MODULE 1.5.5.1.2: PROPOSED CLEAN PACKAGE INSERT FOR DEPRAMIL 10 / 20 / 40 TABLETS

SCHEDULING STATUS:

S5

PROPRIETARY NAME (AND DOSAGE FORM):

DEPRAMIL 10 (Tablets)

DEPRAMIL 20 (Tablets)

DEPRAMIL 40 (Tablets)

COMPOSITION:

DEPRAMIL 10: Each tablet contains citalopram hydrobromide equivalent to citalopram 10 mg.

DEPRAMIL 20: Each tablet contains citalopram hydrobromide equivalent to citalopram 20 mg.

DEPRAMIL 40: Each tablet contains citalopram hydrobromide equivalent to citalopram 40 mg.

Inactive ingredients include colloidal anhydrous silica, hypromellose, macrogol 6000, magnesium stearate, mannitol, microcrystalline cellulose, and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants).

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Citalopram is a bicyclic phthalane derivative with antidepressant effect. Its effect is linked to the selective inhibition of specific serotonin (5-HT) reuptake. Citalopram, primarily through its (S)-enantiomer, blocks 5-HT reuptake, leading to potentiation of serotonergic activity in the central nervous system (CNS). Neither citalopram nor its metabolites have an effect on noradrenaline, dopamine and GABA reuptake. Citalopram also has little or no antidopaminergic, antiadrenergic, antiserotonergic, antihistaminergic or anticholinergic properties.

Pharmacokinetic properties:

Oral bioavailability is about 80 % with maximum plasma levels being reached in 4 hours (range 1 to 6 hours). Volume of distribution is about 14 ℓ/kg (range 9 to 17 ℓ/kg). Time to reach steady state concentration is 1 to 2 weeks. Protein binding is about 80 %. Elimination half-life is 36 hours (range 28 – 42 hours). Citalopram undergoes hepatic metabolism primarily involving the cytochrome P450 3A4 (CYP3A4) and 2C19 (CYP2C19) isoenzymes and to a small extent cytochrome P450 2D6 (CYP2D6) isoenzymes. The metabolites inhibit the reuptake of serotonin, but are less potent than the parent molecule. Citalopram is excreted mainly via the liver with the remainder via the kidneys (approximately 20 % of which 12 % is unchanged medicine). Longer half-lives and decreased clearance due to a reduced rate of metabolism have been demonstrated in the elderly.

INDICATIONS:

DEPRAMIL is indicated for the treatment of:

- Depression and prevention of relapse.
- Panic disorders with or without agoraphobia.
- Obsessive-compulsive disorder (OCD).

CONTRAINDICATIONS:

- Hypersensitivity to citalopram or any of the ingredients in **DEPRAMIL**.
- Concurrent use with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between discontinuing the MAOI and initiating therapy with **DEPRAMIL**. MAOIs should not be introduced for 7 days after discontinuation of **DEPRAMIL** (see **"INTERACTIONS"**).
- **DEPRAMIL** is contraindicated in combination with linezolid (see **"INTERACTIONS"**).
- Severe renal impairment (creatine clearance less than 20 mℓ/min).
- Safety and efficacy in pregnancy and lactation has not been established (see **"PREGNANCY AND LACTATION"**).
- Children under the age of 18 years (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE-EFFECTS"**).
- **DEPRAMIL** is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).

- The concomitant use of **DEPRAMIL** with medicinal products that are known to prolong the QT interval, is contraindicated (see **"INTERACTIONS"**).
- **DEPRAMIL** should not be used concomitantly with pimozide (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

DEPRAMIL should be used with caution in :

- Elderly patients: longer half-life and decreased clearance due to a reduced rate of metabolism. A lower dose is recommended in the elderly (see **"DOSAGE AND DIRECTIONS FOR USE"**).
- Hepatic impairment: clearance of **DEPRAMIL** is reduced. Cautious dosage titration and a lower maximum dose are recommended.
- Renal impairment: elimination is decreased. If creatine clearance is less than 20 mℓ/min, **DEPRAMIL** should not be used (see **"CONTRAINDICATIONS"**).
- Seizures or history thereof: there is an increased risk of seizures. **DEPRAMIL** should be used with caution in patients with controlled epilepsy and avoided in patients with epilepsy who are poorly controlled. Care is advised in patients receiving electroconvulsive therapy.
- Mania or history of mania: condition may be re-activated. **DEPRAMIL** should be discontinued if the patient enters the manic phase.
- Psychosis: treatment of psychotic patients with depressive episodes may increase psychotic symptoms.
- Glaucoma: **DEPRAMIL** can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or a history of glaucoma.

