ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Bysumlog 100 units/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 100 units of insulin lispro* (equivalent to 3.5 mg).

Each pre-filled pen contains 300 units of insulin lispro in 3 ml solution.
Each pre-filled pen delivers 1-60 units in steps of 1 unit.

*Produced in *E.coli* by recombinant DNA technology.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (VitaClick).

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus.

4.2 Posology and method of administration

Posology

The dose should be determined by the physician, according to the requirement of the patient. Dose adjustments may be necessary in case of illness or emotional disturbances, or if patients change their physical activity or usual diet (see section 4.4).

Insulin lispro may be given shortly before meals. When necessary, insulin lispro can be given soon after meals.

Insulin lispro takes effect rapidly and has a shorter duration of activity (2 to 5 hours) given subcutaneously as compared with soluble insulin. This rapid onset of activity allows an insulin lispro injection (or, in the case of administration by continuous subcutaneous infusion, a Bysumlog bolus) to be given very close to mealtime. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. The faster onset of action compared to soluble human insulin is maintained regardless of injection site. As with all insulin preparations, the duration of action of insulin lispro is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Insulin lispro can be used in conjunction with a longer-acting insulin or oral sulphonylurea agents, on the advice of a physician.

Special populations

Renal impairment
Insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
Insulin requirements may be reduced in patients with hepatic impairment due to reduced capacity for gluconeogenesis and reduced insulin breakdown; however, in patients with chronic hepatic impairment, an increase in insulin resistance may lead to increased insulin requirements.

Paediatric population
Bysumlog can be used in adolescents and children (see section 5.1).

Method of administration

Bysumlog is administered subcutaneously by injection in the upper arms, thighs, buttocks, or abdomen. The injection sites should be rotated so that the same site is not used more than approximately once a month, in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

When administered subcutaneously care should be taken when injecting Bysumlog to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use the proper injection techniques.

Bysumlog 100 units/ml solution for injection in pre-filled pen
The Bysumlog 100 units/ml pre-filled pen delivers 1-60 units in steps of 1 unit in a single injection. The number of insulin units is shown in the dose window of the pen regardless of strength and no dose conversion should be done when transferring a patient to a new strength or to a pen with a different dose step.

Bysumlog is only available as 100 units/ml solution for injection in pre-filled pen, for subcutaneous use only. Therefore, if an alternate strength or route of administration is required, other insulin lispro medicinal products offering such options should be used. For detailed instructions on the handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Transferring a patient to another type or brand of insulin

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular/soluble, NPH/isophane, etc.), species (animal, human, human insulin analogue), and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. For fast acting insulins, any patient also on basal insulin must optimise dose of both insulins to obtain glucose control across the whole day, particularly nocturnal/fasting glucose control.

Hypoglycaemia and hyperglycaemia

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease or medications such as beta-blockers.

A few patients who have experienced hypoglycaemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

The use of doses which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Injection technique

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Insulin requirements and dose adjustment

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of dose may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia. A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Combination of Bysumlog with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind, if treatment with the combination of pioglitazone and Bysumlog is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

Avoidance of medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Bysumlog and other insulin products.

Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who

are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by medicinal products with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, $beta_2$ stimulants (such as ritodrine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of medicinal products with hypoglycaemic activity, such as oral hypoglycaemics, salicylates (for example, acetylsalicylic acid), sulpha antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors), certain angiotensin converting enzyme inhibitors (captopril, enalapril), angiotensin II receptor blockers, beta-blockers, octreotide or alcohol.

The physician should be consulted when using other medications in addition to Bysumlog (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn.

It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

Breast-feeding

Patients with diabetes who are breast-feeding may require adjustments in insulin dose, diet or both.

Fertility

Insulin lispro did not induce fertility impairment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of safety profile

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise.

Tabulated list of adverse reactions

The following related adverse reactions from clinical trials are listed below as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1 000 to <1/100; rare: ≥1/10 000 to <1/1 000; very rare: <1/10 000) and not known (cannot be estimated form the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders						
Local allergy		X				
Systemic allergy				X		
Skin and subcutaneous tissue disorders						
Lipodystrophy			X			
Cutaneous amyloidosis						X

Description of selected adverse reactions

Local allergy

Local allergy in patients is common. Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy

Systemic allergy, which is rare but potentially more serious, is a generalised allergy to insulin. It may cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalised allergy may be life-threatening.

Skin and subcutaneous tissue disorders

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Oedema

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Insulins have no specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycaemic episodes will respond to oral administration of glucose or other sugar or saccharated products.

Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC code: A10AB04.

Bysumlog is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu/en.

