For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CORDINE LS

1. Generic Name

Levosalbutamol, Ambroxol Hydrochloride & Guaiphenesin Syrup

2. Qualitative and quantitative Composition:

Each 5 ml contains:

Levosalbutamol Sulphate I.P.

equivalent to Levosalbutamol …….....1mg

Ambroxol Hydrochloride I.P. ……...…….....30 mg

Guaiphenesin I.P. ……...50 mg

In a flavoured syrupy base…….... q.s.

Colour: Tartrazine

The List of excipients used are Sucralose, Sodium Chloride, Sodium Benzoate, Sodium Citrate, Neotame, Tartrazine Supra Colour, Hydroxyethylcellulose, Citric Acid Monohydrate, Menthol. and Disodium EDTA.

3. Dosage form and strength

Dosage form: Syrup

Strength: 1 mg+30 mg, + 50 mg.

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the symptomatic relief of bronchospasm in bronchial asthma & chronic bronchitis.

4.2. Posology and method of administration

Adults

5–10 mL thrice daily.

Paediatric Patients (aged 6–12 years)

5 mL thrice daily

or

As directed by the physician

4.3. Contraindications

CORDINE LS Syrup is contraindicated in patients with the following conditions:

- Known hypersensitivity to any of the components of the formulation.
- Patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- Patients with gastric ulceration.

- It should not be used for threatened abortion during the first or second trimester of pregnancy. Levosalbutamol and beta-blocking drugs such as propranolol should not usually be prescribed together.

4.4. Special warnings and precautions for use

General

Levosalbutamol Sulphate

PARADOXICAL BRONCHOSPASM

Levosalbutamol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, levosalbutamol should be discontinued immediately and alternative therapy instituted. It should be recognised that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use.

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 oral levosalbutamol than usual, this may be a marker of destabilisation of asthma and requires re-evaluation of the patient and the treatment regimen, with special consideration to the possible need for anti-inflammatory treatment, e.g. corticosteroids.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids, and diuretics. Serum potassium levels should be monitored in such situations.

CARDIOVASCULAR EFFECTS

Levosalbutamol, 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 uncommon after administration of levosalbutamol at recommended doses, if they occur, the drug 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, oral levosalbutamol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension.

USE OF ANTI-INFLAMMATORY AGENTS

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

DO NOT EXCEED THE RECOMMENDED DOSE

Do not exceed the recommended dose. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs 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 levosalbutamol or racemic salbutamol. Reactions have included urticaria, angio-oedema, 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 levosalbutamol.

COEXISTING CONDITIONS

Levosalbutamol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes 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.

Changes in blood glucose may occur. Large doses of intravenous racemic salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

HYPOKALAEMIA

As with other beta-adrenergic agonist medications, levosalbutamol may produce significant hypokalaemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects? The decrease is usually transient, not requiring supplementation.

Ambroxol Hydrochloride

Care should be taken to avoid contact with the eyes and skin, and serious ingestion or inhalation.

In the presence of impaired renal function or severe hepatopathy, CORDINE LS Syrup may be used only after consulting a physician. In cases of severe renal failure, an accumulation of metabolites formed in the liver must be considered, and a reduction in the maintenance dose or an increase in the dose interval must be performed.

In patients with a tendency for peptic ulcers, the use of ambroxol hydrochloride should be carefully considered. In patients with malignant cilia syndrome, the advantages of secretion liquefaction should be carefully weighed against the risk of a secretory obstruction. The simultaneous administration of antitussives should definitely be avoided due to the risk of secretory obstruction (see Drug Interactions).

There have been very rare reports of severe skin lesions such as Stevens-Johnson syndrome and toxic epidermal necrolysis ([TEN], Lyell's syndrome) in temporal association with the administration of mucolytic substances such as ambroxol hydrochloride. Mostly, these could be explained by the severity of the underlying disease or concomitant medication. During the early phase of a Stevens-Johnson syndrome or TEN, a patient may first experience nonspecific influenza-like prodromes, e.g. fever, aching body, rhinitis, cough and sore throat. If new skin or mucosal lesions occur, treatment with ambroxol hydrochloride should be discontinued as a precaution. In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

Cordine LS Syrup should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

Guaifenesin

Consult a doctor before use if your child suffers from chronic cough, if he/she has asthma or is suffering from an acute asthma attack.

Stop use and consult a healthcare professional if your child's cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash or persistent headache.

Do not give with a cough suppressant.

Caution should be exercised in the presence of severe renal or severe hepatic impairment.

