# Summary of Product Characteristics

## 1. Name of the Medicinal Product

LIPZ, 0.03 mg/3 mg film-coated tablets
LIPZ ED, 0.03 mg/3 mg film-coated tablets

## 2. Qualitative and Quantitative Composition

LIPZ
21 Active Tablets
Each active tablet contains 3 mg drospirenone and 0.03 mg ethinylestradiol.
LIPZ ED
21 Active Tablets and 7 Placebo Tablets
Each active tablet contains 3 mg drospirenone and 0.03 mg ethinylestradiol.

Each active tablet contains 57.34 mg of lactose monohydrate.
Each placebo tablet contains 57.20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

LIPZ
Round, biconvex, light yellow film coated tablet with embossed "D" in regular hexagon on one side and plain on the other.
LIPZ ED
Active Tablets: Round, biconvex, light yellow film coated tablet with embossed "D" in regular hexagon on one side and plain on the other
Placebo Tablets: Round, biconvex, white-film coated tablet with embossed regular hexagon on one side and plain on the other

## 4. Clinical Particulars

### 4.1 Therapeutic indication

LIPZ and LIPZ ED are contraceptive pills and are used to prevent pregnancy. You may also experience the following additional benefits: improvement in symptoms such as bloating, swelling or weight-gain, due to fluid retention. Improvement in acne, and reduction in greasiness of the skin and hair.
(Ref: Yasmin Leaflet)

### 4.2 Posology and method of administration

***Method of Administration***

Oral use

***Posology***

**When to start taking LIPZ and LIPZ ED**

There are 2 ways to start taking the first tablet if a hormonal contraceptive hasn't been used in the previous month:

1. Start taking the tablet on the first day of the cycle (the first day of the period). No additional contraceptive methods are required.

2. Start taking the tablet on the first Sunday after menstrual bleeding has started. In this case, an alternative contraception method should be employed for the next 7 days.

In case of a switch from another hormonal contraceptive, LIPZ and LIPZ ED can be started immediately if it is certain that the method has been used correctly, or that no pregnancies have occurred. If the previous method was injectable contraceptive, LIPZ and LIPZ ED should be initiated when the repeat injection would have been given. No additional contraceptive protection is needed.

In case of amenorrhea, LIPZ and LIPZ ED can be initiated anytime if it is reasonably certain that no pregnancies have occurred. Additional contraceptive should be used for the next 7 days.

**How to take LIPZ and LIPZ ED**

LIPZ

LIPZ pack contains 21 tablets. Each tablet is marked with the day of the week on which it is to be taken. Take the tablet around the same time each day and follow the direction of the arrows until all 21 tablets have been taken, then stop taking tablets for the next 7 days. A withdrawal bleeding usually starts 2-3 days after the last tablet. On the 8th day, start taking the next pack whether the bleeding has stopped or not.

LIPZ ED

LIPZ ED pack contains 28 tablets – 21 Active Tablets and 7 Placebo Tablets. Each tablet is marked with the number of the day on which it is to be taken. Take the tablet around the same time each day and follow the direction of the arrows until all 28 tablets have been taken. A withdrawal bleeding usually starts 2-3 days after the last active tablet. Each subsequent pack is started the day after the last tablet of the current pack whether the bleeding has stopped or not.

**Missed doses**

Depending on the day of the cycle on which **one** active tablet has been missed, **additional contraceptive precautions** may need to be taken, for example a barrier method such as a condom. **Take the tablets according to the following principles. See also the 'missed pill chart' for details. In case of doubt, contact the doctor.**

- If it is **less than 12 hours late** when taking a tablet, the protection against pregnancy is not reduced. It is advised to take the tablet as soon as the patient remembers and then continues taking the tablets again at the usual time.
- If it is **more than 12 hours late** in taking a tablet the protection against pregnancy may be reduced. The more tablets that have been forgotten, the greater the risk that the protection from pregnancy is reduced. There is a particularly high risk of becoming pregnant if the tablets are missed at the beginning of the pack or at the end (the last of the 21 active tablets). Therefore, advise the patient to follow the rules given below (see also the diagram below).
- **More than one tablet forgotten in a pack**
  Contact the doctor.

**Do not take more than 2 tablets on a given day, to make up for missed pills.**

If the patient has forgotten tablets in a pack, and they do not have the expected bleeding that should start in the normal tablet-free break (in case of LIPZ) or during the placebo week (in case of LIPZ ED), they may be pregnant. It is recommended that they contact the doctor before starting the next pack.