Mechanism of action

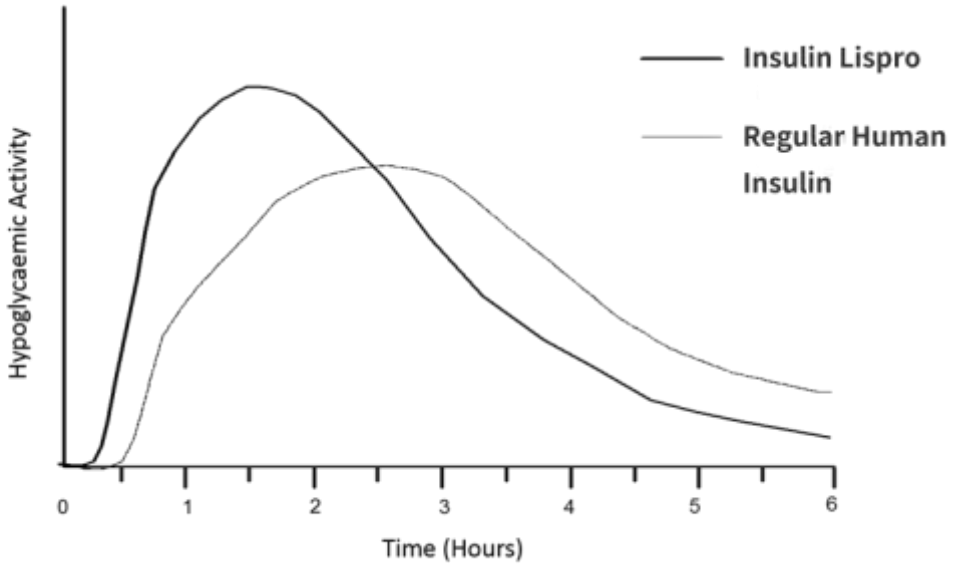
The primary activity of insulin lispro is the regulation of glucose metabolism.

In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

Insulin lispro has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within zero to 15 minutes of the meal) when compared to soluble insulin (30 to 45 minutes before). Insulin lispro takes effect rapidly and has a shorter duration of activity (2 to 5 hours) when compared to soluble insulin.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with insulin lispro compared to soluble human insulin.

As with all insulin preparations, the time course of insulin lispro action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature and physical activity. The typical activity profile following subcutaneous injection is illustrated below.



The above representation reflects the relative amount of glucose over time required to maintain the subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

Clinical trials have been performed in children (61 patients aged 2 to 11 years) and children and adolescents (481 patients aged 9 to 19 years), comparing insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is similar to that seen in adults.

In patients with type 2 diabetes on maximum doses of sulphonylurea agents, studies have shown that the addition of insulin lispro significantly reduces HbA_{1c} compared to sulphonylurea alone. The reduction of HbA_{1c} would also be expected with other insulin products e.g. soluble or isophane insulins.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated a reduced number of episodes of nocturnal hypoglycaemia with insulin lispro compared to soluble human insulin. In some studies, reduction of nocturnal hypoglycaemia was associated with increased episodes of daytime hypoglycaemia.

The glucodynamic response to insulin lispro is not affected by renal or hepatic function impairment. Glucodynamic differences between insulin lispro and soluble human insulin, as measured during a glucose clamp procedure, were maintained over a wide range of renal function.

Insulin lispro has been shown to be equipotent to human insulin on a molar basis but its effect is more rapid and of a shorter duration.

5.2 Pharmacokinetic properties

The pharmacokinetics of insulin lispro reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilisation curves (as discussed in section 5.1).

Insulin lispro maintains more rapid absorption when compared to soluble human insulin in patients with renal impairment. In patients with type 2 diabetes over a wide range of renal function the pharmacokinetic differences between insulin lispro and soluble human insulin were generally maintained and shown to be independent of renal function. Insulin lispro maintains more rapid absorption and elimination when compared to soluble human insulin in patients with hepatic impairment.

5.3 Preclinical safety data

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, insulin lispro behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin lispro is equivalent to human insulin. Acute, one month and twelve month toxicology studies produced no significant toxicity findings.

Insulin lispro did not induce fertility impairment, embryotoxicity or teratogenicity in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Glycerol (E 422)
Anhydrous disodium hydrogen phosphate (E 339)
Zinc oxide
Water for injections
Hydrochloric acid (E 507) (for pH adjustment)
Sodium hydroxide (E 524) (for pH adjustment)

6.2 Incompatibilities

This medicinal product should not be mixed with any other insulin or any other medicinal product.

6.3 Shelf life

Before use

3 years.

After first use

4 weeks. Store below 30 °C. Do not refrigerate. Do not expose to excessive heat or direct sunlight.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze.
For storage conditions of the medicinal product after first use, see section 6.3.

6.5 Nature and contents of container

The solution is contained in type I borosilicate glass cartridges, sealed with bromobutyl disc seals and plunger heads and are secured with aluminium seals. The 3 ml cartridges are sealed in a disposable pen injector.
Packs of 1 and 5 pre-filled pens. Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

To prevent the possible transmission of disease, each pre-filled pen must be used by one patient only, even if the needle on the delivery device is changed. The patient should discard the needle after every injection.

The Bysumlog solution should be clear and colourless. Bysumlog should not be used if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

Preparing a dose

Before using the pre-filled pen, the instructions for use included in the package leaflet must be read carefully. The pre-filled pen has to be used as recommended in the instructions for use.
Do not expose to excessive heat or direct sunlight.
The pre-filled pen should not be stored with the needle attached.
Needles are not included.
Pens should not be used if any part looks broken or damaged.

Injecting a dose

For detailed instructions for preparing the pen and injecting the dose please refer to the instruction for use provided at the end of the package leaflet, the following is a general description.

1. Wash your hands.

2. Choose a site for injection.

3. Clean the skin as instructed.

4. Stabilise the skin by spreading it or pinching up a large area. Insert the needle and inject as instructed.

5. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.

6. Dispose of the syringe and needle safely. For an injection device use the outer needle cap, unscrew the needle and dispose of it safely.

7. Use of the injection sites should be rotated so that the same is not used more than approximately once a month.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Gan & Lee Pharmaceuticals Europe GmbH
Prinzenallee 11a
40549 Düsseldorf
Germany.

8. MARKETING AUTHORISATION NUMBERS

EU/1/26/2030/001
EU/1/26/2030/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Names and addresses of the manufacturers of the biological active substance

Gan & Lee Pharmaceuticals
No.8 Nanfeng West First Road
Huoxian Town
Tongzhou District
Beijing, China, 101109

Names and addresses of the manufacturers responsible for batch release

IL-CSM Clinical Supplies Management GmbH
Marie-Curie-Strasse 8
Loerrach, Baden-Wuerttemberg, 79539, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bysumlog 100 units/ml solution for injection in pre-filled pen.
insulin lispro

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml solution contains 100 units of insulin lispro (equivalent to 3.5 mg).
Each pre-filled pen contains 300 units of insulin lispro in 3 ml solution.

3. LIST OF EXCIPIENTS

Excipients: glycerol, zinc oxide, anhydrous disodium hydrogen phosphate, metacresol, water for injections, sodium hydroxide and/or hydrochloric acid (for pH adjustment). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (VitaClick)

1 pen of 3 ml
5 pens of 3 ml

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use

OPEN HERE

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
During use: Use within 4 weeks. Store below 30 °C. Do not refrigerate. Do not expose to excessive heat or direct sunlight.

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gan & Lee Pharmaceuticals
Europe GmbH
40549 Düsseldorf
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2030/001 1 pen of 3 ml.
EU/1/26/2030/002 5 pens of 3 ml.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bysumlog

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Bysumlog 100 units/ml solution for injection
insulin lispro
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bysumlog 100 units/ml solution for injection in pre-filled pen
insulin lispro
Each pre-filled pen delivers 1 – 60 units in steps of 1 units

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bysumlog is and what it is used for

Bysumlog is used to treat diabetes. It works more quickly than normal human insulin because the insulin molecule has been changed slightly.

You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Bysumlog is a substitute for your own insulin and is used to control glucose in the long term. It works very quickly and lasts a shorter time than soluble insulin (2 to 5 hours). You should normally use Bysumlog within 15 minutes of a meal.

Your doctor may tell you to use Bysumlog as well as a longer-acting insulin. Each kind of insulin comes with another patient information leaflet to tell you about it. Do not change your insulin unless your doctor tells you to. Be very careful if you do change insulin.

Bysumlog is suitable for use in adults and children.

2. What you need to know before you use Bysumlog

Do NOT use Bysumlog
- if you think **hypoglycaemia** (low blood sugar) is starting. Further in this leaflet it tells you how to deal with mild hypoglycaemia (see section 3: If you use more Bysumlog than you should).
- if you are **allergic** to insulin lispro or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Record the brand name ("Bysumlog") and Lot number (included on the outer cartons and labels of each pre-filled pen) of the product you are using and provide this information when reporting any side effects.
- Always check the pack and the label of the pre-filled pen for the name and type of the insulin when you get it from your pharmacy.
- If your blood sugar levels are well controlled by your current insulin therapy, you may not feel the warning symptoms when your blood sugar is falling too low. Warning signs are listed later in this leaflet. You must think carefully about when to have your meals, how often to exercise and how much to do. You must also keep a close watch on your blood sugar levels by testing your blood glucose often.
- A few people who have had hypoglycaemia after switching from animal insulin to human insulin have reported that the early warning symptoms were less obvious or different. If you often have hypoglycaemia or have difficulty recognising it, please discuss this with your doctor.
- If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse
  - Have you recently become ill?
  - Do you have trouble with your kidneys or liver?
  - Are you exercising more than usual?
- You should also tell your doctor, pharmacist or diabetes nurse if you are planning to go abroad. The time difference between countries may mean that you have to have your injections and meals at different times from when you are at home.
- Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible, if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).
- This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.

Skin changes at the injection site

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (See How to use Bysumlog). Contact your doctor if you are currently injecting into a lumpy area before you start injecting a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other medicines and Bysumlog

Your insulin needs may change if you are taking

- the contraceptive pill,
- steroids,
- thyroid hormone replacement therapy,
- oral hypoglycaemics,
- acetyl salicylic acid,
- sulpha antibiotics,
- octreotide,
- "beta$_2$ stimulants" (for example ritodrine, salbutamol or terbutaline),
- beta-blockers, or
- some antidepressants (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors),
- danazol,
- some angiotensin converting enzyme (ACE) inhibitors (for example captopril, enalapril), and
- angiotensin II receptor blockers.

Please tell your doctor, if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (see section "Warnings and precautions").

Bysumlog with alcohol
Your blood sugar levels may change if you drink alcohol. Therefore, the amount of insulin needed may change.

