microcrystalline cellulose (E460), hypromellose 2208 (E464), mannitol (E421), talc (E553b), silica colloidal anhydrous (E551), magnesium stearate (E470b).
  Film coating: methacrylic acid–methyl methacrylate copolymer, talc (E553b), titanium dioxide (E171), triethyl citrate (E1505).

What Lumeblue looks like and contents of the pack

Lumeblue prolonged-release tablets are off-white to light blue, round, biconvex, enteric-coated tablets. The prolonged-release tablets are provided in blister packs containing 8 tablets.

Marketing Authorisation Holder

Cosmo Technologies Ltd
Riverside II
Sir John Rogerson's Quay
Dublin 2
Ireland

Manufacturer

Cosmo S.p.A
Via C. Colombo, 1
20045, Lainate
Milan,
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu