Professional Information for SILEA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SILEA 0,31 mg/ 3 mL (inhalation solution)

SILEA 0,63 mg/ 3 mL (inhalation solution)

SILEA 1,25 mg/ 3 mL (inhalation solution)

Levalbuterol 0,31 mg, 0,63 mg or 1,25 mg per 3 mL inhalation solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 mL inhalation solution contains levalbuterol hydrochloride equivalent to levalbuterol 0,31 mg, 0,63 mg or 1,25 mg [levalbuterol 0,0103 %, 0,021 % and 0,042 % (*w/v*)].

Sugar free.·

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Inhalation solution.

SILEA is a sterile clear, colourless, preservative-free solution of the hydrochloride salt of levalbuterol, the (R-)-enantiomer of the drug substance racemic albuterol. It is filled in a unit dose ampoule.

SILEA inhalation Solution Concentrate supplied in 0,5 mL unit-dose vials should be diluted with sterile normal saline before administration by nebulisation.

Each 0,5 mL unit-dose vial contains levalbuterol 0,36 mg (as 0,31 mg of levalbuterol HCl), levalbuterol 0,73 mg (as 0,63 mg of levalbuterol HCl) and levalbuterol 1,25 (as 1,44 mg of levalbuterol HCl), sodium chloride to adjust tonicity and hydrochloric acid to adjust the pH to 4,0 (3,3 to 4,5).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SILEA is indicated in adults, adolescents and children 6 years of age and older for:

- Treatment of reversible airway obstruction in asthma, chronic bronchitis and emphysema, or
- Prevention of bronchospasm in exercise induced asthma.

4.2. Posology and method of administration

Posology:

Children 6 to 11 years old:

The recommended dose of **SILEA** is 0,31 mg/ 3 mL, administered thrice daily by nebulisation. Routine dosing should not exceed 0,63 mg/ 3 mL three times per day.

Adults and children ≥12 years old:

The recommended starting dose of **SILEA** is 0,63 mg/ 3 mL, administered thrice daily (every 6 to 8 hours) by nebulisation.

Patients 12 years and older with more severe asthma or patients who do not respond adequately to a dose of 0,63 mg/ 3 mL of **SILEA** may benefit from a dosage of 1,25 mg/ 3 mL three times per day.

Patients receiving the highest dose of **SILEA** should be monitored closely for adverse systemic effects, and the risks of such effects should be balanced against the potential for improved efficacy.

The use of **SILEA** can be continued as medically indicated to control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the expected relief, medical advice should be sought immediately, since this is often a sign of seriously worsening asthma that would require reassessment of therapy.

The physico-chemical compatibility of **SILEA** as well as its safety and efficacy when mixed with other medicines in a nebuliser have not been established.

The safety and efficacy of **SILEA** have been established in clinical studies when administered using the PARI LC Jet™ and PARI LC PLUS™ nebulisers, and the PARI Master® Dura-Neb® 2000 and Dura-Neb® 3000 compressors. The safety and efficacy of **SILEA** has not been established when administered using other nebulisers.

Do not exceed the recommended dose.

Special populations

Paediatric population:

There are no data to support use in children under the age of 6 years, see **section 4.3**.

Method of administration

SILEA is administered by inhalation with a nebuliser (with a face mask or mouthpiece) connected to an air compressor.

4.3. Contraindications

Hypersensitivity to levalbuterol hydrochloride, racemic albuterol or any of the inactive ingredients.

Safety and efficacy in children under the age of 6 years have not been established, see **section 4.2**.

4.4. Special warnings and precautions for use

Paradoxical bronchospasms:

Like other inhaled beta-adrenergic agonists, **SILEA** can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, **SILEA** should be discontinued immediately and alternative therapy instituted. It should be noted that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Deterioration of asthma:

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of **SILEA** than usual, this may be a marker of destabilisation of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Use of anti-inflammatory medicines:

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory medicines, e.g., corticosteroids, to the therapeutic regimen.