Pregnancy and breast-feeding
Are you pregnant or thinking about becoming pregnant, or are you breast-feeding? The amount of insulin you need usually falls during the first three months of pregnancy and increases for the remaining six months. If you are breast-feeding, you may need to alter your insulin intake or diet. Ask your doctor for advice.

Driving and using machines
Your ability to concentrate and react may be reduced if you have hypoglycaemia. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor about the advisability of driving if you have:
- frequent episodes of hypoglycaemia
- reduced or absent warning signs of hypoglycaemia

Bysumlog contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Bysumlog
Always use Bysumlog exactly as your doctor has told you. You should check with your doctor if you are not sure. To prevent the possible transmission of disease, each pen must be used by you only, even if the needle is changed.
The Bysumlog is a disposable pre-filled pen containing 3 ml (300 units, 100 units/ml) of insulin lispro. One Bysumlog pre-filled pen contains multiple doses of insulin. The Bysumlog dials 1 unit at a time. **The number of units are displayed in the dose window, always check this before your injection.** You can give from 1 to 60 units in a single injection. **If your dose is more than 60 units, you will need to give yourself more than one injection.**

Dose
- You should normally inject Bysumlog within 15 minutes of a meal. If you need to, you can inject soon after a meal. But your doctor will have told you exactly how much to use, when to use it, and how often. These instructions are only for you. Follow them exactly and visit your diabetes clinic regularly.
- If you change the type of insulin you use (for example from a human or animal insulin to a Bysumlog product), you may have to take more or less than before. This might just be for the first injection, or it may be a gradual change over several weeks or months.
- Bysumlog is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Preparing Bysumlog
- Bysumlog is already dissolved in water, so you do not need to mix it. But you must use it **only** if it looks like water. It must be clear, have no colour and no solid pieces in it. Check each time you inject yourself.

Getting the Bysumlog ready to use (Please see instructions for use)
- First wash your hands.
- Read the instructions on how to use your pre-filled insulin pen. Please follow the instructions carefully. Here are some reminders.
- Use a clean needle. (Needles are not included).
- Prime your Bysumlog before each use. This checks that insulin comes out and clears the air bubbles from your Bysumlog. There may still be some small air bubbles left in the pen these are harmless. But if the air bubbles are too large it may affect the insulin dose.

Injecting Bysumlog

- Before you make an injection, clean your skin as you have been instructed. Inject under the skin, as you were taught. Do not inject directly into a vein. After your injection, leave the needle in the skin for five seconds to make sure you have taken the whole dose. Do not rub the area you have just injected. Make sure you inject at least half an inch (1 cm) from the last injection and that you 'rotate' the places you inject, as you have been taught. It doesn't matter which injection site you use, either upper arm, thigh, buttock or abdomen, your Bysumlog injection will still work quicker than soluble human insulin.
- You must not administer Bysumlog by the intravenous route. Inject Bysumlog as your physician or nurse has taught you.

After injecting

- As soon as you have done the injection, unscrew the needle from the pre-filled pen using the outer needle cap. This will keep the insulin sterile and stop it leaking. It also stops air entering the pen and your needle clogging. **Do not share your needles**. Do not share your pen. Replace the cap on your pen.

Further injections

- Every time you use pre-filled pen you must use a new needle. Before every injection, clear any air bubbles. You can see how much insulin is left by holding the pre-filled pen with the needle pointing up. The scale on the cartridge shows about how many units you have left.
- Do not mix any other insulin in your disposable pen. Once the Bysumlog is empty, do not use it again. Please get rid of it carefully - your pharmacist or diabetes nurse will tell you how to do this.
- Bysumlog is only suitable for injecting just under the skin. Do not use the pen to administer Bysumlog by a different way. Other medicines containing insulin lispro 100 units/ml are available if this is necessary. Speak to your doctor if this applies to you.

If you use more Bysumlog than you should

If you use more Bysumlog than you need or are unsure how much you have injected, a low blood sugar may occur. Check your blood sugar.

If your blood sugar is low **(mild hypoglycaemia)**, eat glucose tablets, sugar or drink a sugary drink. Then eat fruit, biscuits, or a sandwich, as your doctor has advised you and have some rest. This will often get you over mild hypoglycaemia or a minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat quite severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to go to hospital. Ask your doctor to tell you about glucagon.

If you forget to use Bysumlog

If you use less Bysumlog than you need or are unsure how much you have injected, a high blood sugar may occur. Check your blood sugar.

If hypoglycaemia (low blood sugar) or hyperglycaemia (high blood sugar) is not treated they can be very serious and cause headaches, nausea, vomiting, dehydration, unconsciousness, coma or even death (see A and B in section 4 "Possible Side Effects").

Three simple steps to avoid hypoglycaemia or hyperglycaemia are:

- Always keep a spare pen, in case you lose your Bysumlog or it gets damaged.
- Always carry something to show you are diabetic.
- Always carry sugar with you.

If you stop using Bysumlog.

If you take less Bysumlog than you need, a high blood sugar may occur. Do not change your insulin unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Systemic allergy is rare (may affect up to 1 in 1 000 people). The symptoms are as follows:
- rash over the whole body
- difficulty in breathing
- wheezing
- blood pressure dropping
- heart beating fast
- sweating

If you think you are having this sort of insulin allergy with Bysumlog, tell your doctor at once.