Not more than four doses should be given in any 24 hours. Do not exceed the stated dose.

Do not take with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years.

4.5. Drugs interactions

Levosalbutamol Sulphate

Short-Acting Bronchodilators

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

Beta-Blockers

Beta-adrenergic receptor-blocking agents not only block the pulmonary effect of beta-agonists such as levosalbutamol but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, use of beta-adrenergic blocking agents could be considered, although they should be administered with caution.

Diuretics

The ECG changes 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-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-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 salbutamol, 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 levosalbutamol and digoxin on a chronic basis is unclear. Nevertheless, it is advisable to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levosalbutamol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Levosalbutamol should be administered with extreme caution to patients being treated with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levosalbutamol on the vascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

Halogenated Anaesthetics

Owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity have been reported on interaction with halogenated anaesthetics. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with halogenated anaesthetics.

Ambroxol Hydrochloride

Simultaneous use of ambroxol and antibiotics (amoxicillin, cefuroxim, erythromycin, doxycyclin) results in an increase of concentration of the antibiotics in the lung tissue.

Concomitant use with antitussive agents, e.g. codeine should be avoided, because they may inhibit cough reflex.

Guaiphenesin

If urine is collected within 24 hours of a dose of guaiphenesin, its metabolite may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

Expectorants such as guaiphenesin should not be combined with cough suppressants in the treatment of cough since the combination is illogical and patients may be exposed to unnecessary adverse effects.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnant Women

There are no adequate and well-controlled studies of this combination in pregnant women. Hence, this combination should be administered with caution in pregnancy.

Lactating Women

It is not known whether this combination is secreted in breast milk. Therefore, this combination should be used with caution in nursing mothers.

Paediatric Patients

Safety and effectiveness of levosalbutamol in paediatric patients below the age of 6 years have not been established.

Therefore, this combination should not be used for children below the age of 6 years.

Geriatric Patients

Clinical studies of levosalbutamol did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. If clinically warranted due to insufficient bronchodilator response, the dose of levosalbutamol may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose (see Posology and Method of Administration).

It is not known whether this combination will have any effect on geriatric patients.

Patients with Renal Impairment

Salbutamol is known to be substantially excreted by the kidneys, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

It is not known whether this combination will have any effect on renal impaired patients.

4.7. Effects on ability to drive and use machines

The most frequent side effects are palpitation, fine tremors of the skeletal muscle (particularly the hands) and muscle cramps (which may occur due to levosalbutamol). This may affect the ability to drive and the use of machines.

4.8. Undesirable effects

Levosalbutamol Sulphate

Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. This effect may be potentiated by hypoxia. Particular caution is advised in severe asthma; in such cases, monitoring of serum potassium levels is recommended. Other side effects such as palpitation, fine tremors of the skeletal muscle (particularly the hands), and muscle cramps may occur.

The other likely side effects are gastrointestinal disturbances such as nausea, vomiting, burning substernal or epigastric pain, and diarrhoea. In some cases, nervousness, headache, dizziness, fatigue and sleeplessness may occur.

Ambroxol Hydrochloride

Definition of the used frequencies: common (<10% to >1%), uncommon (<1% to >0.1%), rare (<0.1%). The frequency of undesired effects, which did not appear in clinical trials but appeared only spontaneously after marketing introduction, is not known.

Immune System, Skin and Subcutaneous Tissue Disorders

Rare: rash, urticaria, hypersensitivity reactions

Frequency not known: anaphylactic reactions, including anaphylactic shock; angio-oedema, pruritus and other hypersensitivity reactions, severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis)

Nervous System

Common: dysgeusia (e.g. changed taste)

Respiratory and Gastrointestinal Disorders

Common: nausea, oral and pharyngeal hypoesthesia

Uncommon: vomiting, diarrhoea, dyspepsia, abdominal pain, dry mouth

Not known: dry throat

Guaiphenesin

The following side effects may be associated with the use of guaiphenesin:

Body System (System Organ Class)	Incidence	Adverse Drug Reaction
Immune system disorders	Not known	Hypersensitivity reaction (pruritus and urticaria) Rash
Gastrointestinal disorders	Not known	Upper abdominal pain, diarrhoea, nausea, vomiting.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Levosalbutamol Sulphate

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the side effects, e.g. tachycardia, nervousness, headache, tremor, nausea, dizziness, fatigue, and sleeplessness. Hypokalaemia may also occur. Treatment consists of discontinuation of oral levosalbutamol together with appropriate symptomatic therapy. The judicious use of a cardio selective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of levosalbutamol.