- **DEPRAMIL** may cause a reduction in heart rate. Caution is advised in patients with pre-existing slow heart rates.
- QT interval prolongation: **DEPRAMIL** has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia, including torsade de pointes, have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see **"CONTRAINDICATIONS"** and **"SIDE-EFFECTS"**).

  Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

  Electrolyte disturbances, such as hypokalaemia and hypomagnesaemia, increase the risk for malignant (life-threatening) dysrhythmias and should be corrected before treatment with **DEPRAMIL** is started.

  If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

  ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

  If signs of cardiac dysrhythmia occur during treatment with **DEPRAMIL**, the treatment should be withdrawn and an ECG should be performed.
- Diabetes mellitus: occurrences of hypoglycaemia have been reported. In patients with diabetes, treatment with **DEPRAMIL** may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

- Serotonin syndrome: serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. Serotonin syndrome is more likely to occur after an increase in dose. Treatment with **DEPRAMIL** should be discontinued immediately and symptomatic treatment initiated.
- **DEPRAMIL** should not be used with monoamine oxidase inhibitors, imipramine, other serotonergic medicines, moclobemide, alcohol, warfarin, and cimetidine (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).
- St. John's Wort: undesirable effects may be more common during concomitant use of **DEPRAMIL** and herbal remedies containing St. John's Wort *(Hypericum perforatum).* Therefore, **DEPRAMIL** and St John's Wort preparations should not be taken concomitantly (see **"INTERACTIONS"**).
- Hyponatraemia: hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs, such as **DEPRAMIL**, and generally resolves on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.
- Haemorrhage: there have been reports of prolonged bleeding time and/or bleeding abnormalities, such as ecchymosis, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleedings with SSRIs (see **"SIDE-EFFECTS"**). Caution is advised in patients taking **DEPRAMIL**, particularly with concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage,

as well as in patients with a history of bleeding disorders (see **"INTERACTIONS"**).

- SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see **“PREGNANCY AND LACTATION”** and **“SIDE-EFFECTS”**).
- Akathisia / psychomotor restlessness: the use of SSRIs, such as **DEPRAMIL**, has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **DEPRAMIL** should, nevertheless, be observed closely for clinical worsening and suicidality until improvement in depression is observed, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed

when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **DEPRAMIL**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, **DEPRAMIL** should be tapered gradually in order to prevent the possibility of a withdrawal syndrome (see **"SIDE-EFFECTS"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events, such as suicidal ideation and self-harm (see **"CONTRAINDICATIONS"** and **"SIDE-EFFECTS"**).

Class effects:

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Effects on ability to drive and operate machinery:

DEPRAMIL may impair performance of skilled tasks. If affected these patients should not operate machinery or drive.

INTERACTIONS:

Monoamine oxidase inhibitors (MAOIs) including selegiline, linezolid and moclobemide: concurrent use is contraindicated. Serious and potentially fatal reactions have occurred, such as hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuation of vital signs and mental status changes, including extreme agitation progressing to delirium and coma (see **"CONTRAINDICATIONS"**).

Imipramine: an increase in the concentration of desimipramine (the active metabolite of imipramine) may occur. It appears that **DEPRAMIL** does not cause a marked increase in plasma levels of some tricyclic antidepressants.

Other serotonergic medicines or medicines with serotonergic activity (e.g. tramadol, sumatriptan): increased risk of developing the serotonin syndrome, a rare but potentially fatal hyperserotonergic state.
The simultaneous use of **DEPRAMIL** and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Moclobemide: serotonin syndrome has developed after taking overdoses of moclobemide and **DEPRAMIL**.

Lithium and tryptophan: no pharmacodynamic interactions have been found in clinical studies in which **DEPRAMIL** has been given concomitantly with lithium. However, there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of **DEPRAMIL** with these medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Alcohol: the effects of alcohol may be increased.

Warfarin: the anticoagulant activity of warfarin may be increased.

Cimetidine: the AUC and the maximum plasma concentration of **DEPRAMIL** are increased when **DEPRAMIL** is administered concurrently with cimetidine.