Local allergy is common (may affect up to 1 in 10 people). Some people get redness, swelling or itching around the area of the insulin injection. This usually clears up in anything from a few days to a few weeks. If this happens to you, tell your doctor.

Lipodystrophy is uncommon (may affect up to 1 in 100 people). If you inject insulin too often at the same place, the fatty tissue may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

Oedema (e.g. swelling in arms, ankles; fluid retention) has been reported, particularly at the start of insulin therapy or during a change in therapy to improve control of your blood glucose.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Common problems of diabetes

A. Hypoglycaemia
Hypoglycaemia (low blood sugar) means there is not enough sugar in the blood. This can be caused if:
- you take too much Bysumlog or other insulin;
- you miss or delay meals or change your diet;
- you exercise or work too hard just before or after a meal;
- you have an infection or illness (especially diarrhoea or vomiting);
- there is a change in your need for insulin; or
- you have trouble with your kidneys or liver which gets worse.

Alcohol and some medicines can affect your blood sugar levels (see section 2).

The first symptoms of low blood sugar usually come on quickly and include the following:
- tiredness
- nervousness or shakiness
- headache
- rapid heartbeat
- feeling sick
- cold sweat

While you are not confident about recognising your warning symptoms, avoid situations, e.g. driving a car, in which you or others would be put at risk by hypoglycaemia.

B. Hyperglycaemia and diabetic ketoacidosis
Hyperglycaemia (too much sugar in the blood) means that your body does not have enough insulin. Hyperglycaemia can be brought about by:

- not taking your Bysumlog or other insulin;
- taking less insulin than your doctor tells you to;
- eating a lot more than your diet allows; or
- fever, infection or emotional stress.

Hyperglycaemia can lead to diabetic ketoacidosis. The first symptoms come on slowly over many hours or days. The symptoms include the following:

- feeling sleepy
- flushed face
- thirst
- no appetite
- fruity smell on the breath
- feeling or being sick

Severe symptoms are heavy breathing and a rapid pulse. **Get medical help immediately.**

C. Illness

If you are ill, especially if you feel sick or are sick, the amount of insulin you need may change. **Even when you are not eating normally, you still need insulin.** Test your urine or blood, follow your 'sick rules', and tell your doctor.

5. How to store Bysumlog

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

Before the first use store your Bysumlog pre-filled pen in a refrigerator (2 °C – 8 °C). Do not freeze.

After first use keep your Bysumlog pre-filled pen at room temperature (below 30 °C) and discard after 4 weeks. Do not put it near heat or in the sun. Do not keep the pre-filled pen that you are using in the fridge. The pre-filled pen should not be stored with the needle attached.

Do not use this medicine if you notice the solution is coloured or it has solid pieces in it. You must use it **only** if it looks like water. Check this each time you inject yourself.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Bysumlog 100 units/ml pre-filled pen solution for injection contains

- The active substance is insulin lispro. Each ml of the solution contains 100 units (equivalent to 3.5 mg) of insulin lispro. Each pre-filled pen contains 3 ml of solution for injection, equivalent to 300 units.
- The other ingredients are metacresol, glycerol, anhydrous disodium hydrogen phosphate, zinc oxide and water for injection. Sodium hydroxide or hydrochloric acid may have been used to adjust the acidity (see section 2 "Bysumlog contains sodium").

What Bysumlog looks like and contents of the pack

Bysumlog 100 units/ml solution for injection in pre-filled pen (VitaClick) is a sterile, clear, colourless, aqueous solution. Each pre-filled pen contains 300 units (3 millilitres).
Packs of 1 and 5 pre-filled pens. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Gan & Lee Pharmaceuticals Europe GmbH, Prinzenallee 11a, 40549 Düsseldorf, Germany.

Manufacturer
IL-CSM Clinical Supplies Management GmbH Marie-Curie-Strasse 8 Loerrach, Baden-Wuerttemberg, 79539, Germany

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE
Bysumlog solution for injection in pre-filled pen (VitaClick)

Bysumlog (VitaClick) is a pre-filled pen for the injection of insulin lispro.

Talk with your doctor, pharmacist or nurse about proper injection technique before using Bysumlog.

People who are blind or have vision problems should not use the pen without help from a person trained to use the pen.

Read all package leaflet information and instructions carefully before using your Bysumlog. If you are not able to use Bysumlog or follow all the instructions completely on your own, you must use Bysumlog only if you have help from a person who is able to follow the instructions completely.

You can set doses from 1 to 60 units in steps of 1 unit. You can give yourself multiple doses using one pen. If your prescribed dose is more than 60 units, you will need to give yourself more than 1 injection.

Keep this leaflet for future reference.