In the event of serious poisoning, the stomach should be emptied and, if necessary, a beta-blocker administered with caution, especially in patients with a history of bronchospasm.

Ambroxol Hydrochloride

Serious intoxication symptoms have not been observed following overdose of ambroxol. Brief restlessness and diarrhoea have been reported.

Ambroxol has been tolerated well on parenteral administration up to a dosage of 15 mg/kg/day, and on oral administration up to a dosage of 25 mg/kg/day.

In analogy to preclinical examinations, increased salivation, retching, vomiting and a drop in blood pressure may occur following extreme overdose.

Based on accidental overdose and/or medication error reports, the observed symptoms are consistent with the known side effects. If symptoms of overdosage occur, symptomatic treatment should be provided.

Acute measures such as instituting vomiting and gastric lavage are not generally indicated and are only to be considered following extreme overdose. A symptomatic therapy is recommended.

Guaiphenesin

The effects of acute toxicity from guaiphenesin may include gastrointestinal discomfort, nausea and drowsiness. When taken in excess, guaiphenesin may cause renal calculi. Treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1. Mechanism of Action

Activation of β2 adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of 3',5'-cyclic 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. Levosalbutamol 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 the release of mediators from mast cells in the airways. Levosalbutamol acts as a functional agonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all Broncho constrictor challenges.

Ambroxol is a mucolytic agent. Excessive Nitric oxide (NO) is associated with inflammatory and some other disturbances of airways function. NO enhances the activation of soluble guanylate cyclase and cGMP accumulation. Ambroxol has been shown to inhibit the NO-dependent activation of soluble guanylate cyclase. It is also possible that the inhibition of NO-dependent activation of soluble guanylate cyclase can suppress the excessive mucus secretion;

therefore, it lowers the phlegm viscosity and improves the mucociliary transport of bronchial secretions.

Guaifenesin may act as an irritant to gastric vagal receptors, and recruit efferent parasympathetic reflexes that cause glandular exocytosis of a less viscous mucus mixture. Cough may be provoked. This combination may flush tenacious, congealed mucopurulent material from obstructed small airways and lead to a temporary improvement in dyspnea or the work of breathing.

5.2. Pharmacodynamic properties

Like other bronchodilators, Levosalbutamol acts by relaxing smooth muscle in the bronchial tubes, and thus shortening or reversing an acute "attack" of shortness of breath or difficulty breathing.

Guaifenesin is an expectorant which increases the output of phlegm (sputum) and bronchial secretions by reducing adhesiveness and surface tension. The increased flow of less viscous secretions promotes ciliary action and changes a dry, unproductive cough to one that is more productive and less frequent. By reducing the viscosity and adhesiveness of secretions, Guaifenesin increases the efficacy of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway.

5.3. Pharmacokinetic properties

Levosalbutamol Sulphate

Absorption

Whether administered alone or as the racemate, salbutamol enantiomers are well absorbed from the gastrointestinal tract and time to maximum drug concentration (tmax) values ranges from 45 to 360 minutes. (S)-Salbutamol has a longer tmax when administered orally as the pure enantiomer compared with when it is administered in the racemate. This phenomenon may be due to altered gastrointestinal motility subsequent to beta-adrenoceptor stimulation by (R)-salbutamol in the racemate. The bioavailability of (S)-salbutamol is approximately 70% at both steady state and following a single oral dose, whereas the bioavailability of (R)-salbutamol increases from 9% after a single oral dose to 30% at steady state.

Distribution

The blood to plasma ratio for total salbutamol appears to be near unity (0.96 ± 0.13) in healthy volunteers, suggesting that the total blood clearance of salbutamol is equal to the total plasma clearance once steady state has been reached. Values for binding to blood components, along with similar volumes of distribution for salbutamol enantiomers, suggest that protein-binding plays a relatively minor role in the disposition of salbutamol enantiomers

Metabolism

(R)-salbutamol was metabolised up to 12 times more efficiently than its antipode, with large, normally distributed inter-individual variation being observed in human tissue samples. It is clear from these studies that SULT1A3 expression is higher in intestine than in the other tissues studied, notably hepatic tissue. This supports clinical observations that the intestines are the main site of enantio-selective pre-systemic metabolism of salbutamol for drug absorbed in the gastrointestinal tract.