Omeprazole: co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50 %) increase in the plasma concentrations of escitalopram.
Thus, caution should be exercised when **DEPRAMIL** is used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of **DEPRAMIL** may be necessary based on monitoring of side-effects during concomitant treatment.

Medicines which prolong the QT interval: pharmacokinetic and pharmacodynamics studies of **DEPRAMIL** combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of **DEPRAMIL** and these medicinal products cannot be excluded.
Co-administration of **DEPRAMIL** with medicinal products that prolong the QT interval, such as Class IA and III antidysrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine), is contraindicated (see **"CONTRAINDICATIONS"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Pimozide: The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at low dose of pimozide, concomitant administration of **DEPRAMIL** and pimozide is contraindicated (see **"CONTRAINDICATIONS"**).

Medicinal products inducing hypokalaemia / hypomagnesaemia: caution is warranted for concomitant use of hypokalaemia- / hypomagnesaemia-inducing medicines as they, like **DEPRAMIL**, potentially prolong the QT interval.

St. John's Wort: dynamic interactions between SSRIs, including **DEPRAMIL**, and the herbal remedy containing St. John's Wort *(Hypericum perforatum)* can occur, resulting in an increase in undesirable effects (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Medicines which can increase the risk of haemorrhage: caution is warranted for patients who are being treated simultaneously with anticoagulants (e.g. warfarin), medicinal products that affect platelet function, such as non-steroidal anti-inflammatory agents (NSAIDs), acetylsalicylic acid, dipyridamole, and ticlopidine or other medicines (e.g. atypical antipsychotics, phenothiazines, tricyclic antidepressants) that can increase the risk of haemorrhage (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Medicinal products which lower the seizure threshold: SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal

products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).

A pharmacokinetic / pharmacodynamics interaction study with concomitant administration of citalopram, as in **DEPRAMIL**, and metoprolol (a CYP2D6 substrate) showed a two-fold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers.

PREGNANCY AND LACTATION:

Pregnancy:

Safety and efficacy in pregnancy has not been established (see **"CONTRAINDICATIONS"**).

Published data on pregnant women indicate no malformative foeto / neonatal toxicity; however, citalopram, as in **DEPRAMIL**, should not be used during pregnancy.

Neonates should be observed if maternal use of **DEPRAMIL** continued into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see **"WARNINGS AND SPECIAL PRECAUTIONS** and **SIDE-EFFECTS"**).

Breastfeeding:

Safety and efficacy in lactation has not been established (see **"CONTRAINDICATIONS"**). **DEPRAMIL** is excreted into the breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Depression:

20 mg a day as a single dose. Dosage may be increased to a maximum of 40 mg daily, depending on the patient's response.

Panic disorder:

10 mg a day as a single dose for the first week then increasing to 20 mg a day. The dose may be increased thereafter as required to a maximum of 40 mg a day depending on the patient's response.

A low starting dose is recommended to minimise the potential worsening of panic symptoms, recognised to occur early in the treatment of this disorder (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Obsessive-compulsive disorder:

20 mg a day as a single dose. This dose can be increased to a maximum of 40 mg a day depending on the patient's response.

Special populations:

Elderly: 10 to 20 mg a day as a single dose. Depending on the patient's response, the dose can be increased to a maximum of 20 mg a day.

Reduced hepatic function: Dose should be halved.

Reduced renal function: Dose adjustment is not necessary in cases of mild or moderate renal impairment.

The onset of action is seen within 2 to 4 weeks. Treatment should be continued for an appropriate length of time (up to six months) after recovery in order to prevent relapse.

The medicine should be gradually withdrawn over a couple of weeks when stopping therapy (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE-EFFECTS"**).

DEPRAMIL may be taken with or without food in the morning or evening.

SIDE-EFFECTS:

Blood and lymphatic system disorders:

Frequency unknown: Thrombocytopenia.

Immune system disorders:

Frequency unknown: Hypersensitivity, anaphylactic reaction, angioedema.

Endocrine disorders:

Frequency unknown: Inappropriate ADH secretion.

Metabolism and nutrition disorders:

Frequent: Weight changes, decreased appetite.

Less frequent Increased appetite, hyponatraemia.

Frequency unknown:	Hypokalaemia.