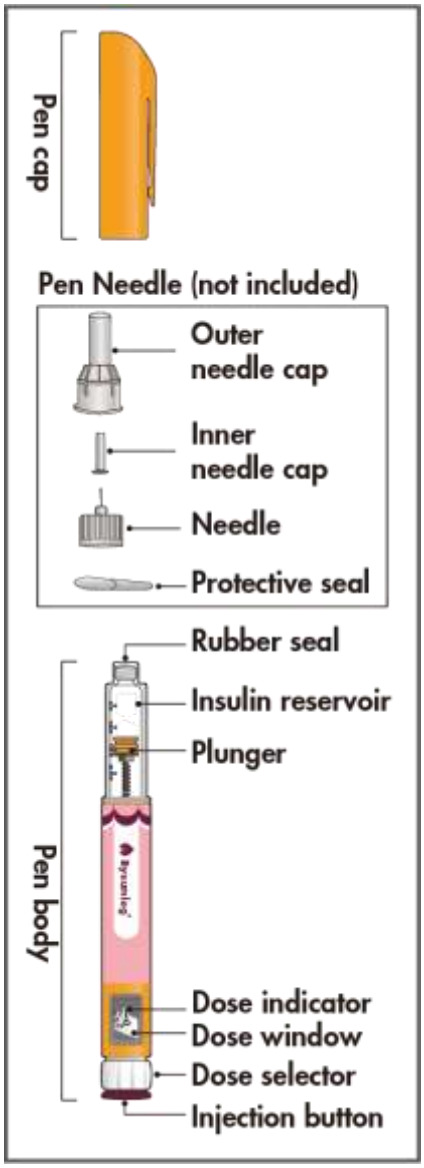


Figure A Overview Bysumlog pre-filled pen (VitaClick) and needles (example)

Important information you need to know before injecting Bysumlog

- **Always read the label of your pen before injecting.** If you use more than 1 type of insulin Pen, store the Pens with different medicine in separate areas and read the label of your pen before injecting. If you take the wrong type of insulin, your blood sugar level may get too high or too low.
- **Do not share your Bysumlog with other people, even if the needle has been changed. This pen is only for your use.** You may give other people a serious infection, or get a serious infection from them.
- **Do not** use your pen, if it is damaged or if you are not sure that it is working properly. Be careful not to bend or damage the needle before use.
- **Do not** select a dose and/or press the injection button without a needle attached.
- **Do not** re-use needles. Always attach a new needle before each use.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Always perform the safety test before each injection (see **Step 3**).
- Always have a spare pen and spare needles in case they get lost or damaged.

Need Help?

If you have any questions about Bysumlog or about diabetes, ask your doctor, pharmacist or nurse or call the local representative number on the front of this leaflet.

Materials needed

Make sure you have the following items:

Included in your carton

- Your Bysumlog (see **Figure A**).

Not included in your carton (Obtain separately)

- New sterile needle. Only use needles that are compatible for use with Bysumlog pre-filled pen, which sizes compatible with this pen:
  - **31G, 5 mm**
  - **32G, 4-6 mm**
  - **33G, 4 mm**
  - **34G, 4 mm**
- Alcohol swab
- Sharps disposal container for used needles

Step 1. Check the pen and insulin

If your Bysumlog is in the refrigerator, take it out 1 to 2 hours before you inject to allow it to reach room temperature. Injecting cold insulin can be uncomfortable.

- Wash your hands with soap and water.

A. Check the name of the pen, to **make sure you have the correct insulin** (see **Figure B**) – this is especially important if you have other pens.
- Bysumlog is orange and pink with a burgundy injection button.

Figure B

B. Check the expiration date (EXP).
- **Do not** use your pen after the expiration date.

C. Pull off the pen cap (see **Figure C**).

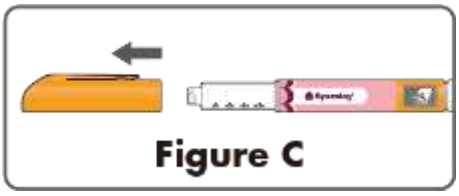


Figure C

D. Check the appearance of the insulin. Bysumlog is a clear insulin.
- **Do not** use your pen, if the insulin is cloudy, coloured or contains visible particles.

Step 2. Attach a new needle

Always use a new sterile needle for each injection. This helps prevent contamination and potential needle blocks.

A. Wipe the rubber seal with an alcohol swab.

B. Remove the protective seal from a new needle.

C. Keep the needle straight and screw it onto the pen until fixed (see **Figure D**).
- If the needle is not kept straight while you attach it, it can damage the rubber seal, cause the insulin to leak, or break the needle.

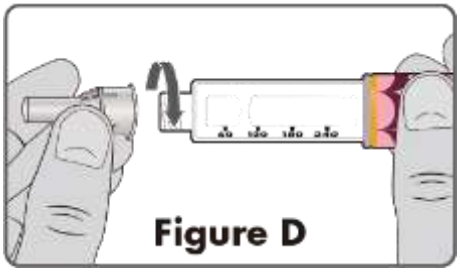


Figure D

Step 3. Perform a safety test

Always perform a safety test before each injection to:
- make sure the pen and needle work properly.

- make sure you get the correct dose by removing air bubbles.

A. Select a dose of 2 units by turning the dose selector (see **Figure E**).
- If necessary, the selected dose can be corrected by turning the dose selector back down.