Cardiovascular effects:

SILEA, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are less frequent after administration of **SILEA** at recommended doses, if they occur, the medicine may need to be discontinued. In

addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T-wave, prolongation of the QTc interval and ST segment depression. The clinical significance of these findings is unknown. Therefore, **SILEA**, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary artery insufficiency, cardiac dysrhythmias and arterial hypertension.

Exceeding recommended dose:

Fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines such as **SILEA** in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate hypersensitivity reactions:

Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by less frequent cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal oedema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving **SILEA**.

Hypokalaemia:

Hypokalaemia may occur through intracellular shifting, which has the potential to produce adverse cardiovascular effects. **SILEA** overdosage may cause cardiac effects.

High doses may increase the risk of serious side effects, including cardiac dysrhythmias. This risk is further aggravated if **SILEA** is administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias, or in the presence of hypoxia and acidosis. The maximum dose of **SILEA** should not be exceeded.

Coexisting conditions:

SILEA should be used with caution in patients with cardiovascular disorders, especially coronary artery insufficiency, arterial hypertension and cardiac dysrhythmias, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant increases in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Blood glucose levels may be increased in diabetic patients. Large doses of intravenous racemic albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

4.5. Interaction with other medicines and other forms of interaction

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic medicines are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta-blockers:

Beta-adrenoceptor blockers not only block the pulmonary effect of beta$_2$-receptor-agonists such as **SILEA**, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers.

Diuretics:

The ECG changes (e.g. QT interval prolongation, flattening and inversion of T waves, dysrhythmias, *torsades de Pointes* and ventricular tachycardia) and/or hypokalaemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-adrenoreceptor agonists, especially when the recommended dose of the beta-agonist is exceeded. The clinical significance of these effects depends on the severity of the hypokalaemia. Caution is advised in the coadministration of beta-adrenoreceptor agonists with non-potassium sparing diuretics.

Digoxin:

Mean decreases of 16 % and 22 % in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving **SILEA** and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are concurrently receiving digoxin and **SILEA**.

Monoamine oxidase inhibitors or tricyclic antidepressant:

SILEA should be administered with extreme caution to patients treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such medicines, because the action of levalbuterol hydrochloride on the cardiovascular system may be potentiated.

4.6. Fertility, pregnancy and lactation

Pregnancy:

SILEA has not been studied adequately in pregnant women.

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight and small for gestational age in the neonate. Pregnant women should be closely monitored and medicine adjusted as necessary to maintain optimal control.

Use in labour and delivery

Because of the potential for beta-adrenergic agonists to inhibit uterine contractility, the use of **SILEA** for the treatment of bronchospasm during labour should be restricted to those patients in whom the benefits clearly outweigh the risk.

SILEA has not been approved for the management of preterm labour. The benefit-risk ratio when **SILEA** is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary oedema, have been reported during or following

treatment of premature labour with beta$_2$-adrenoreceptor agonists, including racemic albuterol.

Breastfeeding:

SILEA has not been studied in breastfeeding women or breastfed children.

4.7. Effects on ability to drive and use machines

SILEA can cause dizziness and syncope (see **section 4.8**), therefore it might have a negative influence on the ability to drive and use machines.

4.8. Undesirable effects

Table 1: List of adverse events

System organ class	**Side effects in adults and children aged ≥ 12 years**	**Side effects in children aged 6 to 11 years**
Infections and infestations	*Frequent*: flu syndrome, rhinitis, sinusitis, viral infection.	*Frequent*: viral infection, pharyngitis, rhinitis.
Immune system disorders	*Frequent*: hypersensitivity reactions including urticaria, angioedema, rash, anaphylaxis and oropharyngeal oedema (see **section 4.3**).	*Frequent*: hypersensitivity reactions including urticaria, angioedema, rash, anaphylaxis and oropharyngeal oedema (see **section 4.3**).