**1 tablet missed during week 1**

If the patient has forgotten to start a new pack, or if they have missed tablet(s) during the first 7 days of the pack, there is a risk that they are already pregnant (if they had sex in the 7 days before forgetting the tablet). In that case, contact the doctor before starting the next pack.

**See also the 'missed pill chart' for details.**

If the patient had no sex in the 7 days before the oversight, it is advised that they take the missed tablet as soon as they remember (even if this means taking two tablets at the same time) and take the next tablets at the usual time. Use extra contraceptive precautions (barrier method) for the next 7 days.

**1 tablet missed during week 2**

Take the missed tablet as soon as the patient remember (even if this means taking two tablets at the same time) and take the next tablets at the usual time. The reliability of the Pill is maintained. The extra contraceptive precautions are not required.

**1 tablet missed during week 3**

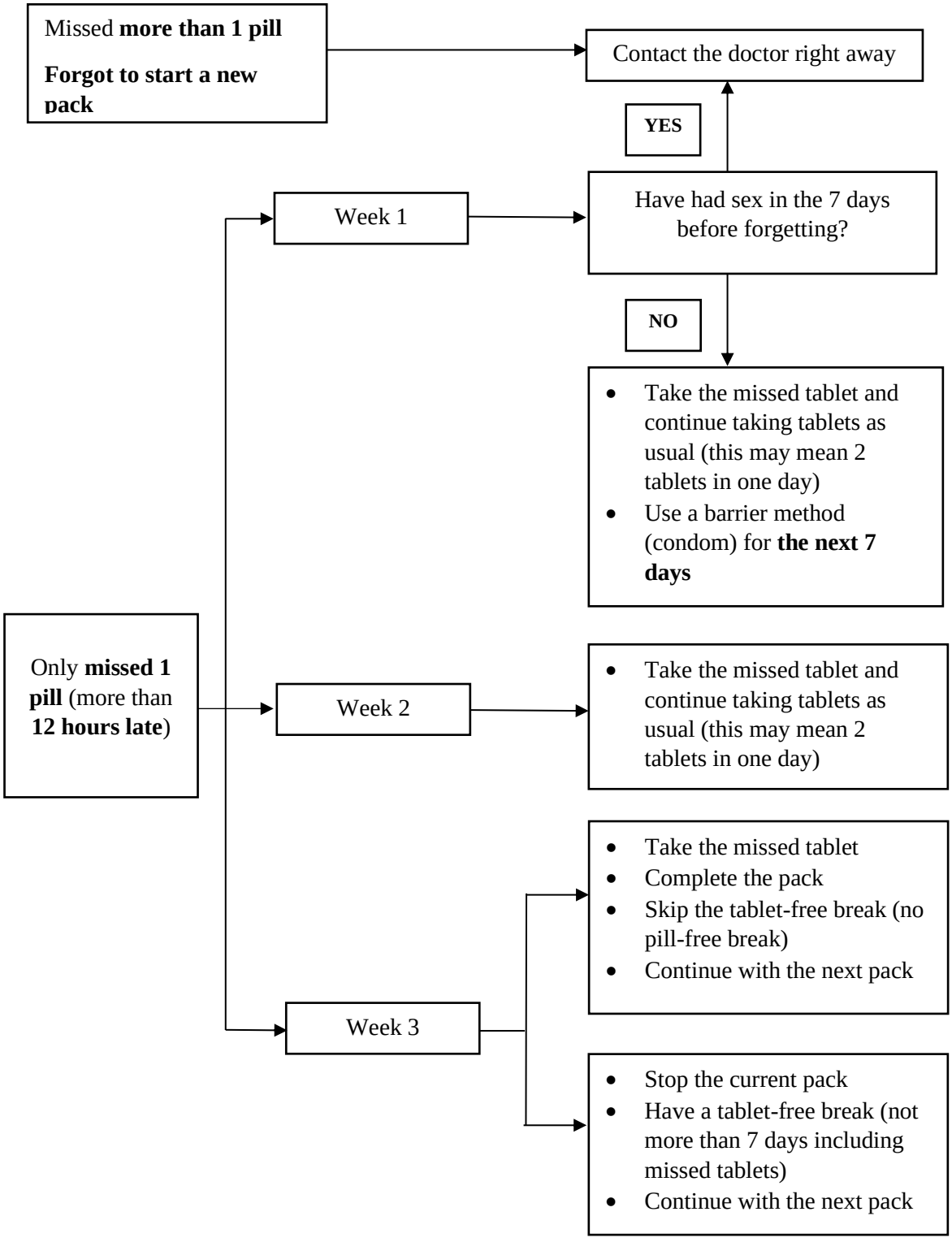
The patient may choose either of the following options, without the need for extra contraceptive precautions.