Elimination

Calculated renal clearance values for both enantiomers were significantly larger than creatinine clearance, indicating active renal excretion. This leads to relatively higher

concentrations of the drug in urine than in plasma. (S)-salbutamol is almost always found in higher amounts in urine than (R)-salbutamol, regardless of the route of administration.

Ambroxol Hydrochloride

Absorption

Ambroxol is rapidly absorbed (70–80%) after oral administration. The time to reach peak plasma concentration is approximately 2 hours.

Distribution

Distribution after oral, intramuscular and intravenous administration from blood to organs is rapid, with maximal concentrations in the lungs. Plasma half-life is 7–12 hours, and accumulation has not been observed

Metabolism

Primary metabolism of ambroxol takes place in the liver by conjugation. The metabolite is dibromoanthranilic acid (activity unspecified).

Excretion

Excretion is primarily via the kidneys. Renal clearance (rate) is approximately 53 mL/minute; approximately 5–6% of a dose is excreted unchanged in the urine. The elimination half-life of ambroxol is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours.

Guaiphenesin

Absorption

Guaiphenesin is well absorbed from the gastrointestinal tract following oral administration, although limited information regarding its pharmacokinetics is available. After the administration of 600 mg guaiphenesin to healthy adult volunteers, the Cmax was approximately 1.4 ug/mL, with Tmax occurring approximately 15 minutes after drug administration.

Distribution

No information is available on the distribution of guaiphenesin in humans.

Metabolism and Elimination

Guaiphenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaiphenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

Pharmacokinetics in Patients with Renal/Hepatic Impairment

There have been no specific studies of guaiphenesin in subjects with renal or hepatic impairment. Caution is, therefore, recommended when administering this product to subjects with severe renal or hepatic impairment.

Pharmacokinetics in Geriatric Patients

Not applicable.

6. Nonclinical properties

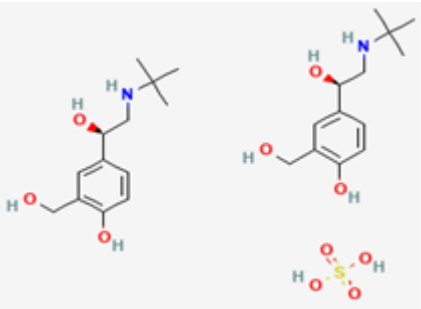
6.1. Animal Toxicology or Pharmacology

NA

7. Description

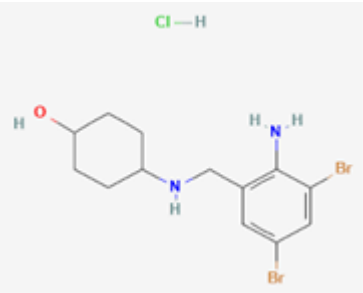
Levosalbutamol Sulphate

Levosalbutamol Sulphate is 4-[(1R)-2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl) phenol;sulfuric acid with molecular weight of 576.7 g/mol and empirical formula is $C_{26}H_{44}N_2O_{10}S$. The chemical structure is:



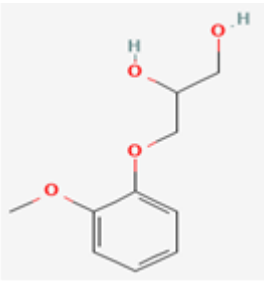
Ambroxol Hydrochloride

Ambroxol Hydrochloride is trans-4-[(2-amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride with molecular weight of 414.56 g/mol and empirical formula is $C_{13}H_{18}Br_2N_2O$, HCl. The chemical structure is:



Guaiphenesin

Guaiphenesin is 3-(2-methoxyphenoxy)propane-1,2-diol with molecular weight of 198.22 g/mol and empirical formula is $C_{10}H_{14}O_4$. The chemical structure is:



Cordine LS

Cordine LS is yellow coloured solution.. .

The List of excipients used are Sucralose, Sodium Chloride, Sodium Benzoate, Sodium Citrate, Neotame, , Tartrazine Supra Colour, Hydroxyethylcellulose , Citric Acid Monohydrate, Menthol and Disodium EDTA.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

CORDINE LS is available in 100ml and 60 ml bottle.

8.4. Storage and handing instructions.

Store below 30°C. Protect from light.

Keep out of reach of children.

Shake well before use.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Ravenbhel Biotech

EPIP, SIDCO, Kartholi,

Bari Brahmana, Jammu-181133

11. Details of permission or licence number with date

Mfg. Licence.No: JK/01/11-12/192 Issue date :27/09/2021

12. Date of revision

APR-2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CORDINE LS /APR 2026/02/PI