Blood and lymphatic system disorders	*Frequent*: lymphadenopathy.	*Frequent*: lymphadenopathy.
Psychiatric disorders	*Frequent:* insomnia.	
Nervous system disorders	*Frequent*: dizziness, hypertonia, nervousness, tremor, anxiety, hypaesthesia of the hand, paraesthesia.	*Frequent*: headache.
Eye disorders	*Frequent*: eye itch.	
Ear and labyrinth disorders		*Frequent*: otitis media.
Cardiac disorders	*Frequent*: chest pain, tachycardia, ECG abnormal, ECG change.	
Vascular disorders	*Frequent*: migraine hypertension, hypotension, syncope.	
Respiratory, thoracic and mediastinal	*Frequent*: cough increased, rhinitis, sinusitis, turbinate oedema.	*Frequent*: asthma, pharyngitis, rhinitis.

Gastrointestinal disorders	*Frequent*: diarrhoea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea.	*Frequent*: abdominal pain, diarrhoea.
Skin and subcutaneous tissue disorders		*Frequent*: eczema, rash, urticaria.
Musculoskeletal and connective tissue disorders	*Frequent*: leg cramps, myalgia.	*Frequent*: myalgia.
General disorders and administrative site disorders	*Frequent*: accidental injury, pain, back pain, chills.	*Frequent*: accidental injury, asthenia, fever, pain.

Post-marketing data:

Immune system disorders:

Angioedema, anaphylaxis, rash, urticaria.

Metabolism and nutrition disorders:

Metabolic acidosis.

Cardiac disorders:

Dysrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), tachycardia, chest pain, angina.

Nervous system disorders:

Nervousness, CNS stimulation.

Ear and labyrinth disorders:

Vertigo.

Respiratory, thoracic and mediastinal disorders:

Asthma, cough increased, dyspnoea.

Gastrointestinal disorders:

Gastroesophageal reflux disease (GORD), nausea.

General disorders and administrative site disorders:

Dysphonia, tremor.

Metabolism and nutrition disorders:

Metabolic acidosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **SILEA** is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 (or to Cipla Medpro (Pty) Ltd via e-mail: drugsafetysa@cipla.com). By reporting side effects, you can help provide more information on the safety of **SILEA**.

4.9. Overdose

The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation and/or occurrence or exaggeration of any of the symptoms listed under **section 4.8**, e.g. angina pectoris, arterial hypertension or hypotension, tachycardia with rates up to 200 beats/min, dysrhythmias, nervousness, headache, tremor, dry mouth, nausea, dizziness, fatigue and sleeplessness. Hypokalaemia may also occur. As with all sympathomimetic medicines, cardiac arrest and even death may be associated with the abuse of **SILEA**. Treatment consists of discontinuation of **SILEA** together with appropriate symptomatic therapy. The judicious use of a cardio selective $beta_2$-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of **SILEA**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Andrenergics, inhalants. Selective beta-2-andrenoreceptor agonists

A. 10.2.1 Inhalants

Mechanism of action:

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges.

While it is recognised that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10 % to 50 % of which are beta$_2$-adrenergic receptors. The precise function of these receptors has not been established (see **section 4.4**). However, all beta-adrenergic agonist medicines can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms and/or electrocardiographic changes.

5.2. Pharmacokinetic properties

Absorption:

Adults and children ≥ 12 years old:

The inhalation pharmacokinetics of **SILEA** investigated in a randomised cross-over study in 30 healthy adults following administration of a single dose of 1,25 mg and a cumulative dose of 5 mg of **SILEA** and a single dose of 2,5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution by nebulisation using a PARI LC Jet™ nebuliser with a Dura-Neb® 2000 compressor.

Following administration of a single 1,25 mg dose of **SILEA**, exposure to (R)-albuterol (AUC of 3,3 ng*hr/mL) was approximately 2-fold higher than following administration of a single 2,5 mg dose of racemic albuterol inhalation solution (AUC of 1,7 ng*hr/mL). Following administration of a cumulative 5 mg dose of **SILEA** (1,25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic albuterol inhalation solution (2,5 mg given every 30 minutes for a total of four doses), C_{max} and AUC of (R)-albuterol were comparable (see **Table 2**).