1. Take the missed tablet as soon as they remember (even if this means taking two tablets at the same time) and take the next tablets at the usual time. Start the next pack as soon as the current pack is finished so that no gap is left between packs (in case of LIPZ) or forgo the Placebo Tablets and start the next pack immediately (in case of LIPZ ED). They may not have a withdrawal bleed until the end of the second pack but they may have spotting or breakthrough bleeding while taking the tablets.

or

2. Stop taking tablets from your current pack, have a tablet-free break of 7 days or less (also count the day you missed your tablet) and continue with the next pack.

**Missed Pill Chart**



**Nausea and Vomiting**

If vomiting or severe diarrhea occur after taking any of the active tablets, the active ingredients in that tablet may not be completely absorbed. In case of vomiting within 3-4 hours after taking the tablet, follow the advice under "Missed doses" section as the contraception effectiveness is similar to missing a tablet. For severe diarrhea, contacting a doctor is recommended.

## 4.3 Contraindication

LIPZ and LIPZ ED are contraindicated in people with:

- Hypersensitivity to ethinylestradiol, drospirenone, or any component of the product (See 6.1 List of excipients).
- Undiagnosed abnormal vaginal bleeding.
- History of or current thromboembolic disorders (e.g., valvular heart disease with thrombogenic complications, deep vein thrombosis, or pulmonary embolism), history of coronary artery disease or cerebral vascular disease (e.g., myocardial infarction or stroke), or uncontrolled hypertension.
- Heavy smoking (at least 15 cigarettes daily) and being older than 35 years of age.
- Headaches with focal neurological symptoms (characterized by visual symptoms, speech disability, or weakness in any part of the body).
- Diabetes with vascular complications.
- Known or suspected breast carcinoma, estrogen-dependent neoplasia, or carcinoma of endometrium.
- Hepatic adenomas or carcinomas, or active liver disease.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Known or suspected pregnancy.
- Major surgery with prolonged immobility.
- Severe kidney insufficiency or acute kidney failure.
- Coadministration with any antiviral medicines containing ombitasvir, paritaprevir, or dasabuvir, or any combinations of these. These antiviral medicines are used to treat chronic (long-term) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus).

## 4.4 Special warning and precaution for use

Use of estrogen-progestin oral contraceptives is associated with an increased risk of several serious conditions including thromboembolism, arterial thrombosis (e.g., stroke, myocardial infarction), liver tumor, gallbladder disease, visual disturbance, fetal abnormalities, and hypertension.

Adverse cardiovascular and cerebral effects:

Cigarette smoking increases the risk of serious adverse cardiovascular effects during oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes daily) and is markedly greater in women older than 35 years of age. Women older than 35 years of age who smoke, and women with ischemic heart disease or a history of this disease, should not use estrogen-progestin contraceptives.

Women receiving LIPZ and LIPZ ED should be advised to notify their clinician if signs or symptoms of thromboembolic or thrombotic disorders occur, including **sudden severe headache or vomiting, disturbance of vision and speech, sudden partial or complete loss of vision, dizziness or faintness, weakness or numbness in an extremity, sharp or**

**crushing chest pain, unexplained cough, hemoptysis, sudden shortness of breath, calf pain,** or **heaviness in the chest**. The drugs should be discontinued if an arterial or venous thrombotic event occurs during therapy.

Additionally, because the use of oral contraceptives reportedly increases the risk of postsurgery thromboembolic complications by 2 to 4-fold, it is advised to discontinue LIPZ and LIPZ ED at least 4 weeks before and 2 weeks after surgery and during and following prolonged immobilization.

Hypertriglyceridemia, hypertension, fluid retention, and decreased glucose tolerance have been reported following the use of oral contraceptives. Women with a history of hypertension, hypertension-related diseases, or renal diseases should be encouraged to use another method of contraception.

Carcinomas:
There are no conclusive evidences whether the use of oral contraceptives correlate with the incidences of breast, endometrial, ovarian, and cervical cancer or not. However, women with history of or current aforementioned cancers should not use LIPZ and LIPZ ED as a form of contraception. In addition, annual clinical surveillance, including medical history and physical examination, breast radiographic or mammographic findings, pap smear, and relevant laboratory tests for those who use them are advised.

Benign and malignant hepatic adenomas have been associated with the use of oral contraceptives. Women receiving LIPZ and LIPZ ED should also be advised to inform their clinician if **severe abdominal pain or mass (indicating a possible liver tumor), jaundice, severe mental depression, edema,** or **unusual bleeding** occurs.