Psychiatric disorders:

Frequent:	Agitation, anxiety, nervousness, apathy, restlessness, decreased libido, confusional state, abnormal dreams, abnormal orgasm, including anorgasmia.
Less frequent:	Confusion, impaired concentration, mania, aggression, hallucinations, depersonalisation, increased libido. Hostility, suicidal ideation and self-harm have been reported in children.
Frequency unknown:	Suicidal behaviour, suicidal ideation, panic attacks, bruxism.

Nervous system disorders:

Frequent:	Amnesia, tremor, paraesthesia, disturbance in attention, sleep disturbances, both somnolence and insomnia, headache, dizziness and fatigue, migraine, taste disturbance.
Less frequent:	Neuroleptic malignant syndrome, convulsions including grand mal convulsions, serotonin syndrome, syncope, dyskinesia.

Frequency unknown:	Extrapyramidal disorder, akathisia, movement disorder.

Eye disorders:

Frequent:	Accommodation disturbances.
Less frequent:	Mydriasis (which may lead to acute narrow angle glaucoma) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Ear and labyrinth disorders:

Frequent:	Tinnitus.

Cardiac disorders:

Frequent:	Palpitations.
Less frequent:	Bradycardia, tachycardia.
Frequency unknown:	QT-prolongation, ventricular dysrhythmia including torsade de pointes.

Vascular disorders:

Less frequent:	Haemorrhage.
Frequency unknown:	Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent:	Yawning, rhinitis.

Less frequent:	Coughing, nasal congestion.
Frequency unknown:	Epistaxis.

Gastrointestinal disorders:

Frequent:	Nausea, constipation, diarrhoea, vomiting, dyspepsia, dry mouth, anorexia, abdominal pain, flatulence, increased salivation.
Frequency unknown:	Gastrointestinal haemorrhage (including rectal haemorrhage).

Hepatobiliary disorders:

Less frequent:	Hepatitis.
Frequency unknown:	Abnormal liver function test.

Skin and subcutaneous tissue disorders:

Frequent:	Sweating, pruritus.
Less frequent:	Urticaria, alopecia, purpura, photosensitivity reaction, rash.
Frequency unknown:	Ecchymosis.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Asthenia, myalgia, arthralgia.

Renal and urinary disorders:

Frequent:	Micturition disorders.
Less frequent:	Urinary retention.

Reproductive system and breast disorders:

Frequent:	Sexual dysfunction, including impotence, ejaculation disorder, ejaculation failure.
Less frequent:	Menorrhagia.
Frequency unknown:	Metrorrhagia, priapism, galactorrhoea, postpartum haemorrhage*.

*This event has been reported for the therapeutic class of SSRIs/SNRIs (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION**).

General disorders:

Frequent:	Fatigue.
Less frequent:	Oedema, pyrexia, malaise.

Discontinuation effects:

There have been spontaneous reports of adverse events occurring upon discontinuation of **DEPRAMIL** particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paraesthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania and nausea. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing

treatment with **DEPRAMIL**. A gradual reduction in dose rather than abrupt cessation is recommended wherever possible (see **"DOSAGE AND DIRECTIONS FOR USE"**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **"SIDE-EFFECTS"**).

Symptoms of overdose:

Tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence and sinus tachycardia.

Treatment of overdose:

Treatment is symptomatic and supportive, including monitoring of ECG.

There is no specific antidote to **DEPRAMIL**.

The stomach should be emptied as soon as possible by emesis or gastric lavage. Monitoring of cardiac and vital signs are necessary and medical surveillance is advisable for about 24 hours.

IDENTIFICATION:

DEPRAMIL 10: White coloured, circular, biconvex, film-coated tablets, plain on both sides. Diameter approximately 6 mm.

DEPRAMIL 20: White coloured, circular, biconvex, film-coated tablets with scoreline on one side and plain on the other side. Diameter approximately 8 mm.

DEPRAMIL 40: White coloured, circular, biconvex, film-coated tablets with crosswise score on one side and plain on the other side. Diameter approximately 10 mm.

PRESENTATION:

DEPRAMIL 10: Blister strips of 10 tablets, packed in 28's or 30's.

DEPRAMIL 20: Blister strips of 10 tablets, packed in 28's or 30's.

DEPRAMIL 40: Blister strips of 10 tablets, packed in 28's or 30's.

STORAGE INSTRUCTIONS:

Store in a cool, dry place at or below 25 °C. Protect from light.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

DEPRAMIL 10: A38/1.2/0488

DEPRAMIL 20: A38/1.2/0489

DEPRAMIL 40: A38/1.2/0490

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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