Table 2: Mean (SD) values for pharmacokinetic parameters in healthy adults

	Single dose		**Cumulative dose**	
	LEVALBUTEROL 1,25 mg CIPLA	**Racemic albuterol sulfate 2,5 mg**	**LEVALBUTEROL 5 mg CIPLA**	**Racemic albuterol sulfate 10 mg**

C_{max} (ng/mL) (R)-albuterol	1,1 (0,45)	0,8 (0,41)***	4,5 (2,2)	4,2 (1,51)***
T_{max} (h)* (R)-albuterol	0,2 (0,17, 0,37)	0,2 (0,17, 1,50)	0,2 (-0,18**, 1,25)	0,2 (-0,28**, 1,00)
AUC (mg/hr/mL) (R)-albuterol	3,3 (1,58)	1,7 (0,99)***	17,4 (8,56)	16,0 (7,12)***
$T_{1/2}$ (h) (R)-albuterol	3,3 (2,48)	1,56 (0,61)	4,0 (1,05)	4,1 (0,97)
*Median (min, max) reported for T_{max}. **A negative T_{max} indicates C_{max} occurred between first and last nebulisations. ***Values reflect only (R)-albuterol and do not include (S)-albuterol.				

Children 6 to 11 years old:

The pharmacokinetic parameters of (R)- and (S)-albuterol in children with asthma were obtained using population pharmacokinetic analysis. These data are presented in Table 3. For comparison, adult data obtained by conventional pharmacokinetic analysis from a different study also are presented in Table 3.

In children, AUC and C_{max} of (R)-albuterol following administration of 0,63 mg **SILEA** were comparable to those following administration of 1,25 mg racemic albuterol sulfate inhalation solution.

When the same dose of 0,63 mg of **SILEA** was given to children and adults, the predicted C_{max} of (R)-albuterol in children was similar to that in adults (0,52 vs. 0,56 ng/mL), while predicted AUC in children (2,55 ng*hr/mL) was about 1,5-fold higher than that in adults (1,65 ng*hr/mL). These data support lower doses for children 6 to 11 years old compared with the adult doses (see **section 4.2**).

Table 3: (R)-Albuterol exposure in adults and paediatric subjects 6 to 11 years old

	Children 6 to 11 years old				**Adults and children ≥ 12 years old**	
Treatment	**SILEA**		**Racemic albuterol**		**SILEA**	
	0,31 mg	**0,63 mg**	**1,25 mg**	**2,5 mg**	**0,63 mg**	**1,25 mg**
$AUC_{0-\infty}$ (ng.hr/mL)[c]	1,36	2,55	2,65	5,02	1,65[a]	3,3[b]
C_{max} (ng/mL)[d]	0,303	0,521	0,553	1,08	0,56[a]	1,1[d]

[a]The values are obtained by assuming linear pharmacokinetics.

[b]The data are obtained from Table 2.

[c]Area under the plasma concentration curve from time zero to infinity.

[d]Maximum plasma concentration.

Metabolism:

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol enantiomers in humans is SULT1A3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pre-treatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that (R)-albuterol is preferentially metabolised in the gastrointestinal tract, presumably by SULT1A3.

Elimination:

The primary route of elimination of albuterol enantiomers is through renal excretion (80 % to 100 %) of either the parent compound or the primary metabolite. Less than 20 % of the medicine is detected in the faeces. Following intravenous administration of racemic albuterol, between 25 % and 46 % of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Special Populations:

Renal Impairment:

The effect of renal impairment on the pharmacokinetics of racemic albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-

life, but there was a 67 % decline in racemic albuterol clearance. Caution should be used when administering high doses of **SILEA** to patients with renal impairment.