Hyperkalemia:
LIPZ and LIPZ ED contains the progestin drospirenone that has antimineralocorticoid activity. They should not be used in patients with conditions that predispose to hyperkalemia (e.g., renal insufficiency, hepatic dysfunction, adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle.

Bleeding between periods:
With all Pills, for the first few months, there might be irregular vaginal bleeding (spotting or breakthrough bleeding) between periods. It is advised to use sanitary protection while continuing taking the tablets as normal. Irregular bleeding usually stops once the body adjusts to the Pill (usually after about 3 tablets-taking cycles). If it continues, becomes heavy or starts again, contact the doctor.

What to do if no bleeding occurs:
If the patient takes all the tablets correctly, have not had any vomiting or severe diarrhea, or have not taken any other medications, it is highly unlikely for the patient to be pregnant. It is advised to continue taking LIPZ and LIPZ ED as usual.

If the patient has taken the tablets incorrectly, or, if they have taken the tablets correctly but the expected bleeding does not happen twice in a row, they might be pregnant. Instruct the patient to contact their doctor immediately as they may be pregnant. It is recommended to not start the next pack until it is certain that they are not pregnant. In the meantime, use non-hormonal contraceptive measures.

**4.5 Interaction with other medicinal products and other forms of interaction**

Decreased effect:

The levels/effects of LIPZ and LIPZ ED may be decreased by: antibiotics (griseofulvin, penicillins, or tetracyclines), aprepitant, barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, HCV protease inhibitors, HIV protease inhibitors, hydantoins, modafinil, NNRTIs (e.g., efavirenz), oxcarbazepine, phenytoin, rifamycins, rufinamide, St. John's worth, topiramate, and thiazolidinediones

LIPZ and LIPZ ED may decrease the levels/effects of: lamotrigine and valproic acid

Increased effect:

The levels/effects of LIPZ and LIPZ ED may be increased by: atorvastatin, tranexamic acid (The risk of hormonal contraceptive related thrombotic events may be increased.)

LIPZ and LIPZ ED may increase the levels/effects of: antidepressants, tricyclic, beta-blockers, caffeine, corticosteroids, theophyllines, cyclosporine, and selegiline

Other effects:

Fluconazole: The therapeutic efficacy of oral contraceptives may be decreased while the blood levels of ethinyl estradiol is increased. Consider an alternate form of birth control.

Anticoagulants: Because hormonal contraceptives can increase levels of certain circulating clotting factors and reduce antithrombin III levels, therapeutic efficacy of the anticoagulants may be decreased by hormonal contraceptives. However, both an increased and decreased effect has occurred.

Benzodiazepines: Hormonal contraceptives may increase the clearance of benzodiazepines that undergo glucuronidation (e.g., lorazepam, oxazepam, temazepam) because of increased metabolism. Combination hormonal contraceptives with alprazolam, chlordiazepoxide, diazepam, and triazolam may inhibit hepatic mixed function oxidases leading to a decrease in benzodiazepine oxidation rate (may prolong the half-life of benzodiazepines).

**4.6 Pregnancy and lactation**

Pregnancy:

Although preliminary evidence suggested that oral contraceptives could cause serious fetal toxicity when administered to pregnant women, the use of oral contraceptives prior to or during early pregnancy is not likely to cause teratogenic effects based on current evidence. However, since the risks of contraceptive use clearly outweigh any possible benefit in women who are pregnant, these agents are contraindicated in such women.

Lactation:

Combination oral contraceptive given in the postpartum period may interfere with lactation, decreasing the quantity and quality of breast milk. Furthermore, small amounts of contraceptive steroids are excreted in breast milk. If possible, defer use until the infant has been weaned.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

**4.8 Undesirable effects**

| | | |
|---|---|---|
| Serious | : | Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, coronary thrombosis, focal nodular hyperplasia of the liver, gall bladder disease, hepatic adenomas or benign liver tumors, hypertension, mesenteric thrombosis, MI, pulmonary embolism, ruptured cyst, thrombophlebitis and venous thrombosis with or without embolism, uterine leiomyoma. |
| Central nervous system: | | Dizziness, headache, mental depression, migraine. |
| Dermatologic | : | Melasma (may persist), rash (allergy). |
| Endocrine | : | Breast pain, tenderness, enlargement, secretion, diminution in lactation when given immediately postpartum. |
| Gastrointestinal | : | Abdominal cramps, bloating, cholestatic jaundice, nausea and vomiting (occurring in approximately 10-30% of patients during the first cycle, less common with low doses, and the majority resolve in 3 months). |
| Genital urinary | : | Amenorrhea during and after treatment; breakthrough bleeding (the majority, more than 80%, resolve in 3 months), spotting, change in menstrual flow, change in cervical erosion and secretions, invasive cervical cancer, temporary infertility after discontinuation, vaginal candidiasis. |
| Ophthalmic | : | Changes in corneal curvature (steepening), contact lens intolerance, neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis). |
| Miscellaneous | : | Edema, reduced carbohydrate tolerance, weight change (increase or decrease), prevalence of cervical chlamydia trachomatis may be increased; hirsutism (rare). |

**4.9 Overdose**

Acute overdosage of large doses of oral contraceptive reportedly results in nausea, vomiting, and withdrawal bleeding. Children who have not yet menstruated may also experience the bleeding.

