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.

Excipients with known effect

Lumeblue contains 3 mg soya lecithin per prolonged-release tablet.

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 population
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

Lumeblue is 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 via the intravenous route 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, discontinue use of Lumeblue, and initiate supportive treatment (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.

Advise patients 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 Lumeblue, 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

Lumeblue 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 route 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).

Lumeblue 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 Lumeblue single dose application.

Transporter interactions

There is limited clinical information regarding the concomitant use of Lumeblue 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 Lumeblue 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 Lumeblue (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 Lumeblue 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. Lumeblue 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 <1/1000), 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
	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 route, 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 route 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 routes 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 of Lumeblue, 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 of Lumeblue 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 Lumeblue 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 2x 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)	**Lumeblue 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 Lumeblue group

without a concomitant increase in 'hit rate' for detecting patients with positive lesions (adenomas or carcinomas). In this occurrence, a positive difference between Lumeblue 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. Lumeblue 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 Lumeblue was numerically slightly greater (+2.63%) than placebo, however this was not considered clinically significant. These data demonstrate the effectiveness of Lumeblue 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)	**Lumeblue / 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)	**Lumeblue / 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	**Lumeblue / placebo**		
Absolute value	55.88% vs. 47.18%		
Adjusted odds ratio (OR)	Point estimate	95% Confidence interval	p-value

		limits	
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	**Lumeblue / 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

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	**Lumeblue / 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 route, 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 Lumeblue 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 µg/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 Lumeblue 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

Lumeblue 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 Lumeblue 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 Lumeblue 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, with Lumeblue, 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

Bridging Pharma Limited
3rd Floor
9 St. Clare Street,
London,
England,
EC3N 1LQ

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 44452/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 August 2020

10 DATE OF REVISION OF THE TEXT

22/03/2024