Hepatic Insufficiency:

The effect of hepatic impairment on the pharmacokinetics of **SILEA** inhalation solution has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Edetate disodium
- Nitrogen
- Sodium chloride
- Sulphuric acid
- Water for injection

6.2. Incompatibilities

N/A

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store in the original packages at or below 25 °C.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

6.5. Nature and contents of container

A single dose fill form seal (FFS) ampoule made up of low density polyethylene (LDPE) granules containing 3 mL inhalation solution. A strip of 5 ampoules are then overwrapped in triple laminated pouch and then further packed into cardboard cartons containing 5 pouches per carton, corresponding to 25 ampoules per pack.

Instructions on how to use SILEA:

Step 1: Open the foil pouch by tearing the notched edge along the seam of the pouch **(see Figure B)**. Remove 1 vial to be used right away. Keep the rest of the unused vials in the foil pouch to protect them from light and heat.

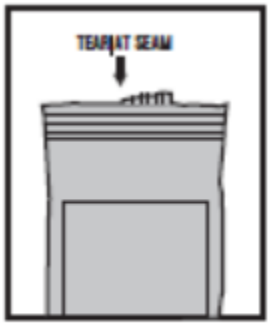

Figure B

Step 2: Hold the vial in your hands. Make sure your thumb and finger cover the twist-off tabs (see **Figure C**).

Figure C

Step 3: While holding the top firmly between your thumb and finger, twist the body of the vial to open the vial (see **Figure C**).

Step 4: Throw away the top of the vial and squeeze the entire contents of the vial into the nebuliser reservoir (see **Figure D**).

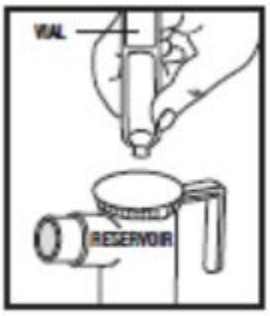

Figure D

Step 5: Connect the nebuliser reservoir to the mouthpiece (see **Figure E.1**) or face mask (see **Figure E.2**).

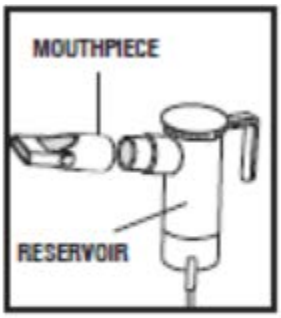

Figure E.1

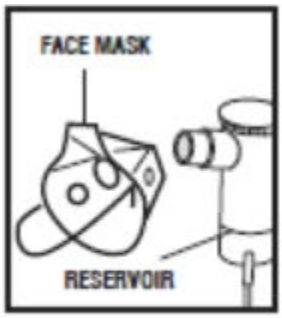

Figure E.2

Step 6: Connect the nebuliser to the compressor (see **Figure F**).

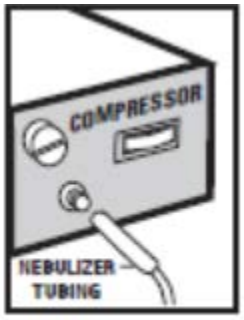

Figure F

Step 7: Sit in a comfortable, upright position. Place the mouthpiece in your mouth (see **Figure G.1**) or put on your face mask (see **Figure G.2**). Turn on the compressor.

Figure G.1

Figure G.2

Step 8: Breathe as calmly, deeply, and evenly as possible until no more mist is seen in the nebuliser reservoir. Your treatment will take about 5 to 15 minutes. When you do not see any mist in the nebuliser reservoir, your treatment is finished.

Step 9: Clean and store your nebuliser. See the manufacturer's instructions that come with your nebuliser for how to clean and store your nebuliser.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

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Customer Care: 080 222 6662

Drug Safety E-mail: drugsafetysa@cipla.com.

8. REGISTRATION NUMBER(S)

SILEA 0,31 mg/ 3 mL: 54/10.2.1/0630.627

SILEA 0,63 mg/ 3 mL: 54/10.2.1/0631.628

SILEA 1,25 mg/ 3 mL: 54/10.2.1/0632.629

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2023

10. DATE OF REVISION OF THE TEXT

N/A