Because drospirenone has antimineralocorticoid properties, serum potassium and sodium concentrations and indicators of metabolic acidosis should be monitored in the event of overdosage with LIPZ and LIPZ ED

## 5. Pharmacological properties

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations
ATC Code: G03AA12

LIPZ and LIPZ ED is a combination oral contraceptive consisting of an estrogen called ethinylestradiol and a progestin called drospirenone. Estrogen-progestin combinations produce a contraceptive effect by suppressing the hypothalamic-pituitary system, which results in prevention of ovulation. Specifically, the estrogen acts mainly by suppressing secretion of

follicle-stimulating hormone (FSH), resulting in prevention of follicular development and the rise of plasma estradiol concentration. In turn, the progestin appears to act mainly by inhibiting the preovulatory rise of luteinizing hormone (LH). Therefore, long-term administration of these combination products results in inhibition of both FSH and LH secretion. The effects on gonadotropins, combining with the alteration in the genital tract, including cervical mucus (which inhibits sperm penetration) and the endometrium (which reduces the likelihood of implantation), may contribute to contraceptive effectiveness.

## 5.2 Pharmacokinetic properties

Absorption

Contraceptive steroids are generally well absorbed from the GI tract. Following oral administration, the absolute bioavailability is 76% for drospirenone and 40% for ethinylestradiol, with peak plasma concentration of both drugs being reached in about 1-2 hours after a dose. The mean peak concentration following single-dose oral administration of drospirenone 3 mg (in combination with ethinylestradiol 30 mcg) was reported to be 36.9 ng/mL at about 1.7 hours.

Distribution

Drospirenone is about 97% protein bound, presumably to albumin. Ethinylestradiol is about 98% protein bound, mainly to albumin. Both drugs do not appear to bind to Sex hormone binding globulin (SHBG). Contraceptive steroids may be distributed into bile, and, in small amounts, into milk.

Metabolism

Drospirenone is metabolized only to a minor extent in vitro, mainly by CYP3A4, to inactive metabolites. Ethinylestradiol appears to undergo extensive first-pass metabolism. It is mainly metabolized via aromatic hydroxylation by CYP3A4. The major hydroxylated metabolite of ethinylestradiol is 2-hydroxy-ethinylestradiol, which is thought to contribute to some of the adverse cardiovascular effects of the drug. The hydroxylated metabolite is further metabolized by methylation and glucuronidation. Ethinylestradiol and its metabolites undergo glucuronide and sulfate conjugation, which consequently undergoes extensive enterohepatic circulation.

Excretion

Contraceptive steroids are excreted in urine and feces, principally as glucuronide and sulfate conjugates of the drugs and metabolites. The elimination half-life has been reported to be 30 hours for drospirenone and about 6 - 45 hours for ethinylestradiol.

## 5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognized pharmacological action. Particularly, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of the drospirenone and ethinylestradiol combination tablets, effects on sexual differentiation were observed in rat fetuses, but not in monkeys.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Active Tablets (LIPZ and LIPZ ED)

Beta-Cyclodextrin
Pregelatinized Starch
Corn Starch
Magnesium Stearate
Lactose Monohydrate
Isopropyl Alcohol
Methylene Chloride
Purified Water
Opadry II White
Iron Oxide Yellow
Carnauba Wax

Placebo Tablets (LIPZ ED)

PVP K-30
Lactose Monohydrate
Corn Starch
Magnesium Stearate
Purified Water
Hypromellose 2910
Propylene Glycol
Titanium Dioxide
Talc
Carnauba Wax

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

See label.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

| | |
|---|---|
| LIPZ | Blister (ALU-PVC) pack contained 21 tablets in a carton. |
| LIPZ ED | Blister (ALU-PVC) pack contained 28 tablets in a carton. |

## 7. Marketing authorization holder

BIOLAB CO., LTD.
SAMUTPRAKARN, THAILAND

## 8. Marketing authorization number(s)

Not applicable.

**9. Date of first authorization/renewal of the authorization**
Not applicable.

**10. Date of revision of the text**
1 October 2024