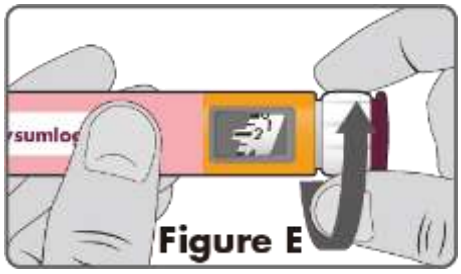


Figure E

B. Pull off the outer needle cap (see **Figure F**) and keep it to remove the used needle after injection.

C. Pull off the inner needle cap (see **Figure F**) and discard it.

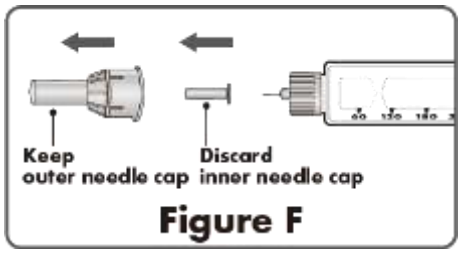


Figure F

D. Hold the pen with the needle pointing upwards. Tap the insulin reservoir (see **Figure G**) so that any air bubbles rise up towards the needle.

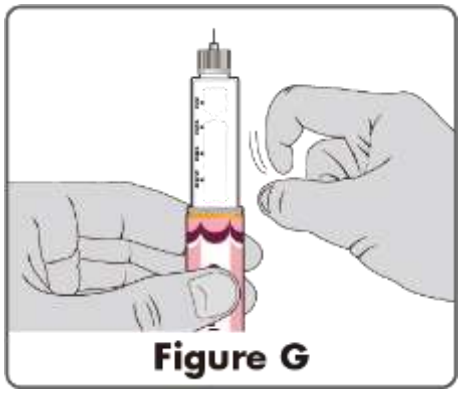


Figure G

E. Press the injection button all the way in (see **Figure H**).
- Check if insulin comes out of the needle tip. Your pen is working correctly if insulin comes out of the needle.

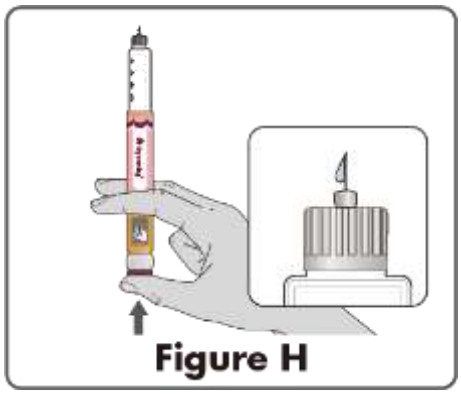


Figure H

You may have to perform the safety test several times before insulin comes out of the needle tip.

- If no insulin comes out of the needle tip, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and repeat the safety test (see **Step 3**).
- If no insulin comes out after changing the needle, your pen may be damaged. **Do not** use this pen. Use a new pen.
- Small air bubbles are normal and will not affect your dose.

Step 4. Select your dose

You can set the dose from 1 to 60 units in steps of 1 unit of insulin (one step equals 1 unit of insulin). If you need a dose greater than 60 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose by turning the dose selector until the dose indicator lines up with your dose (see **Figure I**: selected dose is 30 units in this example).

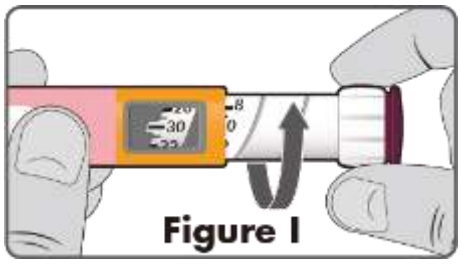


Figure I

- If you turn past your dose, you can turn back down.
- You will hear a click for every single unit dialled. **Do not** set the dose by counting the number of clicks you hear because you may get an incorrect dose. Even numbers are shown in line with the dose indicator, odd numbers are shown as a line between even numbers (see **Figure J**).

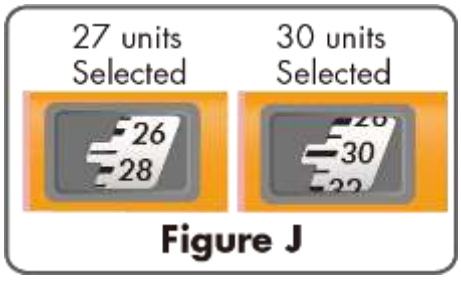


Figure J

- Always check the number in the Dose Window to make sure you have dialled the correct dose.
- The pen will not let you dial more than the number of units left in the pen.
- If the insulin left in the pen is less than your dose, inject what is remaining in the pen and complete your dose with a new pen, or use a new pen for your full dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale. **Do not** use this scale printed on the cartridge to measure your dose of insulin.

Step 5. Inject the dose

Use the injection method as instructed by your doctor, pharmacist or nurse.

A. Choose your injection site.

- The pen can be injected in your thigh, stomach area (abdomen), buttocks or upper arm (see **Figure K**).
- Change (rotate) your injection site for each injection.
- **Do not** inject where the skin has pits, is thickened or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard or into scars or damaged skin.

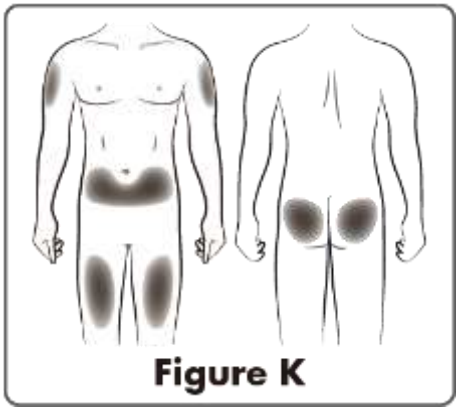


Figure K

B. Clean the injection site with an alcohol swab. Let it dry before injecting.

C. Insert the needle into the skin (see **Figure L**).

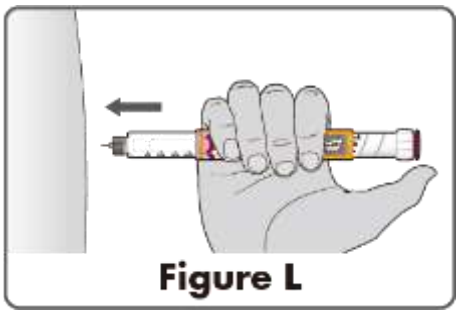


Figure L

D. Press the burgundy injection button all the way in to deliver the dose. The number in the dose window will return to "0" as you inject. **Do not** try to inject your insulin by turning the dose selector. You will not receive your insulin by turning the dose selector.

- Always make sure that the dose selector returns to "0" after the injection. If the dose selector stops before it returns to "0", the full dose has not been delivered and the remaining units still to be injected with a new pen are shown in the dose window.

E. **Keep holding the burgundy injection button pressed all the way in. Slowly count to 5** (see **Figure M**) before you pull out the needle from the skin. This ensures that the full dose is given. A drop of insulin at the Needle tip is normal. It will not affect your dose.

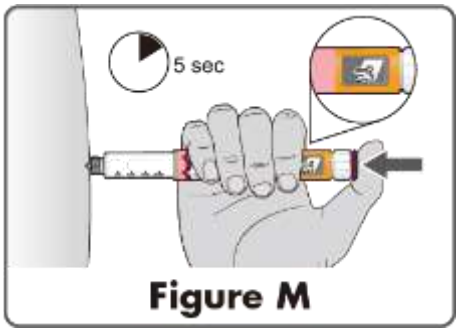


Figure M

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used. If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or a swab.

If you find it hard to press the injection button in:

- **Do not** force it as this may break your pen.
- Change the needle (see **Step 6** and **Step 2**) and prime your Pen (see **Step 3**).
- If you still find it hard to press in, get a new Pen.
- Never use a syringe to remove insulin from your pen.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store the pen without a needle attached. This helps prevent:

- Contamination and/or infection.
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Carefully put the outer needle cap back on the needle (see **Figure N**), to reduce the risk of accidental needle injury.

- **Never** replace the inner needle cap.

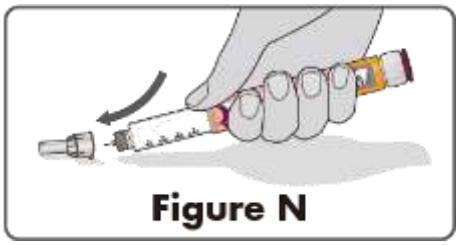


Figure N

B. Pinch the base of the outer needle cap to unscrew the used needle (See **Figure O**).

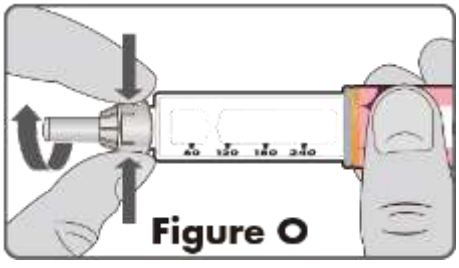


Figure O

C. Dispose of the needle safely, as instructed by your doctor, pharmacist or nurse.

D. Always put the pen cap back on (see **Figure P**). Store the pen until your next injection.

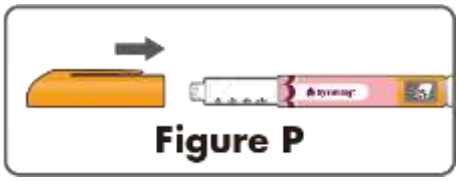


Figure P

Storage instructions

Before first use

- Keep your pen in the refrigerator between 2°C to 8°C until first use.
- **Do not** freeze. Throw away your pen if it has been frozen.
- Unused Pens may be used until the expiration date printed on the Label, if the Pen has been kept in the refrigerator.

After first use

- Store the pen you are currently using at room temperature below 30°C, and away from light, dust and dirt.
- The pen in use must not be stored in a refrigerator.
- Once you take your pen out of the refrigerator, you can use it for up to 28 days. **Do not** use it after this time.
- **Do not** store your pen with the needle attached.
- **Keep your pen out of the reach and sight of children and any other persons who are not supposed to handle it.**
- When the pen is empty, throw it away without a needle on, as instructed by your doctor, pharmacist or nurse.

Maintenance

- You can clean the outside of your pen by wiping it with a damp cloth (water only).
- **Do not** soak, wash or lubricate the pen as this may damage it.
- Your pen should be handled with care. Avoid situations where the pen might be damaged. If you are concerned that your pen may be damaged, use a new one.

This instructions for used was last revised in MM/YYYY